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**BRAIN
RESEARCH
REVIEWS**

Preface

Camillo Golgi and modern neuroscience

This volume celebrates Camillo Golgi of Pavia, Italy, who, through the discovery of a special method of staining individual nerve cells in 1873, was the pioneer of cellular neuroanatomy, and Santiago Ramón y Cajal of Spain, the greatest exponent of the Golgi method, who led the classical histologists in providing the cellular basis for the rise of modern neuroscience. For this work, they jointly received the Nobel Prize in 1906.

In the late 19th century, the cellular basis of nervous function was still unknown, despite the concerted efforts of the greatest laboratories of Europe. Camillo Golgi, an Italian histologist and general pathologist working in isolation, experimenting in his own living quarters while carrying out his duties of being a physician at a hospital for the chronically ill, was able to devise a method that deposited silver chromate within an individual nerve cell, enabling it to be seen for the first time in its entirety. The first report on cells in the cerebellum came out in 1873, quickly followed by the olfactory bulb, hippocampus, and others, culminating in his collected papers in his “Opera Omnia” of 1885–6. The dendrites of neurons, their stereotyped forms, and the branching of axons became visible for the first time (see cover).

Santiago Ramón y Cajal, another histologist working far from the mainstream European laboratories, in Spain, stumbled upon Golgi’s method and, beginning in 1888, poured out a series of studies on many different brain regions. Other European laboratories joined the hunt, and within a few years, the histological basis of nervous function was firmly established. All of this was summarized by Cajal in a monumental work entitled “Histologie du Système Nerveux l’Homme et des Vertébrés”, one of the founding publications of modern neuroscience.

In interpreting his results, Golgi believed in the separateness of the cell bodies and dendrites but could not convince himself of the individuality of the finest axonal branches and considered that they formed a continuous network. He postulated that this network accounted for the unified action of nervous function. Cajal, on the other hand, by developing variants of the Golgi method, was able to discern that axons end in terminals. This became codified in the “neuron doctrine” of von Waldeyer-Harz, the idea that each nerve cell

is a bounded entity. All of this implied that nerve cells interact through functional contacts with each other, contacts that came to be called synapses.

The individuality of the neuron that Cajal fought so hard for appeared to be confirmed by the first electron microscopic investigations in the 1950s, and the neuron as a genetic, anatomical, and functional entity, interacting with other neurons through synapses, has been the main conceptual basis of modern neuroscience. In the modern neuroscience perspective, Cajal won, and Golgi lost, an ageing Senator clinging to an obsolete view, whose work on the fundamental structure of the nerve cell, upon which Cajal was to build, was forgotten. However, modern studies also demonstrated electrical synapses providing for electrical continuity between cells through gap junctions. Recent workers have begun to note that this appears to support Golgi’s concept of neurons interacting through networks, although Golgi’s network was only between fine branches of axons. There has thus been increasing confusion about where things stand with regard to “neuronism vs. reticularism”.

From a conceptual point of view, these issues, originating with Golgi and Cajal, are thus still with us. It has been natural, therefore, for the Cajal Club to promote discussion of these issues as they relate to modern research. The Cajal Club was established in 1947 to further the tradition of Ramón y Cajal in studies of the functional anatomy of the brain in general and, more recently, has focused on the cerebral cortex due to the Krieg Cortical Kudos, an awards program for scientists at different stages of their career. It is the oldest neuroscience organization in North America and has met annually since then, first at the annual meetings of the American Association of Anatomists and recently at the annual meetings of the Society for Neuroscience.

The club began sponsoring international meetings in 2001 with the first at the Cajal Institute in Madrid, which resulted in a volume entitled “Changing Views of Cajal’s Neuron” (2002). The centenary of their Nobel Prize in 2006 was celebrated by an international symposium entitled “A Century of Neuroscience Discovery: Reflecting on the Nobel Prize to Golgi and Cajal in 1906” in Stockholm, hosted by Gunnar Grant, Sten Grillner, and Tomas Hokfelt of the Karolinska Institute and Larry

Swanson, Edward Jones, and John H. Morrison of the Cajal Club. It was a highly successful meeting, resulting in a special issue of the same title in 2007.

Following this meeting, Marina Bentivoglio and Paolo Mazzarello approached the Cajal Club to suggest the possibility of a follow-up symposium on Golgi and Cajal in Golgi's home institution of Pavia. The Club responded enthusiastically to this generous invitation. An attraction of a meeting in Pavia was to enable the Club to lead the way in highlighting the contributions of Cajal and Golgi and bringing about closure on the issue of their differing views of neuronal organization.

The symposium, held September 29–October 1, 2009, was entitled “Camillo Golgi and Modern Neuroscience”, bringing together leading neuroscientists to appreciate the historical background that produced the Golgi method as well as to highlight current advances in molecular and cellular neuroscience (Fig. 1). It was sponsored by the Cajal Club and hosted by the University of Pavia. It was the first international meeting honoring Golgi in his home institution. Contributing to its uniqueness, it also celebrated the awarding of the Nobel Prize to his more recent compatriot Rita Levi-Montalcini in the year of her 100th birthday, with the special treat of participation by Dr. Levi-Montalcini herself (Fig. 2).

The meeting took place in the historic Golgi Amphitheatre in the University of Pavia (Fig. 3). The first morning began with the arrival of Professor Rita Levi-Montalcini from Rome. She had passed her 100th birthday a few months earlier, in April. News of her arrival had preceded her, and it became a media event, with the paparazzi popping flash bulbs and excited students lining the corridor as she made her way to the



Fig. 2 – Edward Jones, Rita Levi-Montalcini, Marina Bentivoglio, and Paolo Mazzarello in the old amphitheatre.

amphitheatre. Several of us sat with her to chat for a few minutes, before Larry Swanson gave a full introduction praising her long career, and presented her with the Cajal Club's Wendell J.S. Krieg Lifetime Achievement Award, named after the founding President of the Cajal Club.

The meeting opened with a warm welcome from Alberto Calligaro, Dean of the Medical Faculty, with an emphasis on the historic nature of this meeting. This was followed by the award and remarks by Professor Levi-Montalcini. The first talk was on Golgi's life and significance for modern neuroscience, by Paolo Mazzarello, Golgi's biographer. The Cajal Club Pinkney J. Harman Memorial Lecture was given by Giacomo



Fig. 1 – (Group photo) The conference participants gathered outside the Department of Experimental Medicine, Section of General Pathology “Camillo Golgi”, Palazzo Botta, University of Pavia, Italy.

Rizzolatti on mirror neurons. The meeting evolved with talks on themes representing the range of topics of current interest in neuroscience that trace their origins to the pioneering studies of Golgi and Cajal (Fig. 3).

The first scientific session was entitled “In Golgi’s Footsteps”, with talks on the theme of the main types of identified neurons that Golgi discovered and for which Cajal provided the definitive descriptions and interpretations. Egidio D’Angelo spoke on the physiology of cerebellar neurons; Marco Sassoé-Pognetto, on molecular and functional heterogeneity of GABA synapses in the olfactory bulb; Tamas Freund, on identified neurons in the hippocampus; and Edward Jones, on identified neurons in the cerebral cortex.

In the first afternoon, talks were given on theme 2: “Mental Disorders and Neuronal Networks”, two of Golgi’s main interests in the nervous system. Huda Akil talked on the neurobiology of mental disorders, and Michael Bennett, on cell continuity and gap junctions.

On the second day, Theme 3 addressed “Cellular Methods and Physiological Correlations”. Takao Hensch spoke on cell and network functional labeling; Alex Thomson, on cell staining and physiological characterization; Winfried Denk, on reconstructing neurons by serial block-face scanning EM; Fritjof Helmchen, on imaging neurons in vivo; and Tomas Hökfelt, on neuropeptides in the twenty-first century.

Theme 4 was on “Neuron–Glia Interactions”. Michela Matteoli described crosstalk among astrocytes, microglia, and neurons; Alexej Verkhratsky, on signalling in neuronal–glial circuits: role of glutamate and ATP transmission; and Marina Bentivoglio, on neural–immune interactions in diencephalic clocks.

The last theme was “Unity of Function”, addressed by Elio Raviola (Fig. 4) in the retina: anatomy as a visible expression of function. He represented the last contact with Golgi through being trained in the 1950s by the last of Golgi’s pupils.

In addition to the talks, a tour of the Museum of the History of the University of Pavia was led by Paolo Mazzarello, with many artefacts of Golgi and other famed scientists of Pavia. The meeting ended with an extraordinary evening in the village of Abbiategrasso, the site of Golgi’s discovery of the “black reaction”, which included a visit to the local Golgi



Fig. 3 – Charles Ribak with the conference poster outside the old amphitheatre.



Fig. 4 – Paolo Mazzarello and Elio Raviola

Museum, a concert in the Santa Maria dell’Annunziata Church, and a dinner hosted by the Camillo Golgi Institute in Abbiategrasso.

The host team, led by Paolo Mazzarello (Fig. 4), carried out the arrangements of the meeting, for both participants and accompanying guests, with extraordinary efficiency. Generous support by Elsevier made possible the meeting and this special issue commemorating this historic event (Fig. 4).

The present Special Issue contains contributions from many of the speakers. As with the previous volume, we have also invited chairs of the different sessions, officers of the Cajal Club, and former award winners to contribute. Continuing the tradition established in the previous volumes, we have encouraged each author to write “an essay of substance and lasting value that reflects on how one’s field has changed since the end of the 19th century, especially in relation to Golgi’s and Cajal’s work, with an eye on where the field may be headed in the future.” We have been particularly interested in assembling a volume of essays that re-evaluate the contributions of Golgi and their significance for Cajal’s work and for modern neuroscience.

The issue begins with a section on “Golgi’s and Cajal’s neurons: then and now”, with reviews of several of the brain regions that were critical for the application of the Golgi method. Egidio D’Angelo gives a modern perspective on the cerebellum, and Marco Sassoé-Pognetto, on the olfactory bulb, among the first two brain regions studied by Golgi. The olfactory bulb was in fact the first region for which Golgi illustrated his new method. The cerebellum was of great importance to both Golgi and Cajal for their views of neuronal organization. Constantino Sotelo reviews the role the cerebellum played in the emerging concept of the neuron doctrine. Alex Thomson reviews biocytin labelling, one of the mainstays of current research on single identified neurons, and shows its impact on recent studies of cortical circuits. These authors show how these regions are at the forefront of current research on the molecular and cellular basis of neuronal organization.

A section on “New perspectives on Golgi’s concepts” provides the modern reader with reassessments of Golgi’s contributions. Paolo Mazzarello charts the rise and fall of Golgi’s school from the 1870s to the middle of the 20th century. Lawrence Kruger and his collaborators provide a new

retrospective on the historical context within which Golgi's achievements should be understood. Elio Raviola reassesses the diffuse neural network in the context of Golgi's view of this central issue.

Current investigators usually know about Golgi and classical histology second-hand through mention in Cajal's numerous works. A section on "New perspectives on Cajal's debt to Golgi" provides a new appreciation of how Golgi led the way, in studies of the cerebral cortex by Edward Jones, and in studies of the olfactory bulb by Gordon M. Shepherd and collaborators.

Modern research recognizes increasingly the important roles of glia in neural function. The section on "New perspectives on neuron–glia interactions" focuses on this exciting area. Claudio Verderio and Michela Matteoli discuss the role of ATP in neuron–glia interactions. The involvement of glia in epilepsy-associated processes in the brain is summarized by Lee Shapiro and colleagues, and their involvement together with the vasculature in spreading depression by Bernice Grafstein. The "diffuse neural net" is discussed by Alexei Verhratsky and his colleagues in the larger context of neuron–glial interactions. Marina Bentivoglio reviews the history and modern perspectives on concepts of brain inflammation and brain infections, with a focus on diseases (such as rabies and malaria) of great interest to Golgi and his disciples, who made seminal discoveries.

"New perspectives on neural systems" includes essays on a variety of topics. Alan Watts reassesses the complex course of

development of concepts of the neuroendocrine system. Ray Guillery and Murray Sherman propose a new concept of the information carried by the branches of thalamic afferent fibers to the cerebral cortex. The history of a new type of cell in the cerebellum, the unipolar brush cell, is recounted by Enrico Mugnaini and his colleagues. Current research on growth cones, discovered by Cajal, is updated by Jacopo Meldolesi, with a focus on exocytosis of distinct types of vesicles. The volume closes with a tribute by Rita Levi-Montalcini to another great Italian neuroscientist, Giuseppe Moruzzi, co-discoverer of the reticular activating system.

Viewed from a long-term perspective, through this meeting and this collection of articles, the great traditions of Golgi and Cajal have finally merged, and new insights given into the full significance of each to modern neuroscience.

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