The centenarian Golgi apparatus

Paolo Mazzarello and Marina Bentivoglio

One hundred years ago, Camillo Golgi described the cellular apparatus that has since become synonymous with his name. Although its existence was questioned for 50 years, this organelle is now established as the cell's centre for the processing and secretion of proteins.

On 19 April 1898 at the Medico-Surgical Society of Pavia, Camillo Golgi (Fig. 1) presented his finding of a hitherto unknown organelle in Purkinje cerebellar cells (Fig. 2). On the basis of its 'net-like' appearance and intracellular location, he termed[1] this organelle the "internal reticular apparatus". He could hardly have foreseen that, over the next century, his name would become the most frequently mentioned in literature on cellular and molecular biology, and the eponym of the structure he had discovered — the Golgi.

A professor of histology and general pathology at the University of Pavia, Golgi had already acquired an international reputation based on a surprising number of original contributions to biology and medicine[2]. In 1873, while searching for a recipe that could effectively stain the nervous tissue, he discovered the so-called 'black reaction', known nowadays as Golgi impregnation or Golgi staining. This reaction was based on the use of silver nitrate and potassium bichromate, and it afforded, for the first time, a full view of single nerve cells and their processes.

Aided by his black-reaction method, Golgi analysed several regions of the nervous system in detail, and provided beautiful illustrations of them. Golgi contested the neuron theory (according to which the nervous system is composed of individual cells, like any other tissue), and he believed that the nerve processes stained by his reaction formed a continuous network along which the nervous impulse propagated. Ironically, it was by using the Golgi stain that another great neuroanatomist, Santiago Ramón y Cajal (1852–1934), became the paladin of the neuron theory. In 1906, Golgi and Cajal shared the Nobel prize for physiology or medicine, for their investigations into the structure of the nervous system.

Figure 1 **Camillo Golgi (1843–1926) in 1898, the year in which he reported the discovery of the organelle that now bears his name.**

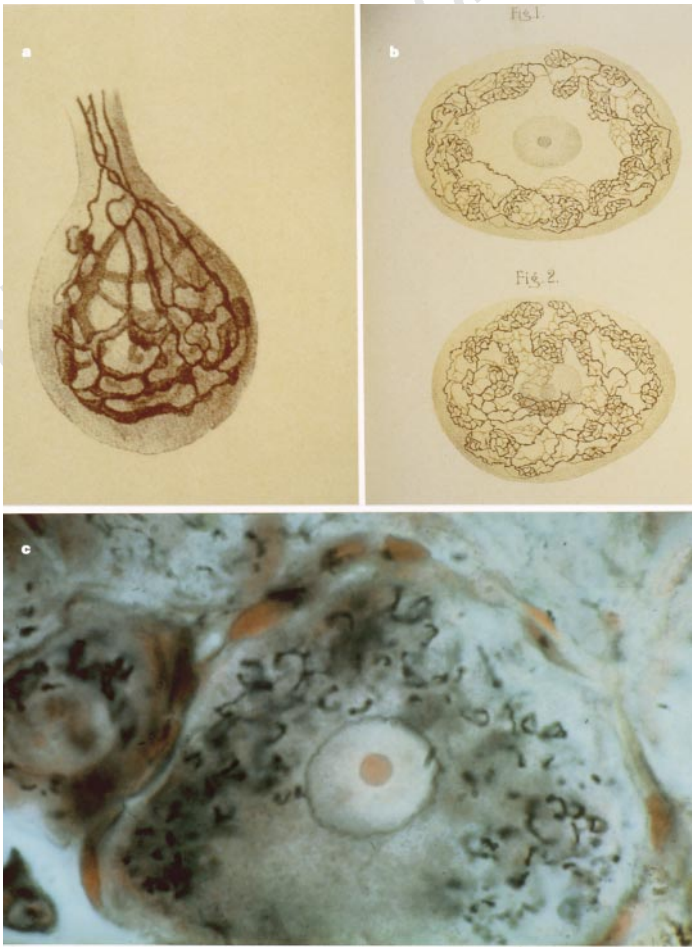

Figure 2 **Illustrations of Camillo Golgi's "internal reticular apparatus".** a, **Golgi's first drawing of the apparatus in the body of a Purkinje cell of the cerebellum in 1898.** b, **The apparatus in spinal ganglion neurons.** c, **Photomicrograph of the apparatus impregnated by the Golgi reaction (which appears as a black-stained network in the cytoplasm) in spinal ganglia neurons. From an original preparation made at Golgi's laboratory in Pavia. (Part** c **supplied by V. Vannini, Institute of General Pathology, University of Pavia.)**

Golgi obtained other important results. In 1878, for example, he described the tendinous sensory corpuscles that bear his name (the Golgi tendon organs). Between 1886 and 1892 he concentrated on studying malaria. Not only did he work out the intra-erythrocytic cycle of the malaria agent *Plasmodium*, but he also discovered the temporal relation between the recurrent chills and fever of the infection, and multiplication of the parasite in human blood. However, he never lost his interest in the nervous system.

Using a variant of the black reaction (the rapid method), he had already observed the "internal reticular apparatus" in 1897, in neurons of spinal ganglia (Fig. 2). But he decided to report the existence of this structure only after his findings were replicated and confirmed by one of his students, Emilio Veratti (1872–1967). Working in Golgi's laboratory, Veratti went on to describe, for the first time, the sarcoplasmic reticulum of skeletal muscle fibres in 1902.

In April 1898, Golgi thus felt confident to report[1] that he had observed "a fine and elegant reticulum hidden within the cell body". This was mainly characterized "by the ribbon-like shape of its threads, by their manner of dividing, forming anastomoses, and coursing of these threads... by the presence in tenuous small plaques or small roundish disks transparent at their centre, which serve as nodal points of the reticulum". Soon after the discovery, Golgi's students

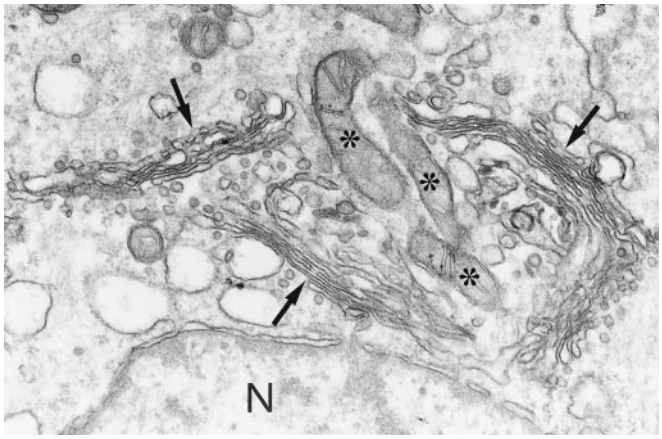

Figure 3 **Electron micrograph of stacks of cisternae of the Golgi apparatus (arrows). These are located, as commonly observed, near the cell nucleus (N). The asterisks mark mitochondria.**

Antonio Pensa (1874–1970), Adelchi Negri (1876–1912) and Edoardo Gemelli (1878–1959) showed that this structure exists in non-nervous cells as well. (Incidentally, Negri later identified the intraneuronal inclusions that bear his name — Negri bodies — in rabies-infected brains.) Golgi, somewhat timidly, put forward the hypothesis that the apparatus could be involved in secretory functions and, more broadly, in cell nutrition.

The report of this new cell constituent gave a great impetus to cytological studies. In 1913, the internal reticular apparatus was officially christened the Golgi apparatus[3]. However, the existence of the organelle was debated for decades. The revelatory power of metallic impregnation, for nervous and non-nervous tissues alike, is wonderful when it works. But the capricious and erratic outcomes when this method was applied raised questions about the reality of an intracellular network such as the Golgi apparatus. The debate was inflamed by heated exchanges but, paradoxically, greatly contributed to the scientific pathway through a unifying theory of the cell and its functions.

The controversy was solved only by the introduction of electron microscopy. In 1954, Dalton and Felix[4], and Sjöstrand and Hanzon[5] showed that metals are selectively deposited on the membrane and associated vacuoles that make up the Golgi apparatus. Only then did the Golgi apparatus (which was also defined as the Golgi complex) reach the status of a widely accepted cell organelle. Thus, by some sort of historical compensation, the electron microscope — the very instrument that had provided incontrovertible evidence for synapses between neurons, against Golgi's stubborn concept of a continuous interneuronal reticulum — also supplied the final proof that his "internal reticular apparatus" was real.

Over the past few decades, advances such as cell fractionation, histochemistry, autoradiography, immuno-gold labelling in electron microscopy, *in vitro* assays and recombinant DNA technology have unravelled the functions of the cisternae and vesicles that form the Golgi apparatus (Fig. 3). These include intracellular transport of proteins to the secretory cell surface, intracellular protein sorting, budding and targeting of protein transport vesicles, and viral protein targeting[6,7]. Research on this key organelle is still blooming.

And what about Camillo Golgi? He would probably have been very surprised and rewarded by the importance of his discovery. But he would have been much less gratified by the loss of his identity — his name is now just a label for an organelle, or a suffix for its constituents, compartments and functions. Titles that we find nowadays in the scientific literature, such as 'Green light for Golgi traffic'[8] or 'Greasing the Golgi budding machine'[9] would probably have raised the professor's eyebrows. □

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Human genetics

Putting the Parkin into Parkinson's

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Parkinson's disease is the second most common form of neurodegenerative disease after Alzheimer's[1], affecting 250,000–500,000 people in the United States alone. The disease is characterized by a movement disorder — parkinsonism — which is a triad of rigidity, resting tremor and bradykinesia (slowness in initiating and carrying out movement), often associated with difficulties in maintaining posture. These symptoms result from the dysfunction and loss of neurons that produce the neurotransmitter dopamine, in a part of the brain called the substantia nigra.

On page 605 of this issue, Kitada *et al.*[2] describe the positional cloning of a previously unknown gene, which they have termed *parkin*. This gene is responsible for a rare autosomal recessive form of parkinsonism, AR-JP, which was discovered[3,4] and described[4] by Japanese neurologists. The movement disorder in AR-JP develops in adolescence or young adulthood and responds to levodopa therapy, but it usually progresses and incapacitates the patients after 20–30 years.

At autopsy, brains from patients with AR-JP or Parkinson's disease show loss of neurons in the substantia nigra and locus coeruleus. However, in classical Parkinson's, but not AR-JP, an eosinophilic inclusion body — the Lewy body — is found in the cytoplasm of neurons in the substantia nigra. Lewy bodies react with anti-ubiquitin antibodies in immunocytochemical studies. They also react with antibodies against α-synuclein, which is a small presynaptic protein of unknown function that is also found in aggregates in ballooned and swollen nerve fibres called Lewy neurites.

The causes of Parkinson's disease are largely unknown, although there are a few rare families with autopsy-proven Lewy bodies in which Parkinson's is inherited in an autosomal dominant manner[5]. The Parkinson's locus has been mapped in some of these families to chromosome 4q, where it encodes α-synuclein[6]. To date, two different mutations in α-synuclein have been found in families with dominant Parkinson's disease[6,7]. In other families, the locus has been mapped to chromosome 2p13, but the gene itself has not been identified[8] and, in others still, the gene and its map location remain unknown[8]. In most cases of Parkinson's disease, however, a genetic contribution (if any) remains obscure.

What does AR-JP due to mutations in *parkin* have to do with Parkinson's disease? Parkinsonism can be a feature of many diseases, some hereditary, some acquired, as well as Parkinson's disease itself. Moreover, at first glance, the differences between AR-JP and Parkinson's, rather than the similarities, stand out. AR-JP is an autosomal recessive disorder, whereas the genetic basis for Parkinson's is complex (except for the few rare families in which it is dominantly inher-