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Cajal, Golgi, Nansen, Schäfer and the Neuron Doctrine

Ortwin Bock[1,*]

1 Park Road, Rosebank, 7700 Cape Town, South Africa

The Nobel Prize for Physiology or Medicine of 1906 was shared by the Italian Camillo Golgi and the Spaniard Santiago Ramón y Cajal for their contributions to the knowledge of the micro-anatomy of the central nervous system. In his Nobel Lecture, Golgi defended the going-out-of-favour Reticular Theory, which stated that the nerve cells – or neurons – are fused together to form a diffuse network. Reticularists like Golgi insisted that the axons physically join one nerve cell to another. In contrast, Cajal in his lecture said that his own studies confirmed the observations of others that the neurons are independent of one another, a fact which is the anatomical basis of the now-accepted Neuron Doctrine (Theory). This much is well documented. Less well known, however, is the fact that evidence against the Reticular Theory had been mounting for some time prior to the Nobel Lecture. The Norwegian Fridtjof Nansen had reported in 1887 that, in his studies of the primitive creatures he studied in the sea near Bergen, he found no connections between the processes of the ganglion cells in their nervous systems. Nor is it adequately appreciated that ten years earlier, in 1877, the Englishman Edward Schäfer had similarly described seeing no connections between the nerve elements in the mantles of the jellyfish. This paper begins by charting the research that led directly to the awarding of the 1906 Nobel Prize. It then shows that long before the ultimate vindication of the Neuron Doctrine, researchers in several countries had been accumulating evidence that undermined or contradicted the Reticular Theory.

> '. . .the nerve cell, the aristocrat among the structures of the body, with its giant arms stretched out, like the tentacles of an octopus, to the provinces on the frontiers of the outside world, to watch for the constant ambushes of the physical and chemical forces . . .' Dr Bacteria 1883[1]

Gerlach and Golgi

In the later nineteenth century the Reticular Theory enjoyed considerable support among leading European neuroscientists. On 4 May 1872 Joseph von Gerlach (1820–1896), Professor of Anatomy at Erlangen University, published a two page article in the *Centralblatt fűr die medizinischen Wissenschaften* with the title 'On the structure of the grey matter in the human cerebrum (Figure 1). Preliminary communication'. The article contains a long sentence which ends with the statement '[these cells] are interconnected with each other as well as connected with the radial bundle, whereby a coarsely meshed network of medullated fibres is produced which can already be seen at 60 times magnification'.[2] Gerlach's work on vertebrates helped to consolidate the evolving Reticular Theory which postulated that all the cells of the central nervous system were joined together like an electricity distribution network. Gerlach was one of the most influential anatomists of his day and the author of many books, not least the 1848 *Handbuch der Allgemeinen und Speciellen Gewebelehre des Menschlichen Körpers*: *für Aerzte und Studirende*. For twenty years he lent his considerable credibility to the Reticular Theory. Well into the twentieth century, the *reticularists* were pitted against the *neuronists* who subscribed to what became known as the Neuron Doctrine.

One of Gerlach's main contributions had been to develop better fixing and staining methods for the microscopic study of nervous tissue. It was he who introduced carmine and gold chloride which improved the visualization of the nerve processes. Reticularists like Gerlach were not being irrational in claiming that the cells of the central nervous systems of animals and humans are all joined together to form a diffuse network: that opinion was based on what they saw through their microscopes when they looked at slices of tissue that had been mounted on thin glass slides and stained with carmine, haematoxylin and gold. Unfortunately, this technique did not show up the finest branches. The basic problem they faced was that the research tools at their disposal were inadequate for the task at hand.

Improvements in the ability to visualize nerve cells were not long in coming (Figure 2). On 16 February 1873, Camillo Golgi, Chief Physician of the Pio Luogo degli Incurabili, a hospital for chronic diseases at Abbiategrasso near Milan, wrote the following words to his friend and fellow microscopy enthusiast Nicoló Manfredi (1836–1916): 'I have regained the energy that for a few months I had completely lost. I spend long hours at the microscope. I am delighted that I have found a new reaction to demonstrate even to the blind the structure of the interstitial stroma of the cerebral cortex.... I have already obtained magnificent results and hope to do even better'.[3] On 2 August of the same year Golgi followed up this letter with a brief report on his technique in the *Gazzetta Medica Italiana-Lombardia*: 'Using a method that I developed and that allows to stain in black the elements of the brain, a staining procedure that requires the prolonged immersion of the pieces, previously fixed in potassium or ammonia dichromate, in a 0.5–1.0% solution of silver nitrate, I could discover some facts concerning the structure of the grey matter of the brain, that I think are worthy of being reported'.[4]

*Tel.: +27 21 6864111.

[1] Ortwin Bock is a retired physician who lives in Cape Town, South Africa. He studied at Oxford University and obtained his doctorate in December 1962.

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Figure 1. The leading German anatomist Joseph von Gerlach.

Figure 2. Camillo Golgi.

Golgi's method permitted the study of nerve cells in their finest morphological details (Figure 3). For reasons still unknown, only 1–5% of the cells in a microscopic field are stained black. This has turned out to be an advantage because relatively thick tissue slices are needed to follow the cellular processes of one cell, something which would not have been possible if all the cells were stained black. Nevertheless, despite the fact that the black reaction was so much better for the study of nervous tissue than the other available stains, it was only in the late 1880s and early 1890s that other neuroscientists starting using it.

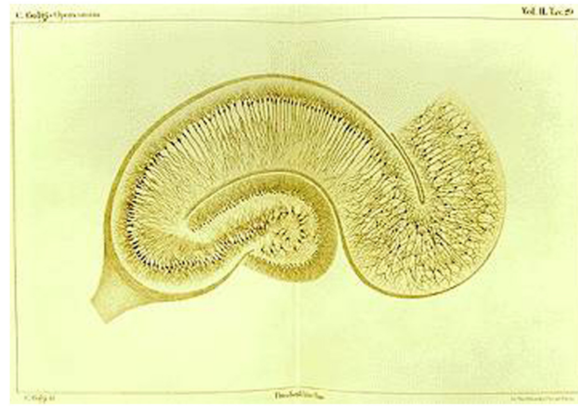

Figure 3. Camillo Golgi's drawing by of a hippocampus stained using his silver nitrate method.

Santiago Ramón y Cajal and the neuron

For reasons of language and geography, Santiago Ramón y Cajal (1852–1934), working in Spain at this time, was isolated from the mainstream of neurological research in Europe. A key event in his career was the visit he made, while Professor of Histology and Pathological Anatomy at the University of Valencia, to Madrid where he met Luis Simarro (1851–1921). Simarro had just returned from Paris where he had studied with Louis-Antoine Ranvier (1835–1922), Professor of Anatomy at Collège de France, who was familiar with the black reaction, but not enthusiastic about it. Simarro showed Cajal slides of nervous tissue stained by the black reaction. Cajal was immediately captivated. There is uncertainty, however, about when this meeting took place. Juan de Carlos of the Cajal Institute in Madrid notes that we 'do not know when it was held.' It is widely believed to have occurred 1887, as Cajal says in his autobiography, but Carlos points out that the Cajal collections contain a 'histological preparation, made with the Golgi method (cerebral cortex), that has a label from the University of Valencia and is dated, handwritten by Cajal, in 1886. So was it a mistake of Cajal? We do not know, for the moment . . .'.[39]

Either way, Cajal was quick to appreciate the significance of the black reaction (Figure 4). 'Realizing that I had discovered a rich field,' he wrote in his autobiography, 'I proceeded to take advantage of it, dedicating myself to work, no longer merely with earnestness, but with fury. In proportion as new facts appeared in my preparations, ideas boiled up and jostled each other in my mind. A fever for publication devoured me.'[5] Cajal improved the stain with his 'double impregnation procedure' in which the tissue was placed for a further one or two days in a solution of 6–7 g potassium dichromate, 100 cc distilled water and 30–35 cc of osmic acid, before being returned to the original solution for another 24 h. In addition, Cajal chose to study the brains of small immature animals in whom better stains were obtained because there is less myelin – the proteinacious substance that cossets the nerve fibre within the nerve sheath – to impede the impregnation of the silver.

Towards the end of 1888 Cajal decided that the time had come for him to meet other neuroscientists because the

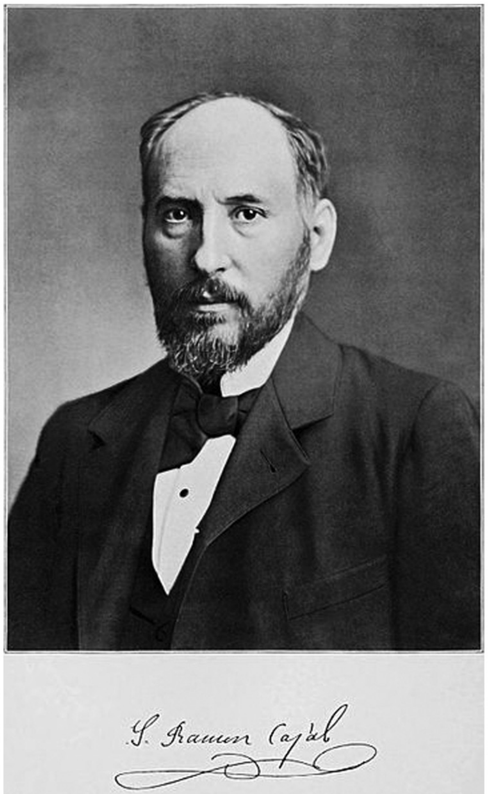

Figure 4. Santiago Ramón y Cajal.

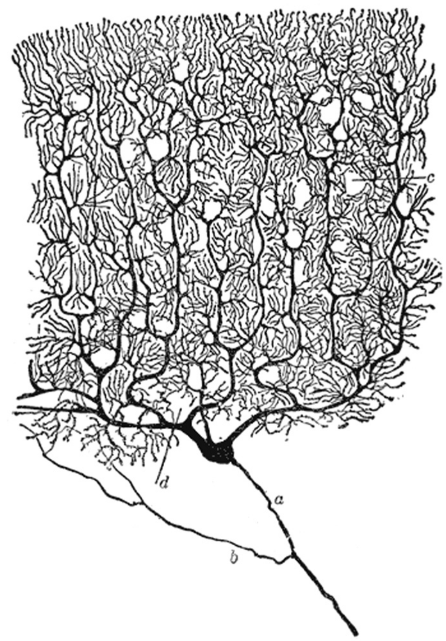

Figure 5. A drawing of a Purkinje cell in the cerebellar cortex of a cat, by Santiago Ramón y Cajal. Legend: (a) axon (b) collateral (c) dendrites.

publications he read '... either did not mention me or did so contemptuously ... and without attributing any importance to my opinions'.[6] He applied for membership of the German Anatomical Society and, in October 1889, went to their meeting which that year was held at the University of Berlin. This was a masterstroke. Not only did he meet 'the then world celebrities', but the demonstration of his work led him later to write: 'Finally, the prejudice against the humble Spanish anatomist vanished and warm and sincere congratulations burst forth'.[7] The most interested of my hearers', he wrote, 'was A. Kölliker, the venerable patriarch of German histology'. Albert Koelliker (1817–1905), the Zurich-born Professor of Anatomy at the University of Würzburg, was also editor of the *Zeitschrift für wissenschaftliche Zoologie*. He was so impressed with Cajal's work that he learnt Spanish and, recalled Cajal, 'it was due to the great authority of Kölliker that my ideas were rapidly disseminated and appreciated by the scientific world'.[8]

Cajal continued his studies of the nervous systems of animals and humans when he went to the University of Madrid in 1892 where he worked until his retirement in 1922. He published more than 200 scientific articles and 22 books, and his last book *Neuron Theory or Reticular Theory*, published in 1933, '... finally laid to rest the issue whether the nervous system was formed by structurally independent units or was a more or less continuous syncytial network as a vocal generation of his contemporaries had believed'.[9] (Figure 5).

The term 'neuron' had been suggested in 1891 by Wilhelm Waldeyer (1836–1921), Professor of Anatomy at Berlin. In the last of six articles reviewing the newer researches in the anatomy of the central nervous system which were published in the *Deutsche medizinische Wochenschrift* between 29 October and 10 December of that year, Waldeyer concluded: 'The nervous system is made up of innumerable nerve units (neurons) which are anatomically and genetically independent of each other. Each nerve unit consists of three parts: the nerve cell, the nerve fibre and the fibre aborizations (terminal aborizations)'.[10] Cajal was rather dismissive of Waldeyer, writing that although '... histology is indebted [to him] for revelations of the utmost importance in other fields, [he] *did not personally investigate the problem of interneuronal connections*, confining himself to making a popular review of my works in a German weekly and inventing the word neuron, etc.!' (Cajal's italics).[11]

The Nobel Prize and after

In October 1906 the Karolinska Mediko-Kirurgiska Institutet in Stockholm announced that that year's prize in physiology or medicine would be shared by Golgi and Cajal. In his Award Ceremony Speech on 10 December 1906 in the Great Hall of the Academy of Music, Professor the Count Karl Mörner (1854–1916), Rector of the Institutet, gave the King and the august audience an overview of the complexities of the structure of the nervous system and concluded by saying that: 'By their achievements ... Professors Camillo Golgi and Ramón y Cajal must be considered as the principal representatives and standard bearers of the modern science of neurology, which is proving so fertile in results. In recognition of their achievements in this field, the Staff of Professors of the Caroline Institute has decided to award to them this year's Nobel Prize for Medicine'.[12] But the event highlighted the divergences among neuroscientists as much as it emphasized the synthetic nature of their discoveries.

Golgi and Cajal met for the first time in Stockholm on 6 December 1906. The shy and reticent 63-year-old Golgi and the ebullient and self-promoting 54-year-old Cajal did not hit it off and never became friends. To make matters worse Golgi, in his Nobel Prize Lecture on 11 December entitled '*The neuron doctrine – theory and facts*'[13] defended the Reticular Theory despite mounting evidence that it was most probably wrong and regardless of some of his own drawings showing free nerve ending dendrites and axon collaterals.[14]

Cajal's reaction to Golgi's lecture is spelled out in his autobiography: 'He had the right to choose the subject of his address. The misfortune was that in defending his extravagant lubrication – which could be excused in 1886, when the basic facts of inter-neuronal connection had not been made known – he made a display of pride and self-worship so immoderate that they produced a deplorable effect upon the assembly. Not even incidentally did he allude to the almost innumerable neurological works which had appeared outside Italy, and even in Italy itself, since the remote date of his great work on the minute structure of the nervous system'.[15]

It is clear that Golgi had not kept up with all the newer developments in the micro-anatomy and understanding of the function of the nervous system. This is not to say that his career in neuroscience had come to an end: in 1898, he described one of the basic constituents of the cell, the internal reticular apparatus (the Golgi Apparatus or Golgi Complex), a series of ribbon-like threads that secrete substances essential for the function of the cell.[16] Golgi's biographer notes that thanks to this discovery 'he is probably the most cited biologist in current scientific literature . . .'.[17] But by this stage he had a number of competing duties and interests. After a brief sojourn at the University of Siena, Golgi had returned to his alma mater, Pavia, in 1876 as Professor of Histology, and in March 1881, moved to the more senior post as Professor of General Pathology. He devoted his energies to the establishment of the Laboratory of Experimental Pathology, the teaching of students and postgraduates, the study of the lifecycles of the malarial parasites, his duties as a local and national politician (he became a Life Senator for High Scientific Merits in June 1900) and his spells as Rector of the University of Pavia.

On 12 December 1906 it was Cajal's turn to give his Nobel lecture. In his autobiography he explains that in *The Structure and Connexions of the Neurons*[18] 'I set forth the most fundamental results of my (25 years) research work, adhering strictly to the facts and to conclusions naturally suggested by them'. This work, he wrote, 'confirms that the nerve elements possess reciprocal relationships *in contiguity* but not *in continuity*' (his italics). 'My lecture was, I believe, to the taste of the public. In any case, it received very kind praises in the local newspapers'.[19]

Cajal has also been treated very generously by posterity for the obvious reason that the Neuron Doctrine that he tirelessly defended was fully vindicated. The evidence that nerves of the central nervous system are not joined together as the Reticularists had insisted but that there are only 'free' nerve endings established the veracity of this theory. In this achievement Cajal unquestionably played a big part and emerged as the foremost neuroscientist of his generation. Throughout the twentieth century Cajal and the Neuron Doctrine were mentioned in the same breath (he died at home on 17 October 1934 surrounded by papers he was working on).

It is, therefore, not too surprising that the articles published in 2006 to commemorate the centenary of the 1906 Nobel prize for physiology or medicine tended to concentrate on Cajal rather than Golgi. One passage, for instance, reads: 'This year sees the centenary of the award of the Nobel Prize for Physiology or Medicine to Santiago Ramón y Cajal (1852–1934), the great ideologue and driving force behind this [neuron] theory. . .'. There is no mention in this article that Golgi shared the prize with Cajal, although Golgi's name does appear later in connection with the black reaction.[20] Also contributing to the impression that the development of the Neuron Doctrine was mainly the work of Cajal have been the activities of the Cajal Club. The club was formed in April 1947 by 14 American neuroanatomists and it is significant to note that the club's original covenant stated that its main aim was to revere Cajal'.[21] The Club, the membership of which has grown to more than 500 worldwide, holds regular meetings at which aspects of Cajal's work and personality are discussed. In 2006 it held its meeting at the Karolinska Institutet in Stockholm.

Wilhelm His Sr., August Forel and Fridtjof Nansen

This heavy emphasis on the achievements of Cajal has distracted attention from the significant contributions to the Neuron Doctrine of other scientists. Acknowledging prior work is especially important because it underlines the difficulty of explaining why the Reticular Theory persisted for so long. And it reinforces the veracity of Max Planck's famous comment that 'A new scientific truth does not triumph by convincing its opponents and making them see the light, but rather because its opponents eventually die, and a new generation grows up familiar with it.'[40]

Three scientists in particular had done much to suggest the credibility of the Neuron Doctrine prior to Cajal: Wilhelm His Sr., August Forel and Fridtjof Nansen. They performed their studies more or less at the same time, but unknown to one another, and came to their conclusions using different techniques and tissues. All three thought the network theory to be incorrect. In October 1886, Wilhelm His (1831–1904), the Swiss born Professor of Anatomy at the University of Leipzig, reported that he had found in the tissues of human embryos, which he stained with hematoxilin, that in the early stages of development of the foetus the nervous system is a mass of independent cells: 'I believe', he concluded, 'that one can also arrive at simple concepts regarding the nervous system if one abandons the idea that the nerve fibres, in order to affect a part, must necessarily be in continuity with each other'.[22] A couple of months later, in January 1887, August Forel (1848–1931), Professor of Psychiatry at the University of Zurich, used the technique of 'secondary degeneration' which he had learned while a student of Bernhard von Gudden (1824–1886) in Munich to trace the finer connections in the brain. The idea was to sever bundles of nerves and see which parts degenerated. Forel reported that degeneration was sharply limited to the cells whose fibres had been cut and did not spread to adjacent cells. He therefore arrived at the opinion that 'a nerve network does not exist and each cell is in contact with, but not in continuity with, its neighbour'.[23]

The articles published in the 2006 study of the 1906 Nobel Prize did acknowledge the work of August Forel and Wilhelm His Sr., but almost completely ignored that of another important researcher: Fridtjof Nansen (1861–1930) (Figure 6). A trainee zoologist, Nansen went to Bergen in late 1882 as Curator of the local museum and soon became interested in the micro-anatomy of the nervous systems of primitive sea creatures in the fjords near Bergen. He went to Pavia in April 1886 to learn more about the black reaction and later that year completed his monograph, 'The Structure and Combination of the Histological Elements of the Central Nervous System' which was published in the *Bergen Museums Årsberetning* for 1886 in 1887. On page 146 he wrote: 'If a direct combination is the common mode of combination between the cells as most authors suppose, direct anastomoses (connections) between their processes ought, of course, to be quite common. When one has examined so many preparations ... as I have, without finding one anastomosis of indubitable nature, I think one must be entitled to say, that *direct anastomosis between the processes of the ganglion cells does not exist, as a rule*' (his italics). This seminal work by Nansen was largely forgotten, perhaps due to the notion that existed for many years that what applied to animals did not necessarily apply to human beings.[28] Only in recent years has the significance of his research been acknowledged. A centenary symposium held at Bergen in 1987 drew attention to it and published in its proceedings a facsimile of Nansen's thesis.[24]

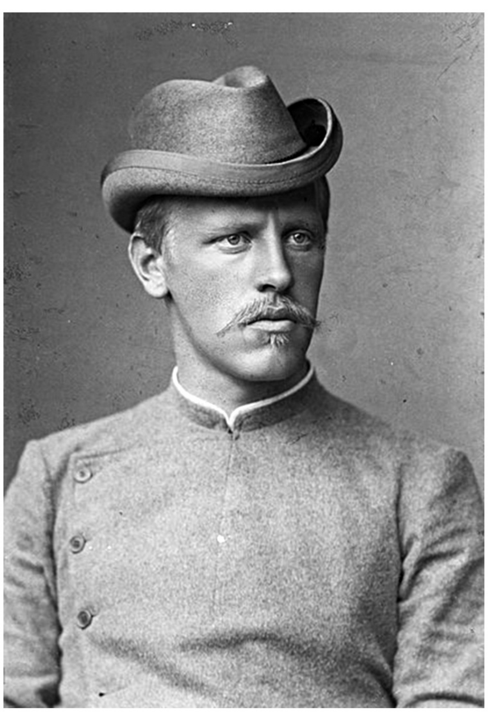

Figure 6. Fridtjof Nansen in 1889.

This generation of neuroscientists benefited from significant technical advances. Nansen, for example, apart from being a superb technician and very familiar with the literature of the time (389 references are listed in his monograph), could cut the blocks of tissue with a much improved microtome and stain the slides with the black reaction before studying them with the latest Carl Zeiss (1816–1888) achromatic microscope given to him by his father Baldur; this microscope permitted high magnifications without the colour aberrations or blurred images which were a feature of earlier high-definition microscopes. It was actually not until the 1950s that the electron microscopic studies of George Palade (1912–2008) and Sanford Palay (1918–2002), and Stanley Bennett (1910–1983) and Eduardo de Robertis (1913–1988) provided final proof that there is no contact between the various neurons.[36] But with the evidence already strongly in favour of a gap between adjoining neurons, in 1897 Charles Sherrington (1857–1952) proposed for it the term 'synapse', from the Greek for a 'clasp'.

As a result of research in recent decades, we are now better able to appreciate how much work Cajal was able to build upon. Accordingly, Gordon Shepherd devotes a chapter to Nansen, His and Forel in his book *Foundations of the Neuron Doctrine* of 1991,[25] while Stanley Finger's *Origins of Neuroscience* (1994)[26] mentions Nansen's conclusion. Moreover, in a review published in 1998, Edwards and Huntford rightly concluded that 'These three, Nansen, His and Forel ... had sown the seeds of doubt concerning the reticular theory. They became the co-founders of the modern view of the nervous system.'[27]

Earlier studies

Although Nansen's statement was the first explicit rebuttal of the Reticular Theory, it is also important to recognize that he was not the first scientist to record that the cells of the central nervous system are not joined together. Several scientists had already found evidence that the nerve cells of several species are not physically connected. The honour of being first to state the discontinuity of nerve cells goes to the Assistant Professor of Physiology at University College London, Edward Schäfer (1850–1935) who, as Edward Sharpey-Schafer, would later make many contributions to medical science. In a text received on 31 October 1877 and communicated to members of the Royal Society by his professor William Sharpey (1802–1880) on 10 January 1878, Schäfer began: 'Last August I undertook, at the request of my friend Mr. G. J. Romanes, an investigation with the view of proving the presence or absence of histologically differentiated nervous structures in the Medusae'. He had used chloride of gold to stain the tissue and found that 'If we trace out the course of the individual nerve-fibres more closely ...we are struck with certain remarkable facts ... each fibre is entirely distinct from and nowhere structurally continuous with ... any other fiber'.[29] The published version of Schäfer's lecture, which does not mention the diffuse nerve network, also contains a footnote on the findings in the monograph *Das Nervensystem und die Sinnesorgane der Medusen* written by the brothers Oskar (1849–1927) and Richard (1850–1937) Hertwig and published in Jena in 1878. They found that the two nerve rings of the jellyfish were separated from one another by a delicate membrane.[30]

In 1881Armauer Hansen (1841–1912), a mentor of Nansen at the Bergen Museum who in 1873 had identified *Mycobacterium leprae* as the cause of leprosy, spent some time with Louis-Antoine Ranvier in Paris and recorded that he found that the motor nerves of leeches were connected to the muscles by triangular thickenings. They did not rejoin as one would expect if nerve cells formed the continuous web described by Gerlach and defended by Golgi.[31] Another significant contributor to the knowledge of the micro-anatomy of the central nervous system was the Swedish anatomist and one-time professor at Karolinska Institutet, Gustaf Retzius (1842–1919). He studied the finer anatomy of the inner ears of amphibians, birds, fishes, mammals and reptiles (1884) and found only free nerve endings.[32] He did not mention the Reticular Theory in his articles.[33]

Contradicting the cell doctrine

Perhaps the most puzzling aspect of the Reticularist school is that its members accepted the concept of the diffuse network in the face of the growing evidence in favour of the Cell Doctrine which states that all animals and plants are made up of a myriad of individual cells. One of the most important concepts in biological science, this doctrine was well established by the 1870s, 200 years after Robert Hooke first saw what he called cells when looking at a thin slice of cork through his homemade microscope. The reticular theory implied, in stark contrast, that the cells of the central nervous system differ fundamentally from those of the rest of the body. Gerlach, when he proposed the concept of the diffuse nervous network in 1872, must have known of the work of Mathias Schleiden (1804–1881), Theodor Schwann (1810–1882), Robert Remak (1815–1865) and Rudolf Virchow (1821–1902) who between them did much to establish the credentials of the Cell Doctrine. They were all former students of Johannes Müller (1801–1858), Professor of Anatomy and Physiology at the University of Berlin, who in 1835 had noted a similarity between animal and plant cells. In 1838, Schleiden, Professor of Botany at the University of Jena, stated that the different parts of the plant are composed of cells. The next year his friend Schwann, a physiologist at the University of Berlin, who is generally regarded as the scientist who first enunciated the Cell Doctrine, wrote that this applied to animals as well. Remak, a Pole from Posen who preferred to work in Berlin as Müller's assistant rather than applying for professorships elsewhere, in 1841 observed that the red cells of chicken embryos multiplied by division of pre-existing cells as opposed to arising spontaneously from elements within the surrounding fluid as some people thought.[34] Virchow, Professor of Pathology at Berlin, in 1858 then gave life to the axiom 'Omnis cellula e cellula' in his book *Cellular Pathology as based upon Physiological and Pathological Histology* '*No development of any kind*', he wrote, '*begins* de novo . . . Where a cell arises, a cell must have previously existed. . .' (his italics).[35] This body of knowledge did not sit comfortably with the notion of a diffuse network upheld by Gerlach, Golgi and others.

Conclusion

In 1994, a little more than 100 years after Wilhelm Waldeyer's definition of the neuron, Edward Jones (1939 – 2011) could write: 'As we look back at the material assembled by Waldeyer, and especially if we consider along with it the additional contributions made almost immediately afterwards by those whom he had quoted, we can make a restatement of the neuron doctrine in the following terms: *The neuron is the structural unit, the embryological unit, the functional unit and the trophic unit of the nervous system*' (his italics).[37] This paper mentions some of the important contributions to the knowledge of the finer anatomy of the neuron. Recent research has highlighted the contributions of scientists like Schäfer and Nansen. In tracing the development of our knowledge of the nervous system one should also mention the still earlier work of pioneers like Robert Remak. In *The Birth of the Cell*, Henry Harris argues that 'If there was one individual who, above any other, was responsible for bringing order into the confusion that shrouded the origin of animal cells it was Robert Remak. It was not acknowledged in his lifetime . . . nor is it adequately recognized even now'.[38] Remak also made important observations on the micro-anatomy of the nervous system, such as that the axons of nerves were continuous with cells in the spinal cord.

In retrospect the Professors of Karolinska Institutet in Stockholm did well in 1906 when they awarded that year's Nobel Prize for Physiology or Medicine to Camillo Golgi and Santiago Ramón y Cajal for their contributions: Golgi for his indispensable black reaction (the silver stain or reazione nera) and the brilliant Cajal for his astonishing non-stop working, thinking, arguing and publishing ethic which anchored the proof for the Neuron Doctrine. But the validation of the Neuron Doctrine required about 50 years of hard work by many scientists.

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References

1. Ramón y Cajal S. (Dr. Bacteria). The wonders of histology. La Clinica (Zaragoza) 1883;301:225–6.
2. Gerlach J von. Ueber die Structur der grauen Substanz des menschlichen Grossheim. Vorläfige Milteilung. Centrallblat für die medizinischen Wissenschaften 1872;10:273–5.
3. Mazzarello P. Golgi. Oxford: Oxford University Press; 2010. 71.
4. Mazzarello P. Golgi. Oxford: Oxford University Press; 2010. 74.
5. Ramón y Cajal S. Recollections of My Life. Cambridge, MA: MIT Press; 1989. 325.
6. Ramón y Cajal S. Recollections of My Life. Cambridge, MA: MIT Press; 1989. 353.
7. Ramón y Cajal S. Recollections of My Life. Cambridge, MA: MIT Press; 1989. 357.
8. Ramón y Cajal S. Recollections of My Life. Cambridge, MA: MIT Press; 1989. 358.
9. Cowan WM. Foreword to Ref. 5; p. x.
10. Shepherd GM. Foundations of the Neuron Doctrine. Oxford and New York: Oxford University Press; 1991. p. 180–93.

11. Ramón y Cajal S. Recollections of My Life. Cambridge, MA: MIT Press; 1989. 587.
12. Mörner K.A.H., Award Ceremony Speech. The Nobel Prize in Physiology or Medicine 1906; http://nobelprize.org/nobelprizes/medicine/laureates/1906/press.html.
13. Golgi C. The neuron doctrine – theory and facts. Nobel Lectures. Nobelprize.org.
14. Jones EG. Cajal's debt to Golgi. Brain Research Reviews 2010;66:83.
15. Ramón y Cajal S. Recollections of My Life. Cambridge, MA: MIT Press; 1989. 552.
16. Mazzarello P. Golgi. Oxford: Oxford University Press; 2010. 291.
17. Mazzarello P. Golgi. Oxford: Oxford University Press; 2010. 5.
18. Ramón y Cajal S. The Structure and Connexions of Neurons. Nobel Lectures Nobelprize.org.
19. Ramón y Cajal S. Recollections of My Life. Cambridge, MA: MIT Press; 1989 551.
20. Lópes-Munoz F, Boya J, Almano C. Neuron theory, the cornerstone of neuroscience, on the centenary of the Nobel Prize award to Santiago Ramón y Cajal. Brain Research Bulletin 2006;70:391–405.
21. Cajal Club; www.cajalclub.org.
22. Clarke E, O'Malley CD. The Human Brain and Spinal Cord. Berkeley and Los Angeles: University of California Press; 1968. 102.
23. Clarke E, O'Malley CD. The Human Brain and Spinal Cord. Berkeley and Los Angeles: University of California Press; 1968. 104.
24. Nansen F. The Structure and Combination of the Histological Elements of the Central Nervous System. Bergens Museum Aarsberetning for 1886. In: Helle KB, Laerum OD, Ursin H, editors. The Nansen Symposium on New Concepts in Neuroscience. Bergen: Sigma Forlag; 1987. p. 146.
25. Shepherd GM. Foundations of the Neuron Doctrine. Oxford and New York: Oxford University Press; 1991. 128.
26. Finger S. Origins of Neuroscience. A History of Exploration into Brain Function. Oxford and New York: Oxford University Press; 1994. 46.
27. Edwards JS, Huntford R. Fridtjof Nansen: from the neuron to the North Polar Sea. Endeavour 1998;22:76–80.
28. Bock O. Fridtjof Nansen and the Nobel Prize in Physiology or Medicine of 1906. Årbok for Universitetsmuseet i Bergen 2011;16:25–32.
29. Schäfer EA. Observations on the Nervous System of Aurelia Aurita. Philosophical Transactions of the Royal Society of London 1878;169:563–75.
30. Hertwig O, Hertwig R. Das Nervensystem und die Sinnesorgane der Medusen. Leipzig: FCW Vogel; 1878. 128.
31. Huntford R. Nansen. London: Abacus; 2001. 54.
32. Grant G. Gustaf Retzius – Scientific Publications in Anatomy, Anthropology, Zoology, Botany. http://ki.se/ki/jsp/polopoly.jsp?d=38441&a=131674&1=sv.
33. Grant G. letter to me 12 August 2010.
34. Harris H. The Birth of the Cell. New Haven and London: Yale University Press; 1999. p. 94–105.
35. Virchow RLK. *Cellular Pathology As Based Upon Physiological And Pathological Histology*. Translated by F Chance. Philadelphia: J.B. Lippincott and Co.; 1863. Kessinger Legacy Reprints; p. 54.
36. Cowan MW, Kandel ER. In: Cowan WM, Südhof TC, Stevens CF, editors. Synapses. Baltimore and London: The Johns Hopkins University Press; 2001 p. 46–7.
37. Jones EG. The neuron doctrine 1891. Journal of the History of the Neurosciences 1994;3:3–20.
38. Harris H. The Birth of the Cell. New Haven and London: Yale University Press; 1999. 128.
39. de Carlo J. letter to author, 28 April 2011.
40. Planck MKEL, Kumar M. Quantum. In: Icon Books. 2009;3.