A path through the forest

Nerve Endings: The Discovery of the Synapse
by Richard Rapport
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It is not often that one can pinpoint a paradigm-shifting moment of discovery that transforms a scientific discipline, but in the 1800s, one such moment erupted from a makeshift laboratory in the kitchen of a young Spanish professor. Using not much more than a simple light microscope, pen and paper, and specimens of brain tissue, Santiago Ramón y Cajal (1852–1934) formulated revolutionary concepts that ignited the field of neuroscience.

Nerve Endings, a book from neurosurgeon Richard Rapport, recounts Cajal's life and times. The book also sheds light on Italian histologist Camillo Golgi (1843–1926), whose own kitchen experiments led to the tissue-staining method Cajal used to great effect. But even though both men's accomplishments are intertwined, and led to their joint winning of the Nobel prize in 1906, Cajal and Golgi were scientific rivals with opposing views on the nature of the brain.

Early microscopic studies hinted that the nervous system was made of individual cells (neurons), with numerous protrusions (dendrites) and single, thin emanations (axons). It was another matter to imagine how neurons were organized to convey information.

A popular view in the nineteenth century was that neurons were continuous with one another and formed one gigantic network. This 'reticular theory' seemed quite reasonable as it was an ideal way for information such as sensory input and motor output to flow through the nervous system in both directions. But inefficient techniques for fixing and staining tissue plagued the study of brain microstructure. Typical procedures labelled virtually all neurons and fibres, revealing the forest, but hiding the individual trees, leaves and roots in the thicket.

Golgi, a reserved figure, overcame this dilemma by developing an almost alchemical process based on soaking brain pieces in potassium dichromate and silver nitrate. The result was striking — only a tiny fraction of neurons were impregnated with a dark silver precipitate, making it possible to follow the outline of a single neuron and its tiniest processes. Why this method, which Golgi named the black reaction, labels neurons with such exquisite randomness remains unknown.

Golgi made important observations with his new technique, including that single axons give rise to numerous branches (collaterals). The fine meshwork of axon collaterals represented to Golgi the reticular elements that linked neurons, whereas dendrites played merely a nutritive role.

Kitchen think: Santiago Ramón y Cajal in his home lab.

Much is known about Cajal's life from his eloquent autobiographical writing. His *Recollections of My Life* (MIT, 1989) should be required reading for any scientist and Rapport draws heavily from it. The son of a small town doctor, Cajal was a mediocre student, obsessed with art, bodybuilding(!) and chess. His compulsive mind became intrigued with deciphering the workings of the brain. Working alone with few resources and only books to guide him, Cajal's neuroscience was done with a passion and fury unrivalled to this day. To him, "an exact knowledge of the structure of the brain was of supreme interest for the building up of a rational psychology. To know the brain … is equivalent to ascertaining the material course of thought and will."

In 1887, Cajal was introduced to the Golgi staining method and immediately grasped its power. Whereas most neuroanatomists studied adult human brains, Cajal focused on embryonic tissue and the more compact brains of mice and birds. Gazing into his microscope, Cajal conjured "the new truth": axons ended and formed contacts (later termed synapses by Charles Sherrington) very close to the dendrites and cell bodies of other neurons. To Cajal, the reticular theory was clearly wrong and the 'neuron doctrine' was set to take its place. He further proposed the law of 'dynamic polarization' which stated that neurons received information at their dendrites and cell bodies and relayed nerve impulses through their axons.

Cajal saw that by studying the relationship between axons and dendrites he could infer in what direction information travelled across neural circuits. His meticulous drawings of brain circuits — works of science and art — are filled with playful arrows showing the direction of information flow. Frustrated by the slow pace of publishing, in 1888 he created his own journal to showcase his findings. When that failed to make an impact, the following year Cajal travelled to Berlin to demonstrate his slides at a meeting of leading anatomists. Fascination over Cajal's preparations led to the rapid confirmation of his conclusions. Despite the quick acceptance of Cajal's neuron doctrine, Golgi stubbornly defended his ideas on reticular theory. It is ironic that the two met for the first time in Stockholm to receive their prizes; Golgi's speech was an attack on neuron theory, Cajal followed with a tactful defense.

As a synaptic physiologist a century later, I find it astonishing that Cajal's simple observa-

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