# A unifying concept: the history of cell theory

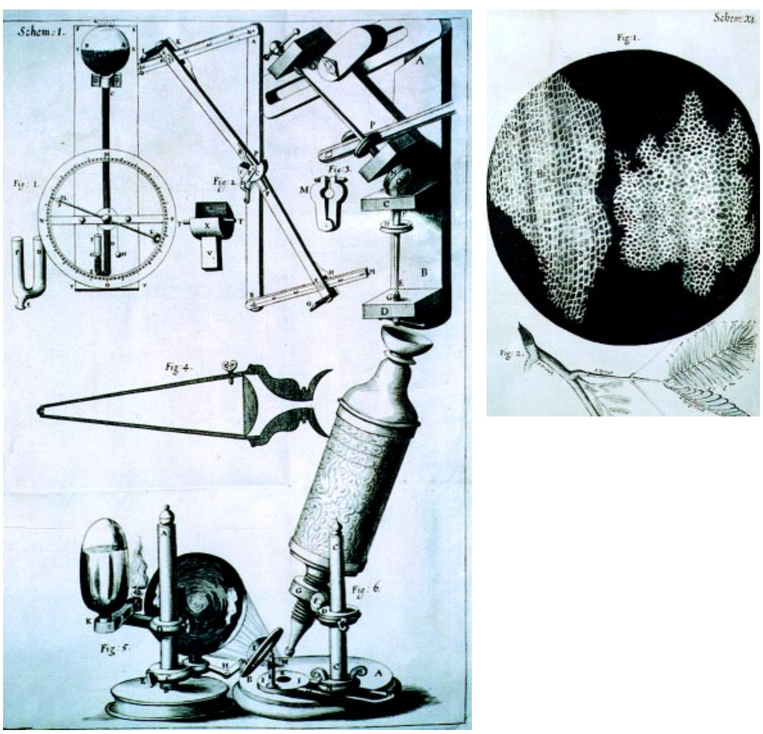
Paolo Mazzarello

**After the first observations of life under the microscope, it took two centuries of research before the 'cell theory', the idea that all living things are composed of cells or their products, was formulated. It proved even harder to accept that individual cells also make up nervous tissue.**

With the invention of the microscope at the beginning of the seventeenth century, it became possible to take a first glimpse at the previously invisible world of microscopic life. A bewildering array of new structures appeared before the astonished eyes of the first microscopists. The Jesuit priest Athanasius Kircher (1601–1680) showed, in 1658, that maggots and other living creatures developed in decaying tissues. In the same period, oval red-blood corpuscles were described by the Dutch naturalist Jan Swammerdam (1637–1680), who also discovered that a frog embryo consists of globular particles[1,2].

Another new world of extraordinary variety, that of microorganisms, was revealed by the exciting investigations of another Dutchman, Antoni van Leeuwenhoek (1632–1723). The particles that he saw under his microscope were motile and, assuming that motility equates to life, he went on to conclude, in a letter of 9 October 1676 to the Royal Society, that these particles were indeed living organisms. In a long series of papers van Leeuwenhoek then described many specific forms of these microorganisms (which he called "animalcules"), including protozoa and other unicellular organisms[3–5].

But the first description of the cell is generally attributed to Robert Hooke (1635–1702), an English physicist who was also a distinguished microscopist (see photographs below). In 1665 Hooke published *Micrographia*, the first important work devoted to microscopical observation, and showed what the microscope could mean for naturalists. He described the microscopic units that made up the structure of a slice of cork and coined the term "cells" or "pores" to refer to these units. *Cella* is a Latin word meaning 'a small room' and Latin-speaking people applied the word *Cellulae* to the six-sided cells of the honeycomb. By analogy, Hooke applied the term "cells" to the thickened walls of the dead cells of the cork. Although Hooke used the word differently to later cytologists (he thought of the cork cells as passages for fluids involved in plant growth), the modern term 'cell' comes directly from his book[6].



**Under the microscope: drawings of the instruments used by Robert Hooke (left) and the cellular structure of cork according to Hooke (right) (reproduced from *Micrographia*, 1665).**

## Bridge between life and 'non-life'?

The existence of an entire world of microscopic living beings was seen as a bridge between inanimate matter and living organisms that are visible to the naked eye[7]. This seemed to support the old aristotelian doctrine of 'spontaneous generation', according to which water or land bears the potential to generate, 'spontaneously', different kinds of organism. This theory, which implied a continuity between living and non-living matter, *natura non facit saltus*, was disproved by the masterful experiments of the Italian naturalist Lazzaro Spallanzani (1729–1799)[8]. He and other researchers showed that an organism derives from another organism(s) and that a gap exists between inanimate matter and life. (But it was a century later before the idea of spontaneous generation was definitively refuted, by Louis Pasteur, 1822–1895; ref. 9.) As a consequence, the search for the first elementary steps in the *scala naturae* was a motif in early-nineteenth-century biological thought: what could be the minimal unit carrying the potential for life?

"there is one universal principle of development for the elementary parts of organisms... and this principle is in the formation of cells"

## The cell theory

Hints at the idea that the cell is the basic component of living organisms emerged well before 1838–39, which was when the cell theory was officially formulated. Cells were not seen as undifferentiated structures. Some cellular components, such as the nucleus, had been visualized, and the occurrence of these structures in cells of different tissues and organisms hinted at the possibility that cells of similar organization might underlie all living matter.

The abbot Felice Fontana (1730–1805) glimpsed the nucleus in epithelial cells in 1781, but this structure had probably been observed in animal and plant cells in the first decades of the eighteenth century[7,10]. The Scottish botanist Robert Brown (1773–1858) was the first to recognize the nucleus (a term that he introduced) as an essential constituent of living cells (1831). In the leaves of orchids Brown observed "a single circular areola, generally somewhat more opake than the membrane of the cell... This areola, or nucleus of the cell as perhaps it might be termed, is not confined to the epidermis, being also found not only in the pubescence of the surface... but in many cases in the parenchyma or internal cells of the tissue"[11]. Brown recognized the general occurrence of the nucleus in these cells and apparently thought of the organization of the plant in terms of cellular constituents.

Meanwhile, technical improvements in microscopy were being made. The principal drawback of microscopes since van Leeuwenhoek's time was what we now call 'chromatic aberration', which diminishes the resolution power of the instrument at high magnifications. Only in the 1830s were achromatic microscopes introduced, allowing more precise histological observations. Improvements were also made in tissue-preservation and -treating techniques.

In 1838, the botanist Matthias Jakob Schleiden (1804–1881) suggested that every structural element of plants is composed of cells or their products[12]. The following year, a similar conclusion was elaborated for animals by the zoologist Theodor Schwann (1810–1882). He stated that "the elementary parts of all tissues are formed of cells" and that "there is one universal principle of development for the elementary parts of organisms... and this principle is in the formation of cells"[13]. The conclusions of Schleiden and Schwann are considered to represent the official formulation of 'cell theory' and their names are almost as closely linked to cell theory as are those of Watson and Crick with the structure of DNA[4,14].

According to Schleiden, however, the first phase of the generation of cells was the formation of a nucleus of "crystallization" within the intracellular substance (which he called the "cytoblast"), with subsequent progressive enlargement of such condensed material to become a new cell. This theory of 'free cell formation' was reminiscent of the old 'spontaneous generation' doctrine (although as an intracellular variant), but was refuted in the 1850s by Robert Remak (1815–1865), Rudolf Virchow (1821–1902) and Albert Kölliker (1817–1905) who showed that cells are formed through scission of pre-existing cells[7]. Virchow's aphorism *omnis cellula e cellula* (every cell from a pre-existing cell) thus became the basis of the theory of tissue formation, even if the mechanisms of nuclear division were not understood at the time.

Cell theory stimulated a reductionistic approach to biological problems and became the most general structural paradigm in biology. It emphasized the concept of the unity of life and brought about the concept of organisms as "republics of living elementary units"[7].

As well as being the fundamental unit of life, the cell was also seen as the basic element of pathological processes. Diseases came to be considered (irrespective of the causative agent) as an alteration of cells in the organism. Virchow's *Cellularpathologie* was the most important pathogenic concept until, in this century, the theory of molecular pathology was developed.

## Protoplasmic constituents

After Schleiden and Swann's formulation of cell theory, the basic constituents of the cell were considered to be a wall or a simple membrane, a viscous substance called "protoplasm" (a name now replaced by Kölliker's term "cytoplasm"), and the nucleus. It soon became evident that the protoplasm was not a homogeneous fluid. Some biologists regarded its fine structure as fibrillary, whereas others described a reticular, alveolar or granular protoplasmic architecture. This discrepancy resulted partly from artefactual and illusory images attributable to fixation and staining procedures that caused a non-homogeneous precipitation of colloidal complexes.

However, some staining of real cellular components led to the description of differentiated elements, which were subsequently identified. The introduction of the oil-immersion lens in 1870, the development of the microtome technique and the use of new fixing methods and dyes greatly improved microscopy. Towards the end of the nineteenth century, the principal organelles that are now considered to be parts of the cell were identified. The term "ergastoplasm" (endoplasmic reticulum) was introduced in 1897 (ref. 15); mitochondria were observed by several authors and named by Carl Benda (1857–1933) in 1898 (ref. 16), the same year in which Camillo Golgi (1843–1926) discovered the intracellular apparatus that bears his name[17].

The protoplasm was not the only structure to have a heterogeneous appearance. Within the nucleus, the nucleolus and a stainable substance could be seen. Moreover, a number of structures (ribbons, bands and threads) appeared during cell division. As these structures could be heavily stained, they were called "chromatin" by Walther Flemming (1843–1905), who also introduced the term "mitosis" in 1882 and gave a superb description of its various processes[18]. Flemming observed the longitudinal splitting of salamander chromosomes (a term introduced only in 1888 by Wilhelm Waldeyer, 1836–1921) during metaphase and established that each half-chromosome moves to the opposite pole of the mitotic nucleus[18]. This process was also observed in plants, providing further evidence of the deep unity of the living world.

## The neuron theory

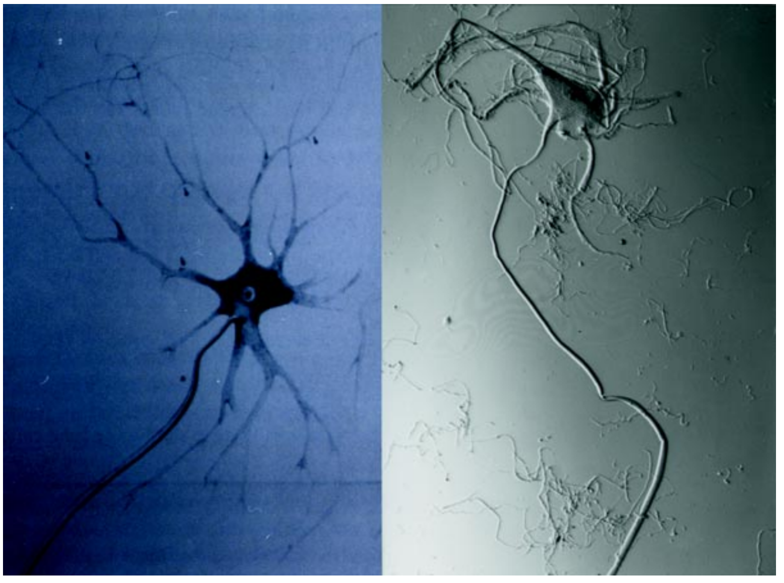
There was, however, a tissue that seemed to belie cell theory — nervous tissue. Because of its softness and fragility, it was difficult to handle and susceptible to deterioration. But it was its structural complexity that prevented a simple reduction to models derived from the cell theory. Nerve-cell bodies, nervous prolongations and nervous fibres were observed in the first half of the nineteenth century. However, attempts at reconstructing a three-dimensional structure of the nervous system were frustrated by the impossibility of determining the exact relationships between cell bodies (somas), neuronal protoplasmic processes (dendrites) and nervous fibres.

A book by Karl Deiters (1834–1863), published posthumously in 1865, contains beautiful descriptions and drawings of nerve cells studied by using histological methods and microdissections made with thin needles under the microscope (see photographs on next page)[19]. Deiters's nerve cells were characterized by a soma, dendrites and a nerve prolongation (axon) which showed no branching. Kölliker, in the fifth edition of his important book on histology, published in 1867, proposed that sensory and motor cells of the right and left halves of the spinal cord were linked "by anastomoses" (direct fusion)[20].

In 1872, the German histologist Joseph Gerlach (1820–1896) expanded Kölliker's view and proposed that, in all of the central nervous system, nerve cells established anastomoses with each other through a network formed by the minute branching of their dendrites. According to this concept, the network or reticulum was an essential element of grey matter that provided a system for anatomical and functional communications, a protoplasmic continuum from which nerve fibres originated[21].

The most important breakthrough in neurocytology and neuroanatomy came in 1873 when Golgi developed the 'black reaction'[22], which he announced to a friend with these few words, "I am delighted that I have



Left, drawing of an isolated neuron by Karl Deiters (reproduced from ref. 19). Right, isolated neuron obtained with the Deiters microdissection technique, using thin needles under the microscope (courtesy of G. Merico). The long axon in both cases does not appear ramified because branchings were disrupted during the procedure.

found a new reaction to demonstrate, even to the blind, the structure of the interstitial stroma of the cerebral cortex. I let the silver nitrate react with pieces of brain hardened in potassium dichromate. I have obtained magnificent results and hope to do even better in the future." This reaction provided, for the first time, a full view of a single nerve cell and its processes, which could be followed and analysed even when they were at a great distance from the cell body. The great advantage of this technique is that, for reasons that are still unknown, a precipitate of silver chromate randomly stains black only a few cells (usually from 1 to 5%), and completely spares the others, allowing individual elements to emerge from the nervous puzzle.

Aided by the black reaction, Golgi discovered the branching of the axon and found that, contrary to Gerlach's theory, dendrites are not fused in a network. Golgi, however, failed to go beyond the 'reticularistic paradigm'. He believed that the branched axons stained by his black reaction formed a gigantic continuous network along which the nervous impulse propagated. In fact, he was misled by an illusory network created by the superimposition and the interlocking of axons of separate cells. Golgi's network theory was, however, a substantial step forward because it emphasized, for the first time, the function of branched axons in connecting nerve cells.

According to Gerlach and Golgi, the nervous system represented an exception to cell theory, being formed not by independent cells but rather by a gigantic syncytium. Its unique structure and function could well justify an infringement of the general rule.

Matters changed quickly in the second half of the 1880s. In October 1886, the Swiss embryologist Wilhelm His (1831–1904) put forward the idea that the nerve-cell body and its prolongations form an independent unit[23,24]. In discussing how the axons terminate at the motor plate and how sensory fibres originate at peripheral receptors such as the Pacinian corpuscles, he suggested that a separation of cell units might be true of the central nervous system. The nervous system began to be considered, like any other tissue, as a sum of anatomically and functionally independent cells, which interact by contiguity rather than by continuity.

Similar conclusions were reached, at the beginning of 1887, by another Swiss scientist, the psychiatrist August Forel (1848–1931), and, in 1891, Waldeyer introduced the term "neurons" to indicate independent nerve cells[25,26]. Thereafter, cell theory as applied to the nervous system became known as the 'neuron theory'.

Ironically, it was by using Golgi's black reaction that the Spanish neuroanatomist Santiago Ramón y Cajal (1852–1934) became the main supporter and indefatigable champion of the neuron theory. His neuroanatomical investigations contributed to the foundations of the basic concepts of modern neuroscience. However, definitive proof of the neuron theory was obtained only after the introduction of the electron microscope, which allowed identification of synapses between neurons[21]. When the nervous system was also found to be made up of independent units, cell theory obtained its final triumph.

## The missing link

With the theory of evolution, the cell theory is the most important generalization in biology. There is, however, a missing link between these theories that prevents an even more general and unifying concept of life. This link is the initial passage from inorganic matter to the primordial cell and its evolution — the origin of life. If it ever proves possible to recreate in the laboratory the prebiotic physicochemical conditions required for the spontaneous generation of life, the link between these two generalizations will be finally at hand and a unifying paradigm will explain all biological phenomena. The theory of spontaneous generation would then be vindicated.

*Paolo Mazzarello is in the Istituto di Genetica Biochimica ed Evoluzionistica – CNR, Via Abbiategrasso 207, 27100 Pavia, Italy.*
*e-mail: mazzarello@igbe.pv.cnr.it*

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