Archives Italiennes de Biologie, 149 (Suppl.): 38-46, 2011.

Neurophysiology to Neuroanatomy: the transition from Claude Bernard to Louis Antoine Ranvier

A. I BOULLERNE

Department of Anesthesiology, University of Illinois at Chicago, Chicago, United States

ABSTRACT

Claude Bernard (1813-1878) and Louis Antoine Ranvier (1835-1922) were born in the same area of the Rhone valley in France, but they met by fate in Paris. Bernard discovered the central physiological concept of "milieu intérieur" – homeostasis – around 1854, but he lacked the technological tools to prove it. In 1867, when Bernard met Ranvier who was a wizard in histological techniques for anatomy, he naturally offered him a position in his laboratory at the famed Collège de France University. What happened next is the merging of two great spirits. Their respective careers collided and generated the transition from neurophysiology to neuroanatomy in an exceptional productivity. Ranvier adopted Experimental Histology from Bernard, which led him to discover the interruptions of myelin. He became immortalized by the name 'nodes of Ranvier'. Ranvier was a master in histology, particularly in microscopy and staining, and his book 'Technical treatise of histology' published in 1875 was later considered a bible by Ramón y Cajal who established the neuronal theory. As for Bernard, his concept of homeostasis was so in advance for his time that it took over half a century for the scientific community to bring experimental proofs. In 1865 Bernard published his now classic book 'Introduction to the study of Experimental medicine', which has been translated in many languages and is still read today. By enunciating the fundamental principles of research, this book laid the ground for modern medicine.

Key words
Claude Bernard • Louis Antoine Ranvier • Homeostasis • Experimental histology • Experimental physiology

The education of Claude Bernard

Claude Bernard (1813-1878) was born on 12th July 1813 in the village of Saint Julien in the rolling hills of France Beaujolais region near Lyons. His family owned a cottage and several hectares of wine. His father came from a farming family and was making a modest living from his vineyards (www.claude-bernard.co.uk/index.htm). Claude Bernard was schooled at the village church, and the priest recommended him to the Jesuit high school in the nearby town of Villefranche-sur-Saône. That was customary at the time for the brightest pupils. He did not excel in the Jesuit school but made many friends. Disappointed, Claude's parents arranged for him to attend another year at the royal college of Thoissey in the area. Claude again was not interested in the academic curriculum, but he developed a passion for Romanticism in literature and art. His favorite romantics were the novelist Victor Hugo and the painter Delacroix. Most important in Thoissey, Bernard was exposed to the work of René Descartes with the Cartesian emphasis on the importance of doubt and the quest for 'truth'. Bernard failed his baccalaureat and hence did not obtain a high school degree. The same year in 1832 at the age of 18 year-old, he joined a friend in the city of Lyons to start a pharmacy apprenticeship. Incidentally, the illustri-

Corresponding Author: Anne Boullerne, University of Illinois at Chicago, Dept of Anesthesiology, 835 South Walcott St., Chicago, Illinois, 60612, USA - Email: abouller@uic.edu

ous chemist Vauquelin[1] also started as assistant in a pharmacy. Bernard was soon puzzled by the number of preparations dispensed without any experimental proof for their efficacy, and for a variety of symptoms and conditions defying diagnosis. Bernard's pharmacist also mixed together leftovers from other prescriptions! This apprenticeship lacked rationality and Cartesianism. A disillusioned Bernard used his imagination to write a vaudeville, *La Rose du Rhône*, which success in theater spurred him to attempt a historical drama in five acts, *Arthur de Bretagne*.

In 1834 at the age of 21 year-old, he went to Paris to succeed in literature. Couple of prominent critics crucified his play and advised him instead to capitalize on his pharmacy experience and enter medicine. Resigned, he studied again for his baccalaureat that he barely passed at the second attempt in 1834, and entered a medical school in Paris. He practiced dissection on bodies that set his first track to success from his excellent technique. In 1836 he began attending lectures and observing in the hospital wards and autopsy room. He would tirelessly question his teachers about treatments for which no proof was available. Bernard discovered François Magendie[2] (1783-1855) teaching experimental medicine at the famed *Collège de France* University. Magendie was a notorious vivisector, shocking many of his contemporaries with live dissections that he performed during public physiology lectures. But his reasoning was flawless and he became a role model to Bernard. In 1839 Bernard barely passed his examination and began internship at the *Hôtel Dieu* hospital in the clinical service of Magendie. In 1841, at the age of 28 year-old Bernard became *préparateur* (research assistant) in Magendie's laboratory at the *Collège de France*. Soon he got permission to pursue ideas of his own and he published his first paper on the nerve conveying taste from the tongue to the brain. Bernard defended his thesis on how the gastric juice modifies glucose and obtained the degree of Doctor in Medicine in 1843. However, the empirical treatments observed at the hospital convinced Bernard that he did not want to work as a physician. Instead, he wanted to devote himself to research and infuse more 'truth' in medicine from proven facts.

Claude Bernard career

He needed a teaching appointment at the university, but failed the important contest in 1844 because of academic politics. His friends Pierre Rayer (dermatologist) and Théophile-Jules Pelouze (chemist) did not want Bernard to waste his potential for research as an obscure village doctor. They arranged for him to marry the daughter of a successful physician who had a substantial dowry, which would allow Bernard to pursue research under the protective wing of Magendie. In the meantime, Bernard won his first prize in Physiology from the *Académie des Sciences*, and he made detailed dissections published in a highly successful anatomy atlas. He resolved to marry Fanny Martin in 1845 and benefited her comfortable dowry. Bernard was very content and went on with his research.

In 1848 he explored where glucose was distributed in the body, and he made his most important discovery: glucose was found in every liver he examined from mammal, bird, reptile and fish, at the exception of any other organ. In 1849 he explored further glucose metabolism and brought the definite proof that the liver generates glucose, naming its precursor *glycogène* (glycogen). This contradicted the contemporary beliefs that liver was only secreting bile and that animals could not synthesize nutrients! This major discovery led Bernard to formulate the concept of internal secretion that was the first step to define the endocrine system. Bernard first years of research were awarded by two prizes in Experimental physiology from the Academy of Sciences in 1849 and 1851. He also received in 1849 the prestigious award of *Chevalier de la Légion d'Honneur* at the young age of 36 year-old. This precocious success led Bernard to be appointed substitute professor of Magendie at the *Collège de France* in 1849, where he told students that 'The scientific medicine which it is my duty to teach you does not exist'. In 1853 he was awarded a doctorate in Natural Sciences for his discoveries.

Bernard's private life however was not as serene, despite the birth of two healthy daughters in 1847 and 1850. He spent his life in his basement laboratory and most of his experimental work involved vivisection. Magendie before him had established the importance of direct experimentation in living mammals, usually cats, dogs and rabbits. Anesthetics had just been discovered in the 1840's, but were not used in animals because of their interference with the nervous system (Gross, 2009). In France at the time there was much less popular opposition to vivisection than in Great Britain. English scientists visiting Bernard attracted by his fame were horrified by his experiments. For Bernard, vivisection was a necessary evil to avoid 'experimenting' on patients with non-scientific medicine. But Fanny Bernard bitterly resented the fact that her husband had a low pay research career and was bringing home dying animals with tubes stuck in them. She became an ardent antivivisection activist, and joined the newly formed Society for the Protection of Animals (SPA) as one of its most vocal members. Bernard legally separated from his wife in 1869, which was shameful for the society at the time. But he was at the peak of his career and his marriage had been a disaster. Subsequently, his wife and daughters became estranged and founded a home for stray dogs and cats. Current legislations in the world now prohibit vivisection without anesthesia.

He worked for twenty years on curare targeting motor nerves, which led him to study asphyxia and anesthetics. Then he switched his research and discovered that the sympathetic nervous system controls blood flow and regulates body heat. In 1854 Bernard got elected to the Academy of Sciences, and simultaneously a chair in General Physiology was created for him at the Sorbonne University. In 1855 after the death of Magendie, Bernard was appointed to his chair of Experimental Medicine at the *Collège de France* University.

In 1859, after many honors and major publications, but also much controversy from French (Bérard, Longet, Figuier) and English (Pavy) scientists, Bernard health started to deteriorate. He was suffering from rheumatic pains, recurrent migraine attacks, abdominal pain and vomiting. He was still working in a damp unhygienic basement laboratory, which together with overwork and constant professional challenges may have caused his illness. He took leave from his academic duties and spent the year of 1860 in his natal village of Saint Julien. There he bought a manor with vineyards where he created a study and a laboratory. He experimented on plants and frogs collected from the countryside. This forced sabbatical leave allowed him to crystallize his research principles, and he embarked on formulating his philosophy of *scientific determinism*.

Bernard returned to research and academic duties in Paris in 1861. Four years later he published his most important book: *An Introduction to the Study of Experimental Medicine* (1865). In that book he enunciated the fundamental principles of research: observation as a starting point; followed by a hypothesis; results must be reproducible; add a counterproof experiment; preconception must be avoided and the mind must stay open. Bernard was the first to suggest the use of blind experiments to ensure objectivity in scientific observations. This book was translated in English in 1927. Since then it has been translated in a dozen languages and is used in courses on physiology and philosophy. It is reprinted on a regular basis in France (2010). At the beginning the brilliance of the book was acknowledged by the literary, but not the scientific world. Consequently in 1865, Bernard got nominated for election at the *Académie Française*, the prestigious institution of 40 immortals representing French cultural elite. The same year in 1865, he was asked to write for the lay public on the physiology of the heart and later of the brain. His writing was so clear that he attracted the praise of Louis Pasteur[3] who denounced his abysmal working condition (underground laboratory) and his poor health. Amazingly, the emperor Louis Napoléon, who had formally met Bernard the year before in 1864, organized two large redesigned laboratory spaces for him at the Natural History Museum and the *Jardin des Plantes* (chemistry school of the former royal botanical garden), together with the chair of General Physiology. In 1868 he was elected to the *Académie Française* which was a prestigious honor. In 1869 following his legal separation from his wife, he moved to an apartment across the street from the *Collège de France* University, as close as he could get to the model of German universities lodging scientists above their laboratories. In 1869, Bernard was appointed to the Imperial senate as a confirmation of his high social standing. In 1871 Bernard returned to Paris after the French-German war episode. His laboratories were intact but his staff had been killed and his research slowed down. In 1873, Bernard was chosen as the first president of the French Association of the Advancement of Science, in recognition of his status as the most prominent scientist in France. He died in Paris on the 10th February 1878 and was accorded a public state funeral – an honor which had never been before bestowed by France on a man of science. Claude Bernard collected more honors and more fame than any French scientist before and since. He was elected to the Academy of Sciences, the Academy of Medicine, was the president of the French Academy, a commander of the *Légion d'Honneur* and a member of the Imperial senate. He became so famous that eventually he was identified in the public mind as the stereotypical scientist, much like Albert Einstein in the twentieth century (Fig. 1). He appears in poetry, memoirs, and novels both in France and abroad (Gross, 2009).

The *milieu intérieur* of Claude Bernard

Milieu intérieur (internal environment) is a term coined by Bernard referring to the extracellular fluid environment and its capacity to ensure physiological constancy for the tissues and organs of multicellular organisms. Claude Bernard used the term *milieu intérieur* in several works from 1854 until his death in 1878 but he really advanced his concept in 1869. Bernard's idea of internal environment was initially ignored in the nineteenth century. This happened in spite of Bernard being highly honored as the founder of modern physiology. Even the 1911 edition of Encyclopedia Britannica does not mention *milieu intérieur*. Internal environment constancy, also known as *homeostasis,* was first mentioned in English in 1926 (Merriam-Webster dictionary). His concept of *milieu intérieur* only became central to the understanding of physiology at the beginning of the twentieth century. The current 15th edition of Encyclopedia Britannica notes that *homeostasis* is Bernard's most important idea.

The concept of *milieu intérieur* attacked the age old theory of *vitalism* which invoked the vague 'forces of nature' to explain life. *Milieu intérieur* or *homeostasis* is a mechanistic process, in which the physiology of the body is regulated through multiple mechanical equilibriums adjusting in feedbacks, hence allowing free life of the organism. A century

Fig. 1. - Claude Bernard in his laboratory (Painting by León Lhermitte 1889, Académie Nationale de Médecine, Paris). Unfortunately Ranvier is not represented.

earlier the Italian physicists Count Alessandro Volta (1745-1827) and Luigi Galvani (1737-1798) had discovered electricity in animals. It inspired them to designate electricity as the force of life in the theory of *vitalism*, hence making one step in the direction to replace it. Bernard concept of *milieu intérieur* went further to definitively replace *vitalism*.

Bernard elaborated his concept of *milieu intérieur* from his first work on the functions of the pancreas gland, the juice of which he proved to be of great significance in the process of digestion. A second and most famous investigation was on the glycogenic function of the liver, which threw light on the cause of diabetes. He found that the liver is the seat of an "internal secretion", by which it prepares sugar at the expense of the elements in the blood passing through it. A third research resulted in the discovery of the vasomotor system. Around 1851, in examining the effects produced in the temperature of various parts of the body by section of the nerve or nerves belonging to them, Bernard noticed that division of the cervical sympathetic nerve gave rise to more active circulation and stronger pulse of the arteries in certain parts of the head. A few months afterwards he observed that electrical excitation of the upper portion of the divided nerve had the contrary effect. He hence established the existence of vasomotor nerves both vasodilatator and vasoconstrictor. The study of the physiological action of poisons was also one of his favorite, his attention being devoted particularly to curare and carbon monoxide gas. The earliest announcements of his results, the most striking of which were obtained in the decade from 1850 to 1860, were generally made in recognized scientific publications. But the full exposition of his views, and even the statement of some of the original facts, can only be found in his published lectures. Bernard published a total of 250 articles and 50 books.

Ranvier the wizard of histology

To our knowledge, no formal biography is available on Louis Antoine Ranvier (1835-1922). The two articles offering the richest source are abundantly cited throughout this article (Jolly, 1922; Barbara, 2007). Hence, less information is available on Louis Antoine Ranvier than on Claude Bernard, who additionally was a prolific writer and recorded his daily thoughts. Ranvier was born on October 2, 1835 in the French city of Lyons, some 40 km south of Bernard home village. The father of Ranvier was a retired businessman reconverted as public servant in hospital administration. Somewhat expectedly, his son attended a preparatory school for Medicine and Pharmacy in the late 1850's. As part of his medical training in Lyons, Ranvier took to study microscopic anatomy (Jolly, 1922) and a high quality course of pathological anatomy (Barbara, 2007).

In 1860 at the age of 25 year-old, Ranvier brilliantly succeeded the examination for internship in Parisian hospitals and went to Paris to pursue medicine. 1860 marked the start of Ranvier scientific career. While preparing internship in Paris, Ranvier met his friend André Victor Cornil (1837-1908) with whom he became a devoted member of the *Société Anatomique* founded by Cruveilhier[4] (Jolly, 1922). Cruveilhier was much renowned at the time, considered by the German Rudolph Virchow (1821-1902) as the founding father of pathological anatomy (Jolly, 1922). Cruveilhier was holding the first chair of Pathological Anatomy created for him in Paris in 1836. Between 1860 and 1865, Ranvier and his friend Cornil developed a passion for the microscope (Jolly, 1922; Barbara, 2007). General anatomy was a valued medical discipline in France after François Xavier Bichat (1771-1802) developed it despite not using a microscope. In Paris, Ranvier learned microscopy applied to tissues which was becoming increasingly popular in France in the 1850's. The achromatic microscope invented by the Englishman Joseph Lister in 1826 allowed for a reliable observation of specimens, and was made available to a large scale in the 1830's (Ford, 2007). Twenty years into the era of 'modern' microscopy, skepticism remained on its usefulness for diagnosis because the observed tissues lacked contrast. The advent of tissue staining had yet to arrive. In 1858, when Virchow coined the term 'neuroglia' it was because neurons were the most visible elements in this pre-staining era, and he assimilated the surrounding of neurons to connective tissue or 'glue' (Virchow, 1858).

In 1865 Ranvier graduated as Doctor in Medicine with a thesis on cartilage and bone lesions. That same year in 1865 he founded with his friend Cornil a small private laboratory located in the Paris 6th arrondissement. Ranvier and Cornil offered in their laboratory a course in histology to medical students which had no equivalent at the time (Jolly, 1922; Barbara, 2007). Drawing from their experience, they published together over the course of seven years the book "Manuel d'histologie pathologique" (Cornil and Ranvier, 1869-1876) which was hugely successful and got translated in English in 1880 and 1882 (American and British versions respectively). Later, Ranvier published solo an important treatise in histopathology entitled "Traité technique d'histologie" (1875) which was completed in 1882. This textbook represented a modern and clear teaching for students interested in normal and pathological histology. As a tribute to its quality it was translated in German in 1888.

Ranvier took the initiative to use and teach the staining techniques available at the time. The German pathologist Friedrich von Recklinghausen[5] (1833-1910) had published in 1860 a method using silver nitrate preserving longer and enhancing better the tissues observed under a microscope. Staining tissue was a revolution for microscopic observation that otherwise was severely limited by lack of contrast and a rapid decomposition. There is reason to believe that Ranvier was able to read German publications, since he always referenced the original publications of German scientists in German and wrote notes in translations. Ranvier describes as early as 1871 (Barbara, 2007), and amply in 1875 numerous staining methods over 1,000 pages. In example, are described the metal impregnations with silver nitrate and gold sublimate; the fixations with osmic acid, alcohol and dichromate; the colorations with hematoxylin, eosin, picrocarminate and methyl violet; and injection with Prussian blue. Note that Camillo Golgi (1843-1926) published his legendary staining first in 1873 then in 1883, and used potassium dichromate silver. Ranvier distrusted Golgi staining as not reliable enough to always see the fine cellular details and favored silver nitrate and gold sublimate (Jolly, 1922). Ranvier not only used revolutionary staining methods, but he was also precursor for his use of new immersion objectives which allowed a 1,000 fold magnification (Barbara, 2007). We can only imagine the enthusiasm of students attending Ranvier and Cornil's course and discovering minute anatomical details never seen before under a microscope.

The private histology course taught by Ranvier soon attracted the attention of Bernard. In 1867 Ranvier became the assistant (*préparateur*) of Claude Bernard at the *Collège de France* university which was a promising position, considering the fame of Bernard, for a young physician freshly graduated 2 years earlier. Bernard was probably favorably impressed that Ranvier became highly successful in setting up a private laboratory when he attempted but failed at a similar age. Bernard probably saw some complementarities between him and Ranvier. Bernard was looking for experimental proofs of his newly discovered physiological functions. Bernard saw histological anatomy as a mean to bring these proofs. Ranvier was simply the most promising fellow at the time. In Bernard words: "Ranvier is going to explain us" (Jolly, 1922). In 1872 Ranvier small private laboratory became officially associated to the chair of Experimental Medicine held by Bernard at the *Collège de France* and renamed '*Laboratoire d'Histologie de l'Ecole des Hautes Etudes*'. Ranvier was put in full charge of the large facilities. His laboratory of histology at the *Collège de France* grew in reputation and fame so rapidly that a chair of General Anatomy was recreated for him by Bernard at the *Collège de France,* into which he was installed in 1875 (Jolly, 1922). For the next thirty years Ranvier was associated with this university where he made his most important discoveries. His entire life was devoted to science. He never married and lived in a student apartment. His enthusiasm and energy were legendary (Jolly, 1922; Ranvier, 1922). His field of investigation was exceedingly vast. There is no tissue and scarcely any organ which he did not investigate thoroughly, but he did work most on the nervous system (Jolly, 1922). Many subjects of his investigations are not known from being published only in French, such as neuroglia "névroglie", or his discovery that the neuron was a polarized cell with dendrites input and axon output inferred from the work of Waller (Wallerian degeneration). He published a total of 174 articles and books. Ranvier must be considered as the father of experimental histology. His manipulative dexterity was unequalled, and the laboratory practice of early twentieth century is largely founded on his methods (Ranvier, 1922). In 1897, he founded the journal "Archives d'Anatomie microscopique" with Edouart-Gérard Balbiani. In 1900 at the age of 65 year-old he retired to his country estate in Thélys and died in reclusion at Vendranges, France, on March 23, 1922.

The merging of two spirits

Bernard and Ranvier both believed in the cellular theory enunciating the cell as the basic functional unit of all organisms. The cell theory was born some twenty years earlier in Berlin, Germany, formulated for the first time by Theodor Schwann (1810-1882) in his 1839 book 'Cell Theory for Animal Bodies' (Bielka and Kettenmann, 1998). Schwann defined a cell as a membrane containing a cellular substance and a nucleus. Building on Schwann theory, Rudolph Virchow postulated in his 1858 book 'Cellular Pathology' that all diseases should manifest changes in cells, although for Virchow a cell was protoplasmic without membrane (Virchow, 1858). The cell theory was staunchly opposed by French scientists at the time, who were supporting instead the reticular theory (Barbara, 2007). The clash between the reticular and the cell theories reached its climax when the Nobel prize was jointly attributed to its most prominent proponents Golgi (reticularist) and Cajal (neuronist) in 1906. Bernard adopted the cellular theory because he could escape the old concept of *vitalism* and remain grounded in experimental facts. Ranvier believed in cells from seeing them under his microscope, stained and dead, or alive with moving organelles. Ranvier founded experimental histology from attending Bernard's lectures at the *Collège de France*. Of note, Ranvier profoundly disliked vivisection and always killed the animals that Bernard used for his lessons. Experimental histology for Bernard was a mean to localize a physiological function in a particular organ. In contrast, Ranvier approached histology at the cellular level with concerns for development, nutrition, and function with physiology and anatomy in mind. Whenever possible, he favored the microscopic observation of live tissues.

In 1871 Ranvier published that the pigment picrocarmine can penetrate isolated myelinated nerve fibers only at localized sites, hence identifying interruptions in the myelin sheath (*myéline*). In 1872 he published the same observation, this time applying silver nitrate on sciatic nerves of frog and rabbit (Fig. 2). The nerves were discontinuously stained at points periodically spaced that he called annular constrictions (étranglements annulaires). Because myelin appears constricted at these gaps, they were later named 'nodes of Ranvier'. Wondering about the function of the 'nodes' of myelin, Ranvier hypothesized that myelin was protective and prevented the nutriente to reach the 'axis-cylinder' (not yet named axon). He suggested the nodes allowed nutrients to reach the cell and were involved in physiological exchanges between nerves and blood. Ranvier experimented further on isolated myelin and observed that in presence of water, myelin swelled and became disheveled with disappearance of the nodes. In parallel, when water was added to the wound of an animal, it led to nerve paralysis. Ranvier hence inferred that the nodes were necessary for nerve conduction (1878), which would be definitively proven in a distant future.

Legacy

Ranvier wrote on the front page of his 1881 general anatomy book "I dedicate this volume to the memory of my illustrious and regretted mentor Claude Bernard". In the book introduction, Ranvier spent several pages explaining the *scientific determinism* of Claude Bernard. Page 4: "Claude Bernard attached a paramount importance to the care that physiologists had in determining the exact various conditions that could modify the observed results. He raised these principles into a doctrine, to which he gave the name *déterminisme*". To summarize, *determinism* is the choice of the conditions to study an object. Ranvier applied the determinism to histology. Ranvier was very precise in his technology and was detail-oriented. He was not leaving anything to hazard to increase the reproducibility of his observations. His writing is hence surprisingly modern. In example, he was providing the origin and quality grade of every reagent he was using. including water that he was filtering. His technical textbook on histology (1875) had an influence for decades on scientists.

Ramón y Cajal gives testimony to the talent of Ranvier in his biography (Cajal, 1917 translated in 1937) on page 275: "I commenced to try out my investigative powers, drawing my inspiration mainly from the wise counsels of Ranvier's *Tratado de Técnica Histológica*", and on page 304: "In my systematic explorations through the realms of microscopic anatomy, there came the turn of the nervous system, that masterpiece of life. I examined it eagerly in various animals, guided by … above all the incomparable works of Ranvier, of whose ingenious tech-

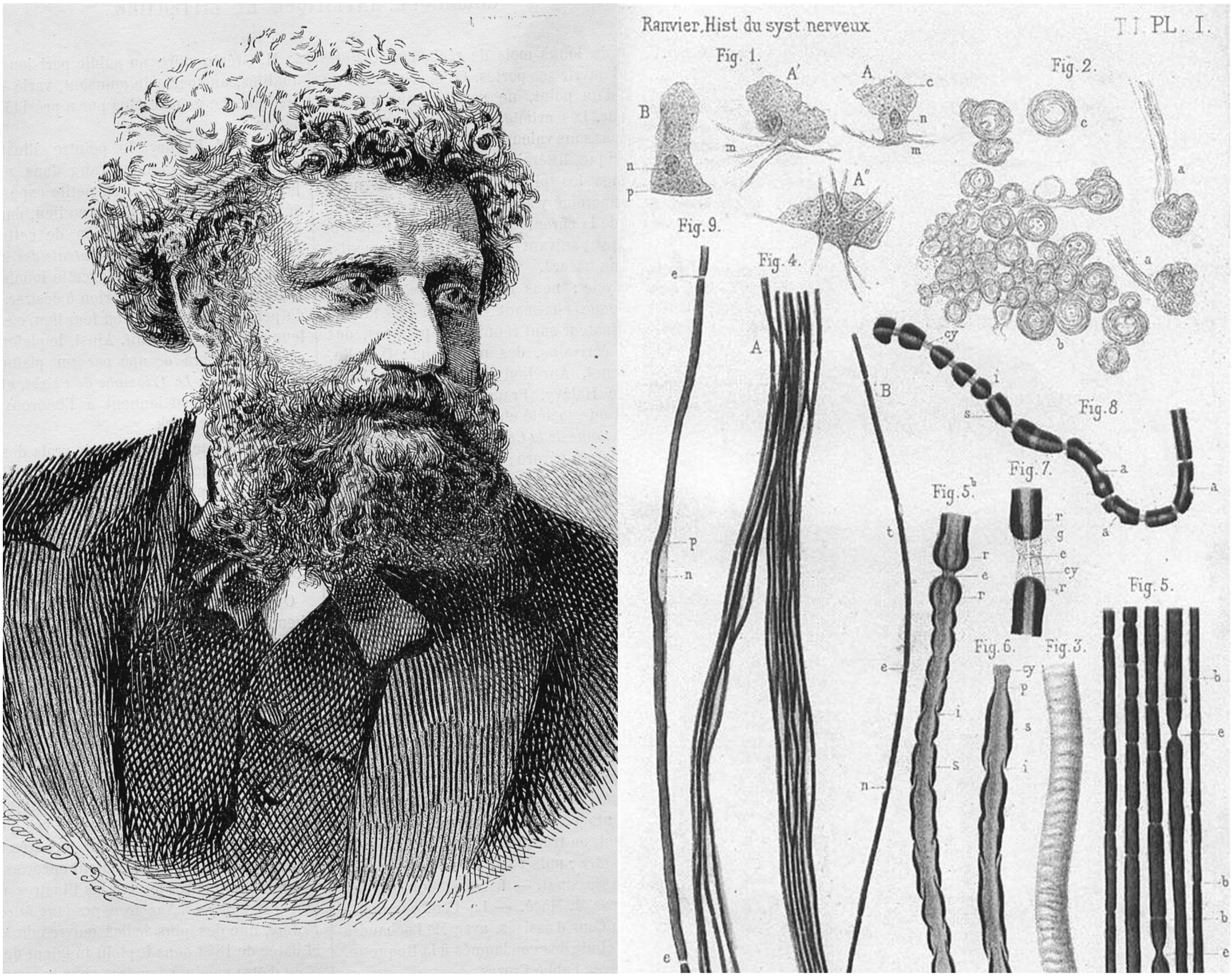

Fig. 2. - Left: Louis Antoine Ranvier (1882, personal archive). Right: plate I, volume 1, nodes of myelin reprinted from Ranvier textbook (1878).

nique I made use with conscientious determination". Cajal went on to great scientific accomplishments, not the least being the definitive discovery of neurons which sealed the cell theory, for which he won the Nobel prize in 1906. Now days the modern legacy of Ranvier is reduced to his discovery of T-shape spinal cells, the nerves ending in muscles, skin and cornea and the nodes of myelin bearing his name, but he was one of the great physiologist of the 19th century.

Notes

[1] Nicolas-Louis Vauquelin (1763-1829) was a prominent 18th century chemist from rural background similarly as Claude Bernard. He launched modern chemistry and was the first to analyze the chemical content of human brain.

[2] François Magendie (1783-1855) was a physiologist considered pioneer in experimental physiology. He discovered the differentiation between sensory and motor nerves in the spinal cord.

[3] Louis Pasteur (1822-1895) is one of the three main founders of microbiology. He invented pasteurization and vaccination.

[4] Jean Cruveilhier (1791-1874) was a pathologist and anatomist. He was one of the first to describe the brain lesions of multiple sclerosis in 1842. He founded in 1826 the Anatomical Society that he presided for 40 years.

[5] Friedrich von Recklinghausen (1833-1910) was a German pathologist known for discovering the Neurofibromatosis type I or Recklinghausen syndrome.

Acknowledgements

This article is adapted from a personal website created in 2005, and oral presentations given at the annual American Society for Neurochemistry meeting in San Antonio, Texas, USA in March 2008; the biennial Euroglia meeting in Paris, France in September 2009; and the Satellite meeting of the annual International Society for the History of the Neurosciences at the Villa di Corliano, Pisa, Italy in June 2010.

References

Barbara J.G. Louis Ranvier (1835-1922): the contribution of microscopy to physiology and the renewal of French general anatomy. *J. Hist. Neurosci.*, **16**: 413-431, 2007.

Bernard C. *Introduction à l'étude de la médecine expérimentale*. Paris, J.-B. Baillière, 1865. Reprinted in 2010, Paris, Collection Les livres qui ont changé le monde, Flammarion. First English translation by Greene H.C. *An Introduction to the Study of Experimental Medicine*, London, Macmillan & Co. Ltd, 1927; reprinted in 1949.

Bernard C. Life and publications (http://www.claude-bernard.co.uk/index.htm)

Bielka H., Kettenmann H. *Medical history of Berlin*. Berlin-Buch, Max Delbrück Center for Molecular Medicine, 2005.

Cornil A.-V. and Ranvier L. *Manuel d'histologie pathologique*. Paris, J.-B. Baillière, 1869-1876. Translated with notes and additions in English by Shakespeare E.O. and Simes H.C., *Manual of Pathological Histology*, Philadelphia, H.C. Lea, 1880.

Ford B.J. Enlightening neuroscience: Microscopes and microscopy in the eighteenth century. In: Whitaker H., Smith C.U.M., Finger S. (Eds.), *Brain, Mind and Medicine*, New York, Springer, 2007, pp. 39.

Golgi C. Recherche sur l'Histologie des centres nerveux. *Arch. Ital. Biol.*, **3**: 285, 1883.

Gross C.G. Claude Bernard and the constancy of the internal environment. In: *A hole in the head: more tales in the history of neuroscience*, Cambridge, Massachusetts, London, England, The MIT Press, 2009, pp. 183-200.

Jolly J. Louis Ranvier (1835-1922): Notice Biographique. *Archives d'Anatomie Microscopique*, **19**: 1-72 (I-LXXII), 1922.

Kettenmann H., Verkhratsky A. Neuroglia: the 150 years after. *Trends Neurosci.*, **31**: 653-659, 2008.

Ramón y Cajal S. *Recollection of my life*. Translated from *Recuerdos de mi vida* (1917) by Craigie E.H. and Cano J., Cambridge, Massachusetts, London, England, The MIT Press, 1937.

Ranvier L. Contributions à l'histologie et à la physiologie des nerfs périphériques. *Comptes Rendus de l'Académie des Sciences*, **73**: 1168-1171, 1871.

Ranvier L. Recherches sur l'histologie et la physiologie des nerfs. *Archives de Physiologie Normale et Pathologique*, **4**: 129-149, 1872.

Ranvier L. *Traité technique d'histologie*. Paris, Librarie F. Savy, 1875 (completed in 1882). Translated in German by Nicati W. and Wyss H., *Technisches Lehrbuch der Histologie*, Leipzig, F.C.W. Vogel, 1888.

Ranvier L. *Leçons sur l'histologie du système nerveux*. Paris, Librarie F. Savy, 1878.

Ranvier L. *Leçons d'anatomie générale. Terminaisons nerveuses sensitives Cornée*. Paris, Librarie F. Savy, 1881.

Ranvier L. Obituary. *Nature*, **2741**: 620-621, 1922.

Von Recklinghausen F. Eine Methode, mikroskopische hohle und solide Gebilde von einander zu unterscheiden. *Virchows Archiv*, **19**: 451, 1860.

Virchow R. *Die Cellularpathologie in ihrer Begründung auf physiologische und pathologische Gewebelehre*. Berlin, August Hirschwald, 1858. Translated in English based on the first German edition by Chance F. *Cellular Pathology*, London, John Churchill, 1860. Translated in French based on the second German edition by Picard P. *Pathologie Cellulaire*, Paris, J.-B. Baillière, 1868.