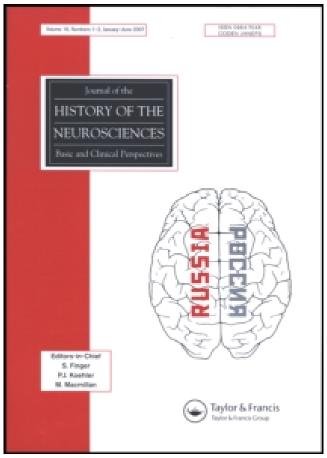


Journal of the History of the Neurosciences
Basic and Clinical Perspectives
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713658018

Louis Ranvier (1835-1922): The Contribution of Microscopy to Physiology and the Renewal of French General Anatomy

Jean-Gaël Barbara [ab]
[a] CNRS UMR7102, Université Pierre et Marie Curie, Paris, France
[b] CNRS UMR7596, Université Denis Diderot, Paris, France

Online Publication Date: 01 October 2007
To cite this Article: Barbara, Jean-Gaël (2007) 'Louis Ranvier (1835-1922): The Contribution of Microscopy to Physiology and the Renewal of French General Anatomy', Journal of the History of the Neurosciences, 16:4, 413 - 431
To link to this article: DOI: 10.1080/09647040600685503
URL: http://dx.doi.org/10.1080/09647040600685503

Journal of the History of the Neurosciences, 16:413–431, 2007

ISSN: 0964-704X print / 1744-5213 online
DOI: 10.1080/09647040600685503

Taylor & Francis
Taylor & Francis Group

Louis Ranvier (1835–1922): The Contribution of Microscopy to Physiology and the Renewal of French General Anatomy

JEAN-GAËL BARBARA

CNRS UMR7102, Université Pierre et Marie Curie, Paris, France
CNRS UMR7596, Université Denis Diderot, Paris, France

The French neurohistologist Louis-Antoine Ranvier (1835–1922), somewhat neglected in classical histories of nineteenth-century studies on the nervous system, developed a personal style, traditionally referred to as a synthesis between histology and physiology. Ranvier's research was not centered on the brain. Rather, he remained attached to the intimate nature of minute structures, with a style marked by the concept of generality. Ranvier's original style and role in the development of French histology and anatomie générale *are analyzed, and their significance evaluated. Ranvier is reassessed as a prominent figure and as the leader in the renewal of the French anatomy.*

Keywords Ranvier's node, general anatomy, histophysiology

Introduction

The name of Louis-Antoine Ranvier (1835–1922) will always be associated with the "nœuds de Ranvier," which he discovered in the context of Claude Bernard's (1813–1878) experimental medicine. However, Ranvier the scientist is less well-known, and his researches have not been recently subjected to an extended appraisal.

Why should we reexamine Ranvier's career as a neurohistologist, since he did not participate directly in the foundation of the neuron doctrine, nor did he make outstanding descriptions of nerve centers? In part because Ranvier made valuable discoveries, on fiber nodes, T structures[1] of dorsal root ganglion cells, nerve sheaths, and nerve fiber's degeneration and regeneration. All were noticed by Ranvier's most illustrious contemporaries including Santiago Ramón y Cajal (1852–1934). But most of all, Ranvier's career must be placed in the perspective of French physiology and the anatomie générale of François-Xavier Bichat (1771–1802). In this context, Ranvier's work appears with its original style,

[1]The T structure of sensory ganglion neurons refers to the T-shape of their axon, one branch coming from the periphery, the other converging into the spinal cord. In these neurons, often termed T sensory neurons in the literature, Ranvier discovered the bifurcation of their axon near the nerve cell body at the site of the first node of Ranvier. Ranvier referred to the T structures as "tubes nerveux en T" (Ranvier, 1875c).

The author wishes to thank Dr. Richard Miles for careful reading of the manuscript and Evelyne Maury for kindly providing photographs from Ranvier's fund in the Collège de France.

All translations by the author.

Address correspondence to Jean-Gaël Barbara, CNRS, UMR7102, Université Pierre et Marie Curie. Case 14, 7, quai Saint Bernard, 75005, Paris. Tel.: 00 33 1 44 27 25 87. E-mail: jean-gael.barbara @snv.jussieu.fr

distinct from mainstream topographic studies on the human brain, and offers a new perspective on French contributions to the origins of neurohistology. In this essay, I trace how Ranvier's studies on the nervous system developed from his early medical training up to the summit of a chair at the Collège de France in the context of cellular theory, German histology, and Parisian anatomy and physiology.

Medical Training in Lyons and Paris

The Context of Ranvier's Choice of Microscopy

Ranvier was born in Lyons (1835), in a family devoted to politics and public affairs, including hospital administration. He naturally took up medical studies at the Ecole Préparatoire de Médecine et de Pharmacie in Lyons, which soon led him to Paris (1860), after he succeeded in the highly competitive examination for the internship of Parisian hospitals. During his medical training, Ranvier became acquainted with normal and pathological anatomy,[2] and soon turned to microscopy as a means for further studies on tissues. This attitude was not popular among French scholars, after Bichat had inspired Henri Ducrotay de Blainville (1777–1850) and Auguste Comte (1798–1857) in their attacks over microscopy (see Canguilhem, 1952, pp. 63–64; Bichat, 1799, p. 35). However, the French context of medical microscopy was changing. Since the early 1830s, physicians trained in Paris, including Alfred Donné (1801–1878), Hermann Lebert (1813–1878), David Gruby (1810–1898), Louis Mandl (1812–1881), and later Charles-Philippe Robin (1821–1885), Paul Broca (1824–1880), Eugène-François Follin (1823–1867), and Aristide Verneuil (1823–1895) devoted some of their research and teaching to microscopical studies (La Berge, 2004). Donné and Robin had published memoirs and microscopy manuals, some of them addressed to students, which may have influenced Ranvier (Foucault & Donné, 1844–1845; Robin, 1849, 1854, 1856). Nevertheless, Ranvier was probably more influenced by German studies, including the French translations he would later quote (Kölliker, 1856; Virchow, 1858; see Jolly, 1922, p. 10; Jolly, 1932, p. 213).

During the 1850s, microscopical studies in medicine became increasingly numerous in France, but questions were still raised on the utility of the microscope for diagnosing diseases. A national scientific debate had been raging at the Académie de Médecine in Paris, until the essay of a professor from Strasbourg closer to German histological traditions was honored in 1856 (La Berge, 2004; Michel, 1856). From then on, microscopy was increasingly taught in France (Palluault, 2003, p. 143), even though most medical students abandoned the field later in their professional careers (La Berge, 1994). In contrast, Ranvier retained his faith in microscopy, when he moved from Lyons to Paris.

The Context of Pathological Anatomy in French Medical Training

Microscopy emerged in French medical science when it was recognized as a valuable tool to classify diseases (La Berge, 2004, pp. 431–434). Donné,[3] free professor of the Faculté de Médecine in Paris, was among the first to study normal and pathological body fluids including blood, pus, and mucus (Foucault & Donné, 1844–1845). Students attracted to microscopy, including Victor André Cornil (1837–1908), Ranvier, and Louis-Charles

[2]When Ranvier was a student, the anatomy course of the Ecole de Médecine in Lyons was of high quality and attracted many students, including some from other Faculties (Bouchet, 1982, p. 40).

[3]Donné gave a private course of microscopy in Paris, 30 years before Cornil and Ranvier.

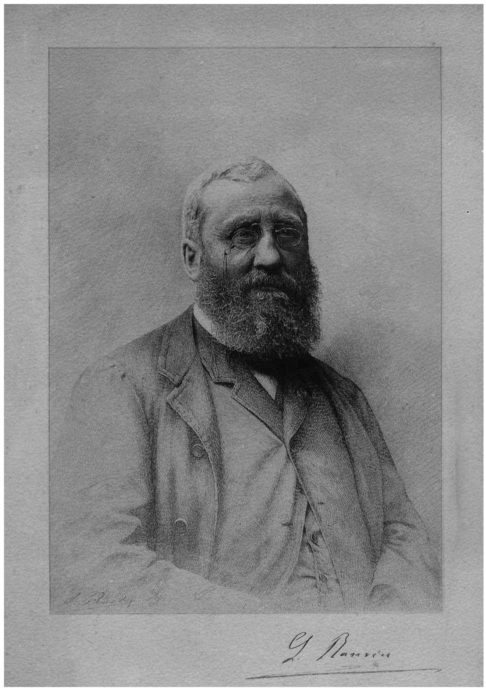


Figure 1. Louis Ranvier (1835–1922) (Courtesy of Collège de France).

Malassez (1842–1909) were often simultaneously fascinated by pathological anatomy and autopsies (Jolly, 1910).[4]

Pathological anatomy was a dominant medical discipline in France, and particularly in the internship examination (Michaut, 1899, p. 81). Léon Jean Baptiste Cruveilhier (1791–1874), its foremost French defender, was honored outside France, and Rudolf Virchow (1821–1902) considered him a major founder of the field in Europe. Therefore, students attracted to this discipline were favored to access internship.

When microscopy became popular, successful students, first attracted to microscopy as amateurs, maintained a professional interest. Among them Cornil and Ranvier met while preparing for the internship examination. They became regular members of the Société anatomique of Cruveilhier (Jolly, 1922, p. 3). This period of intense study provoked an interest leading to a continued collaboration in microscopical histopathology, after both passed the internship examination (1860) and medical thesis.

A Passion for the Microscope: The Private Course of Cornil and Ranvier

During 1860–1865, Cornil and Ranvier devoted part of their time to microscopy. Besides observing tumors and other pathological tissues, Ranvier focused on bone preparations, which led him to study cartilage and bone lesions for his medical thesis

[4]Ranvier practiced autopsies in his later career at the Collège de France. In 1871, he reported on a possible case of "lymphadénie" in a note by Louis Théophile Joseph Landouzy (1845–1917), an intern of Parisian hospitals close to Jean-Marie Charcot (1825–1893) (Landouzy, 1871).

(Ranvier, 1865). By 1865, they had started collaborating on epithelial tumors. They developed a small private laboratory on rue Christine in Paris, which soon attracted young interns, among whom were Malassez, Joseph-Louis Renaut, Georges Maurice Debove (1845–1920), and Jacques-Joseph Grancher (1843–1907). During 1866–1867, Cornil and Ranvier's one semester course in microscopy had no equivalent in France (Jolly, 1922). It ended when Ranvier agreed to join Claude Bernard at the Collège de France. This course was published in three parts, as an authoritative manual, two years later (Cornil & Ranvier, 1869, 1873, 1876). It was translated into English, with notes and additions both in England and the United States (Cornil & Ranvier, 1880, 1882). It represented a well-written and useful modern textbook for medical students interested in normal and pathological histology.

In the early 1870s, microscopical studies had gained academic recognition at the Faculté de Médecine de Paris. A chair of histology had been created in 1862 for Robin. However, according to Broca, the vast majority of French medical micrographers remained opposed to cell theory. They did not accept the concept of the cell but rather recognized the "specificity of diverse cells" meaning different histological entities should replace the German unitary concept (Canguilhem, 1952, pp. 66–67; La Berge, 2004, p. 438).

Surprisingly, the first paragraph of Cornil and Ranvier's manual clearly stated their faith in the German theory:

> Chez les êtres plus compliqués, les cellules s'entourent d'une substance intercellulaire variable pour composer des tissus et des organes dont elles sont les parties essentielles; ou bien elles sont tellement modifiées dans leur forme, qu'on aurait de la peine à les reconnaître si l'on n'avait pas assisté à leurs métamorphoses: là encore les cellules jouent le rôle principal. (Cornil & Ranvier, 1869, pp. 1–2)
>
> [In more complex animals, cells cover themselves with an intercellular substance in order to build various tissues and organs of which they represent the essential parts; or they may be so modified in their shape as to remain uneasily recognized without following their metamorphosis: here again cells play the principal role.]

This text refers to the difficulty French microscopists encountered in proving the cellular nature of a plurality of anatomical elements. Ranvier attacked Robin's opposition to cell theory and his idea of "special bone elements." Ranvier's views on cell theory encouraged him to demonstrate "bone corpuscles" as cells in the line of Virchow's studies (see Barbara, 2004). This attitude did not help his later career in the Faculté de Médecine de Paris, but Ranvier had family contacts with Bernard who looked favorably upon cell theory for theoretical reasons. Recognition of cell theory, both by Ranvier and Bernard, seemed a precursor for their future collaboration.

Dialogue Between Histology and Physiology at the College de France

From Virchow's Ideas to a Dynamical Approach of Histology in Ranvier's Studies

Ranvier was influenced by Virchow's extension of cellular theory to pathology. In Ranvier's introductions to studies on cartilage and bone, Virchow's observations are emphasized (Cornil & Ranvier, 1869, pp. 19–29; Ranvier, 1863). While Cornil further investigated pathological tissues, Ranvier focused on normal histology. He was not only concerned with cell theory but also, as a student of Bernard, with development, nutrition, and functions of normal tissues.

Ranvier learnt from Bernard how histology could serve physiology. He followed Bernard's lessons at the Collège de France: *Leçons sur les propriétés physiologiques et les altérations pathologiques des liquides de l'organisme* (Bernard, 1859), and *Leçons sur les propriétés des tissus vivants* (Bernard, 1866), both being relevant to microscopy. In the 1860s, French experimental physiology encouraged histologists to localize the function of organs at the level of tissues and cells. This physiological approach contrasted with the static descriptive histology of Robin, which refused generalization and theorizing, as practiced in German schools (see Jolly, 1922, p. 12). Ranvier was to fill in this gap between Bichat and Bernard, by adopting what Bernard would later call *experimental histology*.[5]

The Collège de France and the Ecole Pratique des Hautes Etudes were necessary institutions for the development of such original programs. Both French institutions functioned as a balance to the Faculties by favoring marginal researchers such as Ranvier. They played a dominant role in France in accepting cell theory, and fulfilled their mission in teaching new scientific ideas, while Faculties tended to teach established facts (see Bernard, 1877, pp. 23–26, p. 215). Thanks to Bernard, Ranvier settled into a small histological laboratory, founded in the Ecole Pratique des Hautes Etudes,[6] and later established in Ranvier's lodgings at the Collège de France (1867), where many of his colleagues followed his research.

Bernard and Ranvier's Conceptions of Function

Ranvier's first studies are often regarded as a synthesis between histology and physiology, since both were relevant to defining functions of organs (see Jolly, 1922, 1932; Appel, 1978). However, Bernard's and Ranvier's conceptions of function differed on the role of generalized anatomical observations used as norms in the determination of function.

The French epistemologist Georges Canguilhem (1904–1995) has analyzed some of the reasons why Bernard accepted cell theory. He emphasized how it justified experimental physiology, providing Bernard with a new organization of living organisms and escaping both materialism and vitalism (Canguilhem, 1994a). Bernard's theory defined parts both as independent units and by their relations to the organism, with function localized into *histological elements* (Bernard, 1877, p. 135). For Bernard, function could be revealed by experimental physiology, whereas histology was only concerned with localization. He discounted anatomical deductions of function, believing that cells of similar appearance could have radically different functions. Conversely, cells with different morphologies and sizes might have similar functions, a view supported by Ranvier, in his work on small and large spinal cord neurons (Ranvier, 1875a, p. 1061).

[5]Ranvier's view of experimental histology aimed at defining modes of preparations and observations before establishing new reliable and reproducible histological facts (Ranvier, 1872a).

[6]The Ecole Pratique des Hautes Etudes hosted another histological laboratory devoted to comparative zoology and associated with the "Chaire d'Anatomie Comparée du Muséum d'Histoire Naturelle" of Georges Pouchet (1833–1894). Pouchet became director of the marine laboratory at Concarneau, where Ranvier worked on torpedoes (1872–1875).

Nevertheless, Ranvier developed an apparently opposed and radical view based on his faith in assigning functions to particular cell types by histological criteria. In Bernard's view (1872), such criteria were to be established by physiology, since anatomy alone could not directly derive function. Nevertheless, Ranvier was to prove functions could be proposed by experimental histology.

> La physiologie est liée à l'histologie d'une manière si intime que la structure d'un organe étant bien connue, il est presque toujours possible d'en déduire la fonction et le mode de nutrition. (Ranvier, 1872a, p. 442)
>
> [Physiology is linked to histology in so intimate a way that, once the structure of an organ is known, its function and mode of nutrition can almost always be correctly deduced.]

Ranvier further extended this conception to tissues and cellular elements (Ranvier, 1872a, p. 443). For him, experimental histology was a way to study cellular physiology. Ranvier's studies on nerves showed he was able to follow this path and accordingly his biographer Justin Jolly (1870–1953) later defined Ranvier as a physiologist (Jolly, 1922, 1932).

Ranvier's Studies On Nerves: Where Histology Meets Physiology

For Bernard, nutrition was a general cellular function to be studied by the methods of experimental physiology[7] (Bernard, 1877, p. 85). The concept of nutrition was adopted in Ranvier's work after 1869 (Ranvier, 1869a, 1869b). His description of nerve fiber nodes was made in a search for how nutrients were continuously exchanged with the blood for nerve cell function (Ranvier, 1871a, p. 1168). Physiology had demonstrated a loss of motor nerve function by interruption of blood flow and a return to function by perfusion of oxygenated blood. An acidic reaction and a rise in temperature, noticed by Ugo Schiff (1834–1915), suggested nerve fibers might be a locus for oxygen consumption (Ranvier, 1871a, pp. 1168–1169). The question was then clear to Ranvier: what is the path for oxygen between oxygenated blood and nerve fibers? For Ranvier, the continuous and impermeable myelin sheath of nerve fibers prevented exchange of fluids and thereby nutrition. He demonstrated the point histologically showing that soluble carmine could not penetrate isolated myelinated nerve fibers (Ranvier, 1871b, p. 131). However, Ranvier showed picrocarminate could penetrate fibers, at localized sites identified as interruptions of the myelin sheath, and later marked with silver nitrate (Ranvier, 1871a, pp. 1169–1170; Ranvier, 1871b, p. 133). Ranvier had discovered what was soon called the "nœuds de Ranvier." Nodes discovered in the context of Bernard's ideas on nutrition were localized subcellular elements; Ranvier suggested they were involved in the physiological exchange of nutrients between fibers and blood. Although the function of nodes remained an open question for decades, Ranvier demonstrated experimental histology could propose hypothetical physiological functions at the level of cells and cell parts.

[7]Nutrition provided a theoretical conceptual framework providing physiological explanations as a working hypothesis. Nerve poisoning by curare was explained in Bernard's work by its toxic action on the nutrition of nerve histological elements (Bernard, 1877, p. 153).

Ranviers's Normative Histology

With the aim of correlating histological observations to physiology, Ranvier favored studies examining the loss of nervous function induced by nerve lesions (Ranvier, 1872a). According to Ranvier, nerves were surrounded by *perifascicular conjunctive tissue* and contained *intrafascicular conjunctive tissue*. For both, function was defined in the context of nutrition.[8] While the first supported blood and lymphatic vessels delivering nutrients, the second was an elastic protection against mechanical forces and a chemical barrier permitting access to nutrients by a *colloid path* (Ranvier, 1871a, p. 1171; Ranvier, 1872a, p. 443). When this latter was destroyed by lesion, Ranvier observed the effect of introducing water in the wound of a living animal. Nodes disappeared and the myelin sheath was swollen at their former sites (Ranvier, 1872a, p. 444). The effect of water therefore paralleled the loss of nerve function, and later paralysis of the nerve itself. Ranvier inferred nodes of nerve fibers were necessary for nervous conduction.

This approach was replicated in studies on nerve degeneration, where Ranvier precisely defined histological norms for nerve fiber nodes (Ranvier, 1872b). Ranvier observed a single Schwann cell with a single nucleus was located between each two successive nodes. Thus, he recognized as a norm the cellular nature of interannular segments. This led him to the first precise account of nerve degeneration, where morphological changes were noticed in Schwann cells of injured fibers, while newly formed fibers were normal (Tello, 1877–1887, Part I, p. 102). The disappearance of nodes in pathological conditions or the multiplication of nuclei in Schwann cells were deviations from a norm, which caused nerve fiber malfunction. Hence, Ranvier's work showed how histological norms, derived from minute anatomical details, could help understand loss of function in response to pathological lesions.

Ranvier's Histological Studies on Nerve Fibers: A Step to the Neuron Doctrine

Ranvier and the Polemic on Nerve Degeneration and Regeneration

After Ramón y Cajal won his Nobel Prize in 1906, reticularists continued to attack neuron doctrine, rejecting the monogenist theory that Wilhelm His (1831–1904) and Auguste Forel (1848–1931) adopted for nerve fiber neuropathological regeneration. According to reticularists, newly formed fibers could not originate in single neuroblasts, but only from chains of neuroblasts. This view, adopted by Arthur Van Gehuchten (1861–1914), a former ardent supporter of neuronism, was first developed by the French physiologist Félix Alfred Vulpian (1826–1887), contemporary to Ranvier, and later popularized by the reticularist Albrecht Bethe (1872–1954) (DeFelipe & Jones, 1991, p. 6). In the 1870s, the polemic might have seemed less relevant to nerve cells than it was in 1903, but it encouraged Ranvier to reexamine degeneration and regeneration of nerve fibers using his personal methods of staining nodes and myelin sheaths. His studies complemented prior observations by Augustus Volney Waller (1816–1870). When Ramón y Cajal finally demonstrated the full details of the monogenist

[8]Ranvier made extensive contributions to the histology of conjunctive tissues and especially conjunctive tissues of nerves (Ranvier, 1871a).

theory in various parts of the nervous system, he quoted Ranvier's work[9] as a major step towards truth.

Ranvier's research on nerve degeneration was made in the Bernardian perspective of nervous elements, seen as regulators of the activity of tissues. Sectioning nerves was believed to relieve negative nervous regulations of all sorts, including regulation of growth and development, thereby inducing morphological changes in surrounding tissues. Multiplication of nuclei in Schwann cells of injured fibers was interpreted in this way as a loss of control in cell division. Cell theory was also important in recognizing newly formed fibers originating from cellular and central parts of cut fibers. Thus, Ranvier's new histological techniques allowed observations in agreement with his heuristic theoretical background.

As a general goal, as seen in his studies on the effect of water on nerve sections, Ranvier searched for histological explanations of physiological observations. In this perspective, he adopted a mechanistic approach to explain the loss of function of degenerated fibers. Three days after section of a nerve, loss of function was correlated with multiplication of nuclei and swelling of Schwann cells. Ranvier concluded that swelling of protoplasm exerted pressure on nerve fibers, thereby preventing conduction. Nevertheless, Ranvier's approach and interpretations were sometimes contradicted. Joseph Jules Déjerine (1849–1917), and later Ramón y Cajal, contradicted Ranvier, demonstrating protoplasm invaded gaps initially formed by myelin sheath fragmentation prior to any mechanical constraint (Barbara, 2005; Ramón y Cajal, 1913, p. 70). Furthermore, his mechanical theory of nerve fiber growth along a line of least resistance[10] was similarly refuted in 1900 (see Ramón y Cajal, 1913, p. 70). However, both Ramón y Cajal and his pupil Jorge Francisco Tello Muñoz (1880–1958) were indebted to Ranvier for his remarkably precise observations. Ranvier was first to recognize fatty accumulations along Schwann cells as migrating leucocytes, which he had observed in experimental lesions of conjunctive tissue (Ranvier, 1871c, p. 124). Ranvier gave the first account of the exaggeration of node striation in living central fibers (Ramón y Cajal, 1913, p. 138). Spiral structures were described as aberrant new structures (Ramón y Cajal, 1913, p. 159).

The successes of Ranvier were intimately linked to the perfection of his techniques, including precise manipulations, careful dissociations by hand, and special uses of acids and stains (see Ranvier, 1872b, for technical details). Ranvier's use of silver nitrate reduction by light to observe nodes revealed new details of nerve fibers and surrounding cells[11] (Ranvier, 1871a, p. 1169). According to DeFelipe and Jones, the improvement of that same technique by Ramón y Cajal in 1903 was crucial in his last confrontation with reticularism (DeFelipe & Jones, 1991, p. 6). Although Ranvier did not become involved in the controversy over neuron doctrine,[12] Ramón y Cajal considered him an early monogenist, together with His and Forel.

[9]Ramón y Cajal (1913) quoted Ranvier 56 times, Waller 9 times, Vanlair, a successor of Ranvier in degeneration studies, 36 times.

[10]According to His and Ranvier, fibers contained a force enabling a continuous growth in an environment devoid of external stimuli (Ramón y Cajal, 1913, p 380).

[11]Ramón y Cajal remarked on the scientific and technical contributions of Ranvier stating: "It is only the talent of such men as Waller and Ranvier that has been able to supply the methodological deficiencies [to show the genesis, growth and evolution of the axons]" (DeFelipe & Jones, 1991, p. 16).

[12]Reticularists were mainly powerful in Germany and Italy and did not have strong influence in France and England.

Ranvier's Ideas on Nerve Cells Between Cell Theory and Neuron Doctrine

Ranvier's general aim was to recognize the cellular nature of specialized histological elements. In this perspective, he studied both bone corpuscles and cellular elements of conjunctive tissues (1869), where "plasmatic channels" for nutrition were described (Ranvier, 1869a). This study was published as a full article in the *Quarterly Journal of Microscopical Science*, the first journal entirely devoted to microscopy (Ranvier, 1869b; Ranvier, 1870).[13]

Between 1869 and 1873, Ranvier pursued his studies on conjunctive tissues from various organs, including spinal cord, where he tried to differentiate conjunctive cellular elements from nerve cells. These studies were relevant to the intimate nature of nerve cells. A debate on reticularism and anastomosis arose from questions on the relations between nerve cells and conjunctive fibers. Ranvier criticized dissociation in water by Friedrich Gustav Jacob Henle (1809–1885) and used gelatin injection in tissues to preserve histological elements (Ranvier, 1869c). Elastic fibers and cells either free or in contact with fiber bundles were recognized in conjunctive tissues (Ranvier, 1869c, p. 1482). In contrast, Otto Deiters (1834–1863) had previously described small conjunctive cells with numerous filiform endings anastomosed with neighboring nerve cells in nervous tissue (Deiters, 1865, Plate II, figs. 10, 11). However, Ranvier described bundles of fibers as containing *independent* cells of both neuronal and lymphatic origin. Ranvier showed independent nerve cells, defined following Deiters (with an axon, protoplasmic endings, and a nerve cell body), were not continuous to conjunctive tissue elements or other nerve cells (Ranvier, 1873, p. 1302). He thus opposed anastomosis and reticularism, favoring instead a meticulous definition of independent cellular elements. Between cell theory and neuron doctrine, Ranvier always carefully demonstrated independent elements in nerve centers, cooperating for nutrition and with specific functions.

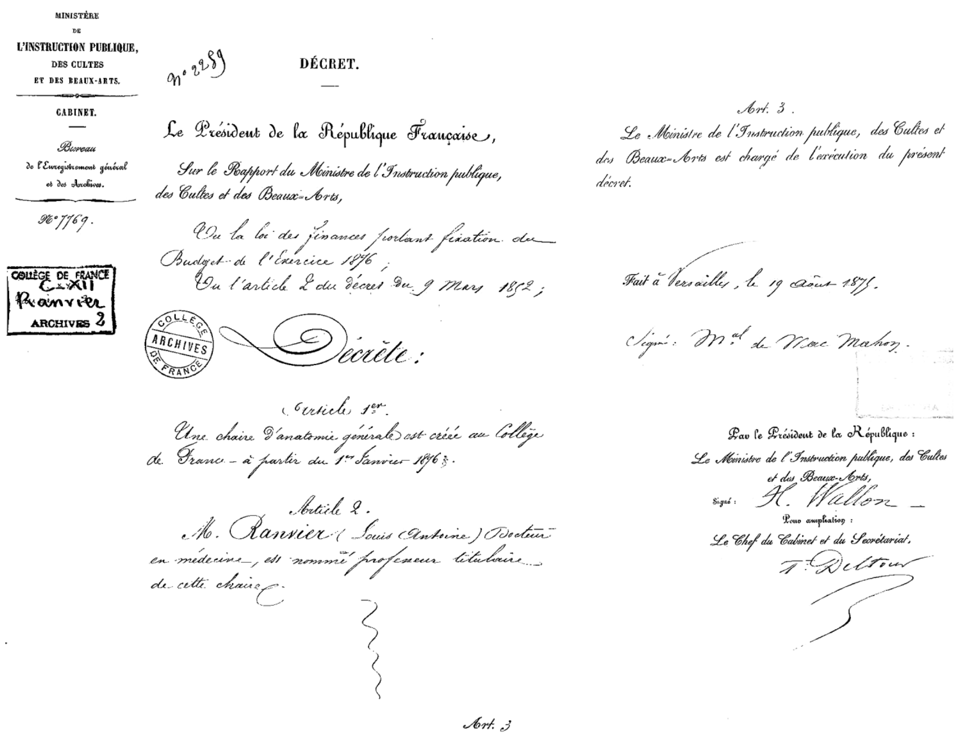
Anatomie Générale and the Question of Conduction from End-organs and Across Sensory Ganglia

During the early 1870s, Ranvier had the opportunity to work on ray and torpedo in the marine laboratory of Victor Coste (1807–1873) in Concarneau.[14] In a note of anatomie comparée, he described nodes and sheaths in the motor nerve of the torpedo's electric organ (Ranvier, 1872c). In 1875, observations on torpedo motor nerve endings were communicated by Bernard to the Académie des Sciences as being relevant to anatomie générale. This shift from comparative to general anatomy occurred in parallel with Ranvier's appointment by Bernard in 1875 to a chair of anatomie générale at the Collège de France.

Although Ranvier wrote further notes on histology and physiology, most of his subsequent papers concerned anatomie générale, previously illustrated by authors such as Robin and Virchow in the *Comtes Rendus Hebdomadaires de l'Académie des Sciences*. This turn to general anatomy was based on elegant and refined studies on the anatomical independence of nerve fiber terminals as a general refutation of fiber nets. In the notes he added to

[13]Later, Ranvier created a French equivalent of this journal, with Edouard-Gérard Balbiani (1823–1899), *Les Archives d'Anatomie Microscopique* (1897). In Germany, Max Schultze founded the *Archiv für mikroskopische Anatomie* (1865).

[14]Coste, professor at the Collège de France, founded the first marine biological station in Concarneau (1859).



MINISTÈRE DE L'INSTRUCTION PUBLIQUE, DES CULTES ET DES BEAUX-ARTS.
CABINET.
Bureau de l'Enregistrement général et des Archives.
N° 7769.

COLLÈGE DE FRANCE CLXXII Ranvier ARCHIVES 2

N° 2289

DÉCRET.

Le Président de la République Française,

Sur le Rapport du Ministre de l'Instruction publique, des Cultes et des Beaux-Arts,

Vu la loi des finances portant fixation du Budget de l'Exercice 1876 ;
Vu l'article 2 du décret du 9 Mars 1852 ;

COLLÈGE ARCHIVES DE FRANCE

Décrète :

Article 1er.
Une chaire d'anatomie générale est créée au Collège de France – à partir du 1er Janvier 1876.

Article 2.
M. Ranvier (Louis Antoine) Docteur en médecine, est nommé professeur titulaire de cette chaire.

Art. 3

Art. 3.
Le Ministre de l'Instruction publique, des Cultes et des Beaux-Arts est chargé de l'exécution du présent décret.

Fait à Versailles, le 19 août 1875.

Signé : Mal de MacMahon.

Par le Président de la République :
Le Ministre de l'Instruction publique, des Cultes et des Beaux-Arts,
Signé : H. Wallon
Pour ampliation :
Le Chef du Cabinet et du Secrétariat,

Figure 2. Decree of Ranvier's Chair of general anatomy (1876) (Courtesy of Collège de France).

his translation of the *Handbuch der Histologie und Histochemie des Menschen* by Heinrich Frey (1822–1890), Ranvier described his first studies on nerve endings in salivary gland, cornea, and skin (Frey 1859, 1871). Together with most histologists, he had been impressed by the gold chloride staining technique of Julius Cohnheim (1839–1884), which allowed unequivocal demonstrations of free nerve endings in cornea and skin (Frey, 1871, pp. 717, 735). However, Ranvier first preferred his chromic acid technique (Frey, 1871, p. 711). Only, when he succeeded in Concarneau to combine Cohnheim's technique with chromic acid, was he able to refute fiber nets in the electric organ of torpedo, previously described by Rudolf Albert von Kölliker (1817–1905), Max Schultze (1825–1874), and Franz Christian Boll (1849–1879) (Ranvier, 1875b). Ranvier's success in this field was based not only on his use of refined staining procedures but also on new immersion objectives, such as number 12 of Hartnack and Prazmowski, which allowed a magnification of x1000[15] (see Ranvier, 1875a, p. 789). Furthermore, the technique of Joseph von Gerlach (1820–1896) enabled Ranvier to visualize branching fibers, prior to endings, similar to a chiasma.[16]

Ranvier's move to general anatomy, which led him to a chair at the Collège de France, (Fig. 2), was possible after he could reproduce his general observations on nerve fiber terminals in various structures. Following Franz von Leydig (1821–1908) and Friedrich

[15]Hartnack and Prazmowski from Paris produced in 1867 a new water-immersion objective of 1/12th inch (No. 9) and 1/21th inch (No. 12). Previous studies on torpedo were performed when first immersion objectives were being developed by Tolles and Hartnack.

[16]"L'Image d'un Chiasma de Fibrilles" (Ranvier, 1875b).

Sigmund Merkel (1845–1919), he made a precise study of Grandy's tactile end organs of the papillæ of the beak and tongue of the duck (Ranvier, 1877). Ranvier described a disk-like nerve ending similar to Merkel's tactile disk, occurring in the epidermis of the pig's snout. The generalization of these finding to tactile end organs of skin, cornea, and smooth muscle was published as *Leçons d'Anatomie Générale* and *Leçons sur l'histologie du système nerveux* (Ranvier, 1878b, 1881). Similarly, Ranvier demonstrated free nerve endings in his studies on smooth muscle.

However, Ranvier's conception of nerve plexi was far more complex. The existence of free endings was not for Ranvier a radical argument against fiber nets, which according to him did occur in some preparations before nerve fibers ended. Ranvier's careful examination of plexi required an improvement of Cohnheim's and Löwit's techniques, replacing formic acid with lemon juice. Ranvier's method was published as a novel contribution to the *Quarterly Journal of Microscopical Science* (Ranvier, 1880b). Plexi were demonstrated as small peripheral nerve centers in particular tissues. They were suggested to mediate nonvoluntary movements, as in the mammalian oesophagus and arthropod's digestive tract (Ranvier, 1878a, p. 1144; Ranvier, 1879, p. 1088). Thus, Ranvier was also concerned with the functional significance of plexi, which he felt represented terminal arborizations of single fibers.

Using this approach, Ranvier came to a major discovery, while examining another minute nervous structure. Observations made from 1870 to 1875 in studies of different ganglia, with the aim to find a common internal structure, led to the discovery of the T structure[17] of nerve fibers from sensory ganglion cells (Ranvier, 1875c). He concluded that nervous conduction in sensory and motor neurons should not be seen as linear chains. Although Ranvier could not ascribe a direction to the circulation of nervous impulses in T structures, he suspected complex fiber branching might occur in nerve centers and modify current views on their physiology.

These studies portray Ranvier as a rather pragmatic scientist, more concerned with facts and precise descriptions of histological elements with refined techniques than with new ideas on the nervous system. While some of his observations were relevant to the neuron doctrine, Ranvier did not participate in the polemic, but rather he founded French general anatomy as a joint anatomical and histological discipline.

The Significance of Ranvier's Career and His Contribution to General Anatomy in France

Ranvier's Career in the International Context

While he gained limited international recognition, Ranvier should be remembered for three major achievements. Certainly, he lives on as the discoverer of the "nœuds de Ranvier." His and Arthur Van Gehuchten (1861–1914) paid tribute to Ranvier's first observation of T structures of fibers from dorsal root ganglion cells (see Shephered, 1991, p. 108; Van Gehuchten, 1897, p. 210). Ranvier was honored by Ramón y Cajal for his precise description of nerve fiber degeneration and regeneration (see Ramón y Cajal, 1913). Besides, he was also respected for his talented teaching on histological techniques (see Fernandez & Breathnach, 2001; Ranvier, 1875a). In particular, Ramón y Cajal paid tribute to Ranvier's manual, referred to as his "technical bible of those days [1887]" (Ramón y Cajal, 1917, p. 307). When speaking of the preparation for his competitive exams in 1879 he wrote:

[17]See note 1.

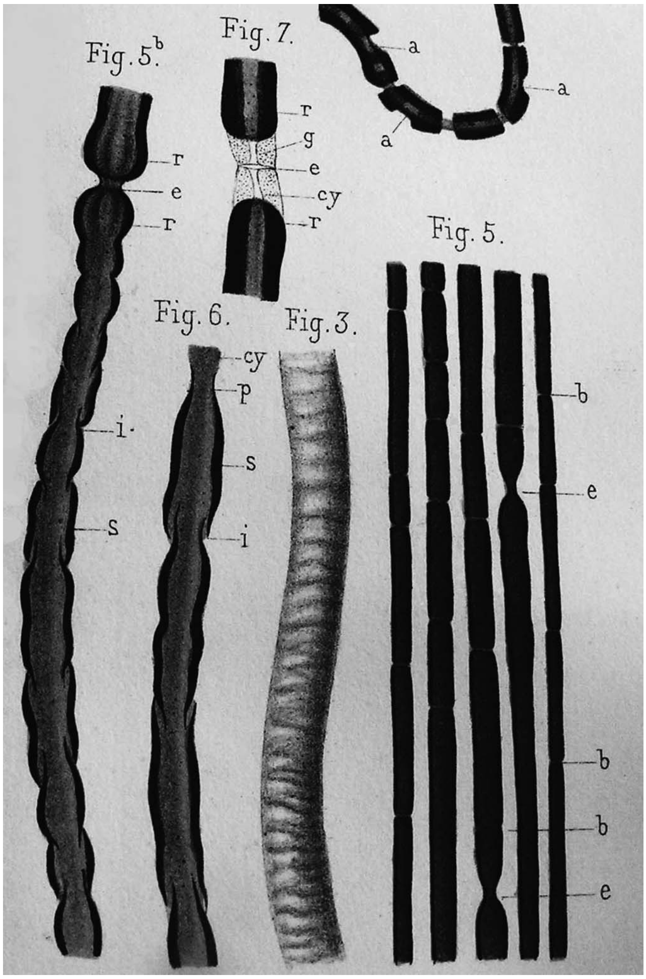


Figure 3. Sciatic nerve tubes fixed in osmic acid (1%) when physiologically extended. Dissociation was made in water. A whole sciatic nerve is shown as seen with a magnifying glass (fig. 3). Other figures show nerve tubes observed through a microscope, (a) neck when "Schwann's membrane" is removed, (b) incision provoked by myelin retraction, (cy) "axis cylinder" (flowing out in fig. 6), (e) "étranglement annulaire," "annular constriction," or "node of Ranvier," (g) granular mass, (p) thinning of "cylindroconical segment" on axis cylinder's surface, (r) terminal nerve tube bulge (bulges are extended in fig. 7), (s) "cylindroconical segment." Reprinted from Ranvier (1878b, Plate I, volume 1).

> Conscious of my defects, I had endeavored to overcome them so far as possible. I perfected myself in histological technique, using as a guide the admirable book entitled *Manuel technique d'histologie*, written by Ranvier, the illustrious professor at the Collège de France. (Ramón y Cajal, 1917, p. 255)

In contrast to his teaching manuals, which were widely translated, Ranvier's research was little known and quoted in the specialized international literature. Ranvier's nodes and

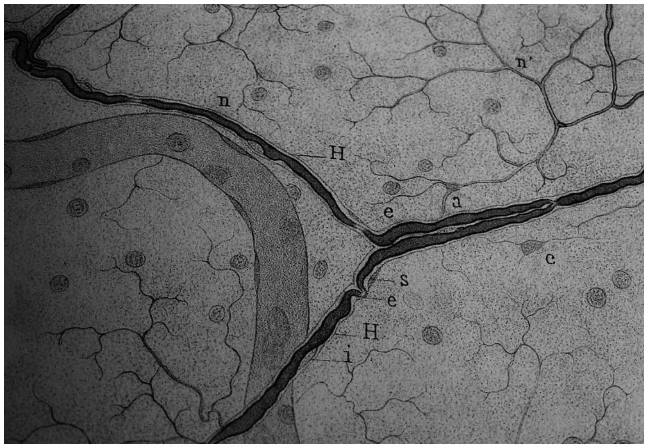


Figure 4. Ventral side of electric organ of torpedo after injection of osmic acid (2%) and maceration for 24 hours. A blood capillary is shown with red and white blood cells, (a) recurrent ramifications from a myelin nerve tube, (c) "stellate cell" of "muquous tissue" between "electrical lamellae", (e) "annular constriction" or "node of Ranvier," (H) secondary sheath, (i) nucleus of "interannular segment," (n) nerve tube with myelin, (n') second-order nerve fibers with no myelin, (s) nucleus of secondary sheath. Reprinted from Ranvier (1878b, Plate IV, volume 2).

T structures were generally described as anatomical details, without mention of his observations. Similarly, his studies on nerve fiber degeneration and regeneration were only properly recognized many years later (Ramón y Cajal, 1913). The functional significance of both observations was not fully appreciated at the time of Ranvier's work. Today, Ranvier's nodes and the study of axon regeneration are two fascinating and active fields of inquiry (Clark et al., 2005; Ishibashi et al., 2003; Sherman & Brophy, 2005).

Another reason for the relative obscurity of Ranvier's research was that it was published in French journals, and never as translated treatises. His published lessons, primarily devoted to students, were also little read and quoted by experts. Although, Ranvier was known as an eminent professor in histological techniques, his rough personality and the tedious nature of his lectures did not encourage foreign medical students. However, Luis Simaro Lacabra (1851–1921) attended Ranvier's lessons, where he learnt Golgi's method, which he later demonstrated to Ramón y Cajal in Madrid (Fernandez & Breathnach, 2001). Thus, Ranvier's influence was rather limited to a small circle of French histologists, to colleagues at the Salpêtrière hospital (Barbara, 2005), and to foreign students and colleagues praising his techniques, on which Ramón y Cajal commented:

> In my systematic explorations through the realms of microscopic anatomy [. . .] I examined [the Nervous System] eagerly in various animals, guided by the books of Meynert, Huguenin, Luys, Schwalbe, and above all the incomparable works of Ranvier, of whose ingenious technique I made use with conscientious determination. (Ramón y Cajal, 1917, p. 304)

Ranvier's influence in these circles was significant. He inspired the development of pathological histology, histophysiology, and the introduction of neuron doctrine in France.

Ranvier's Personal Research Style and the Re-foundation of General Anatomy in France

A major reason that Ranvier was not recognized as a leading international neurohistologist at the turn of the twentieth century probably lies in his personal research style and interest in general anatomy, which developed at the fringes of cell theory and the neuron doctrine. These theories were aimed at generalizing the fundamental concepts of the cell and the neuron. In contrast, Ranvier focused primarily on defining cell types by the analytical approach of describing their constituents, in a cellular histophysiological perspective.

Perhaps Ranvier's style should be interpreted as a new means to adapt both Bichat's and Bernard's theoretical views to microscopical histology. This approach finally led him to general anatomy, which aimed to interpret tissues and cells of a same type as analogous structures composed of specific elements, and suggesting insights into their function. This approach relied on Ranvier's interest in subcellular elements, such as nodes, T structures, sheaths, and fibrils, and also in decomposing structures by soft dissociations, often in living tissues, rather than studying the topography of fixed-tissue slices. Ranvier's histology was thus methodologically totally opposed to the mainstream neurohistology of the time, as practiced in topographical studies on nerve centers by Van Gehuchten, Edward Klein (1844–1925), Heinrich Obersteiner (1847–1922), and Ramón y Cajal. Rather, it was relevant to microscopic studies devoted to understanding the function of single-cell types, which became increasingly numerous at the turn of the twentieth century.[18]

The theoretical foundation of Ranvier's career can be traced to Bichat's and Bernard's texts published before Ranvier started his career. It is particularly striking to note that Ranvier's research interests in the 1870s covered those main points of the general anatomy of the nervous system summarized in Bernard's lesson on January 14, 1857 (Bernard, 1858). Bernard emphasized nerve constituents and envelopes, which Ranvier studied both at the level of nerves and nerve cells.[19] Bernard next discussed ganglion cells, quoting Robin's study of bipolar cells, a work Ranvier pursued to the discovery of T structures. Bernard's lesson then described touch corpuscles and their nerve fiber endings and finally examined the degeneration and the heterogenous matter of nerve fibers. These were later Ranvier's main subjects of research. Bernard's aim was to discuss "les détails anatomiques généralement admis" on which Ranvier based his research style. Bernard's influence on Ranvier's physiological style also extended to the definition of an analytical approach to the nervous system, directly aimed at physiology.

This perspective was largely shared by Bichat, considered the founder of general anatomy in France (Bichat, 1801; Canguilhem, 1994b). Bichat's "anatomical analysis" focused on organs and elementary tissues observed with the naked eye (see Flourens, 1858). Bichat aimed at examining different tissues of the same type, focusing on their general characters and seeking to illuminate how they assembled and collaborated to perform

[18]Studies on the intimate structure and role of muscle fibers in contraction and studies on the function of blood elements, such as thrombocytes, based on their intracellular constituents are two typical examples, taken from Laguesse (1902).

[19]Myelin sheaths, nerve sheaths, as the "lamellar sheath of Ranvier" cited by Ramón y Cajal, and Ranvier's "intrafascicular connective tissue."

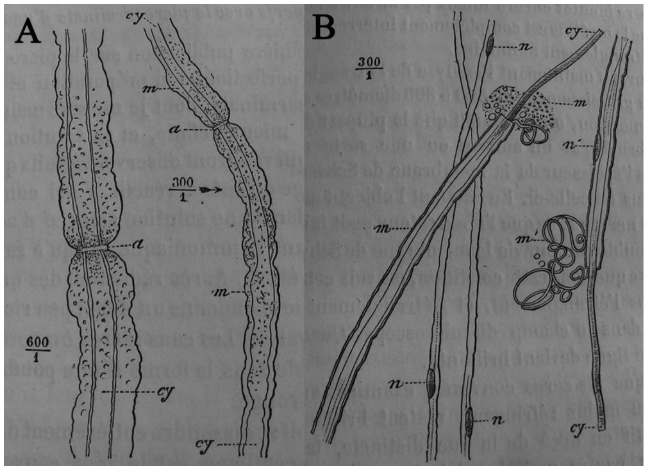


Figure 5. Large sciatic nerve tube dissociated in picrocarminate ammonium (1%). Tubes were drawn after one hour incubation. (A) Axis cylinder is stained in red near annular constriction, indicating picrocarminate penetrates the nerve tube at this level. Staining is illustrated by dots, x600 magnification. (B) Axis cylinder and myelin flow outside the sheath. Red picrocarminate staining is indicated by hatched lines. Picrocarminate stains the extruded axis cylinder and invades the inner portion of the nerve tube, showing myelin is impermeable to picrocarminate. (a) "annular constriction" or "node of Ranvier," (cy) "axis cylinder" stained, (m) myelin, (n) nucleus of "interannular segment." Adapted from Figures 1 and 2 from Ranvier (1872a).

a common function into specific organs.[20] This is basically the approach Ranvier adopted at a lower scale.

Both Bichat and Bernard believed general anatomy was relevant to physiology. The full title of Bichat's treatise was *Anatomie Générale Appliquée à la Physiologie et à la Médecine* (Bichat, 1801). The teaching of Ranvier at the chair of anatomie générale was a natural extension of Bernard's chair of medicine. However, he greatly extended Bichat's and later Robin's concept of generality from the level of tissues to that of their constituents (see Papillon, 1829). The generality of the cell was taken as an established theory, enabling Ranvier to describe analogous cell types in related tissues, their general parts, and relations with other cells. In contrast to most of his German counterparts, Ranvier's normal histology did not center on human tissues. Instead, using multiple simpler animal preparations, Ranvier studied single cells, their parts, functions, and pathological disorders. As a cellular histophysiologist, Ranvier was trained to localize anatomical details in the structures he studied, always with an eye on their possible function.

[20]Pierre Augustin Béclard (1785–1825), a French anatomist and surgeon, described Bichat's method: "L'anatomie générale considérant ensemble les organes semblables par leur texture, et se bornant à ce qu'ils ont de commun ou de générique, a pour objet spécial, mais non unique, leur texture" [General anatomy, grouping related organs by their texture and only considering what they share in common or as generic, focuses primarily on texture] (Béclard, 1827).

Ranvier's approach has often been neglected by some neuroscience historians, perhaps due to his physiological research style he followed in the 1870s and the 1880s. Ranvier was scarcely involved in the history of the neuron doctrine, since he simply defined a nerve cell as a cell body with continuous contacts with nerve fibers and neglected Golgi's method for its unreliability (Ranvier, 1875a, p. 1062). While he certainly recognized the beauty of silver chromate deposits, he felt the technique could not reliably demonstrate relations between nerve cell processes and nerve fibers (Ranvier, 1875a, p. 1097). In retrospect, a convincing demonstration of contiguity between neurons did not emerge before the advent of electron microscopy. In these respects, Ranvier was a typical French figure, in the line of Magendie and Bernard, more concerned to rectify outdated theories and ideas and to construct histology as a new discipline on a solid base of unquestionable facts, derived by a rigorous experimental approach.

Ranvier's School in France

Ranvier's style of research and scientific contributions were greatly honored in France. Mathias Duval (1844–1907), successor of Robin to the chair of histology at the Faculté de Médecine of Paris, and later biologist Maurice Caullery (1868–1958) both recognized Ranvier's role in the great renewal of anatomy after Robin[21] (Caullery, 1941, p. 162; Duval, 1900, p. 14).

Ranvier was not alone in his enterprise and shared close relations with several colleagues, who later obtained academic positions. His lifelong colleague Cornil became professor of pathological anatomy at the Faculté de Médecine in Paris. Charles Rouget (1824–1904), a former student of Bernard, shared interests in histology with Ranvier[22] and became professor of physiology at the Université de Montpellier. Edouard-Gérard Balbiani (1823–1899), who came to histology in the Bernardian circle, was asked to direct a histological research laboratory at the Muséum d'Histoire Naturelle. He held the chair of embryology at the Collège de France (1874) and founded, with Ranvier, *Les Archives d'Anatomie Microscopique* (1897).

Ranvier's most famous students were Louis-Félix Henneguy (1850–1928), Joseph Louis Renaut (1844–1917), and Malassez. Malassez became director of the histological laboratory of the Collège de France. Renaut created a prolific school of histology in Lyons. Henneguy obtained a chair of embryology at the Collège de France. Justin Marie Jolly (1870–1953) and Jean Nageotte (1912–1937) were two later successors of Ranvier. Both obtained chairs at the Collège of histophysiology and comparative histology, respectively.[23] Ranvier's influence in France was immense. Since 1870, a single French histological school was competing after the transfer in Nancy of the Faculté de Médecine de Strabourg.[24] We should remember Ranvier as a major founder of modern French histology, anatomie générale, and as a remarkable and original scientist of his time.

[21]Robin was increasingly reluctant to adopt new techniques and developed erroneous theoretical conceptions, which progressively paralyzed the evolution of Parisian histology.

[22]Especially anatomo-physiological correlations in muscle fibers, nerve endings, and retina.

[23]Other names related to Ranvier include E. Laguesse, Cl. Regaud, A. Policard.

[24]Among members of this faculty were Dominique Auguste Lereboullet (1804–1865), Emile Kuss (1815–1871), Charles Morel (1822–1884), and Duval.

References

Appel TA (1978): Louis Ranvier. In: Gillispie CC, ed., *Dictionary of Scientific Biography*. New York, Scribner's Sons.

Barbara JG (2004): Les étranglements annulaires de Louis Ranvier (1871). *Lettre des Neurosciences 28*: 3–4.

Barbara JG (2005): Louis Antoine Ranvier (1835–1922). *Journal of Neurology* (in press).

Béclard PA (1827): *Elémens d'anatomie générale ou description de tous les genres d'organes qui composent le corps humain*. Paris, Béchet jeune.

Bernard C (1858): *Leçons sur la physiologie et la pathologie du système nerveux*. Tome I. Paris, Baillière.

Bernard C (1859): *Leçons sur les propriétés physiologiques et les altérations pathologiques des liquides de l'organisme*. Paris, Baillière.

Bernard C (1866): *Leçons sur les propriétés des tissus vivants*. Paris, Cours de médecine du Collège de France.

Bernard C (1872): De la physiologie générale. In: *La science expérimentale*. Paris, Baillière.

Bernard C (1877): *Principes de médecine expérimentale*. Paris, PUF.

Bichat X (1799): *Traité des membranes*. Paris, Richard, Caillé et Ravier.

Bichat X (1801): *Anatomie générale appliquée à la physiologie et à la médecine*. Paris, Brosson, Gabon.

Bouchet A (1982): Histoire de l'anatomie à Lyon. In: Ollier L, ed., *Conférences d'histoire de la médecine, cycle 1981–1982*. Lyon, Fondation Mérieux.

Canguilhem G (1952): *La Connaissance de la vie*. Paris, Hachette.

Canguilhem G (1994a): *Etudes d'Histoire et de Philosophie des Sciences*. Paris, Vrin.

Canguilhem G (1994b): Claude Bernard et Bichat. In: Canguilhem G, ed., *Etudes d'Histoire et de Philosophie des Sciences*. Paris, Vrin.

Caullery M (1941): Les Sciences biologiques dans la France contemporaine. In: *La France et la civilisation contemporaine*. Bibliothèque de Philosophie scientifique. Paris, Flammarion.

Clark BA, Monsivais P, Branco T, London M, Hausser M(2005): The site of action potential initiation in cerebellar Purkinje neurons. *Nature Neuroscience 8*:137–139.

Cornil V, Ranvier L (1869): *Manuel d'histologie pathologique*. Paris, Baillière.

Cornil V, Ranvier L (1873): *Manuel d'histologie pathologique*. Paris, Baillière.

Cornil V, Ranvier L (1876): *Manuel d'histologie pathologique*. Paris, Baillière.

Cornil, V, Ranvier L (1880): *A Manual of Pathological Histology*. Translated and with notes and additions by Shakespeare EO and J Henry C. Philadelphia, Henry Lea.

Cornil, V, Ranvier L (1882): *Manual of Pathological Histology*. Translated by Hart AM. London, Smith, Elder & Co.

DeFelipe J, Jones EG (1991): *Cajal's Degeneration and regeneration of the Nervous System*. Oxford, Oxford University Press.

Deiters OFK (1865): *Untersuchungen über Gehirn und Rückenmark des Menschen und der Säugetiere*. Braunschweig, Vieweg.

Duval M (1900): *Précis d'Histologie*. Paris, Masson.

Fernandez N, Breathnach CS (2001): Luis Simarro Lacabra [1851–1921]: From Golgi to Cajal through Simarro, via Ranvier? *Journal of the History of the Neurosciences 10*:19–26.

Flourens P (1858): *De la vie et de l'intelligence*. Paris, Garnier frères.

Foucault L, Donné A (1844–1845): *Cours de microscopie complémentaire des études médicales. Anatomie microscopique et physiologie des fluides de l'économie*. Paris, Baillière.

Frey H (1859): *Handbuch der Histologie und Histochemie des Menschen*. Leipzig, Verlag von Wilhelm Engelmann.

Frey H (1871): *Traité d'histologie et d'histochimie*. Translated from the German third edition by Spillmann P, with notes and one appendix by Ranvier. Paris, Savy.

Ishibashi T, Ikenaka K, Shimizu T, Kagawa T, Baba H (2003): Initiation of sodium channel clustering at the node of Ranvier in the mouse optic nerve. *Neurochemical Research 28*:117–125.

Jolly J (1910): Notice sur la vie et les travaux de Louis Malassez. *Comptes-Rendus de la Société de Biologie 68*: 1–18.

Jolly J (1922): Louis Ranvier (1835–1922): Notice biographique. *Archives d'Anatomie Microscopique 19*: 1–72.

Jolly J (1932): Ranvier et la méthode expérimentale. In: Abel Lefranc, ed., *Le Collège de France, 1530–1930, livre jubilaire composé à l'occasion de son quatrième centenaire*. Paris, Presses universitaires de France.

Kölliker A (1856): *Éléments d'histologie humaine*. Translated by MM. J. Béclard and M. Sée, revised by the author. Paris, Masson.

La Berge A (1994): Medical microscopy in Paris, 1830–1855. In: La Berge A, Feingold M, eds., *French medical culture in the XIXth century*. Amsterdam, Rodopi.

La Berge A (2004): Debate as scientific practice in nineteenth-century Paris: The controversy over the microscope. *Perspectives on Science: Historical, Philosophical, Social 12*: 424–453.

Laguesse E (1902): Revue anuelle d'anatomie générale. *Revue générale des sciences pures et appliquées 13*: 1088–1099.

Landouzy TJ (1871): Lymphadénie cutané. Mycosis fongoïde. *Comptes-Rendus de la Société de Biologie 23*: 184–185.

Michaut P (1899): *Pour devenir médecin*. Paris, Reinwald et Schleicher.

Michel P (1856): Du microscope et de ses applications à l'anatomie pathologique, au diagnostic et au traitement des maladies, *Mémoires de l'Académie de Médecine 21*: 241–442.

Palluault F (2003): *Medical Students in England and France, 1815–1858. A Comparative Study*. D. Phil, Oxford.

Papillon F (1829): L'Anatomie Générale et les travaux de M. Charles Robin. *Revue des deux mondes 88*: 330–361.

Ramón y Cajal S (1913): *Estudios sobre la Degeneración y Regeneración del Sistema Nervioso*. Vol. 1. *Degeneración y Regeneración de los Nerviosos*. Vol. 2. *Degeneración y Regeneración de los Centros Nerviosos*. Madrid, Moya. English translation by May (1928), Oxford, Oxford University Press, *Degeneration and regeneration of the Nervous System*. New edition (1991), *Cajal's Degeneration and regeneration of the Nervous System*, DeFelipe J & Jones EG, eds., *Cajal's Degeneration and regeneration of the Nervous System*. Oxford, Oxford University Press.

Ramón y Cajal S (1917): *Recuerdos de mi vida, historia de mi labor científica*. Madrid, Moya. English translation by Craigie and Cano (1937), *Recollections of my life*. American Philosophical Society memoirs, VIII, Philadelphia, University of Philadelphia. New edition (1989) Cambridge, Mass, MIT Press.

Ranvier L (1863): De quelques modes de préparation du tissus osseux. *Journal de Physiologie de l'Homme et des Animaux 6*: 549–553.

Ranvier L (1865): *Considérations sur le développement du tissu osseux et sur les lésions élémentaires des cartilages et des os*. Thèse inaugurale. Paris.

Ranvier L (1869a): Des cellules et des noyaux tubulaires des tendons. *Comptes Rendus de l'Académie des Sciences 68*: 274–276.

Ranvier L (1869b): Des éléments cellulaires des tendons et du tissu conjonctif lâche. *Archives de Physiologie 2*: 471–487.

Ranvier L (1869c): Des cellules du tissu conjonctif. *Comptes Rendus de l'Académie des Sciences 68*: 1478–1479.

Ranvier L (1870): On the cellular elements of tendons and of loose connective tissue. *Quarterly Journal of Microscopical Science 10*: 367–380.

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

Ranvier L (1871b): Séance du 11 novembre. *Comptes-Rendus de la Société de Biologie 23*: 130–134.

Ranvier L (1871c): Des lésions du tissu conjonctif lâche (tissu cellulaire) dans l'œdème. *Comptes Rendus de l'Académie des Sciences 73*: 124–126.

Ranvier L (1872a): Recherches sur l'histologie et la physiologie des nerfs. *Archives de Physiologie Normale et Pathologique 4*: 129–149, 427–446.

Ranvier L (1872b): De la dégénérescence des nerfs après leur section. *Comptes Rendus de l'Académie des Sciences 75*: 1831–1835.

Ranvier L (1872c): Des étranglements et des segments interannulaires chez les Raies et les Torpilles. *Comptes Rendus de l'Académie des Sciences 75*: 1129–1132.

Ranvier L (1873): Sur les éléments conjonctifs de la moelle épinière. *Comptes Rendus de l'Académie des Sciences 77*: 1299–1302.

Ranvier L (1875a): *Traité technique d'histologie*. Paris, Savy, 1875.

Ranvier L (1875b): Sur les terminaisons dans les lames électriques de la Torpille. *Comptes Rendus de l'Académie des Sciences 81*: 1276–1278.

Ranvier L (1875c): Des tubes nerveux en T et de leurs relations avec les cellules ganglionnaires. *Comptes Rendus de l'Académie des Sciences 81*: 1274–1276.

Ranvier L (1877): De la terminaison des nerfs dans les corpuscules du tact. *Comptes Rendus de l'Académie des Sciences 85*: 1020–1023.

Ranvier L (1878a): De la méthode de l'or et de la terminaison des nerfs dans le muscle lisse. *Comptes Rendus de l'Académie des Sciences 86*: 1142–1144.

Ranvier L (1878b): *Leçons sur l'histologie du système nerveux*. Paris, Savy.

Ranvier L (1879): Recherches expérimentales sur la signification physiologique du plexus nerveux terminal de la cornée. *Comptes Rendus de l'Académie des Sciences 88*: 1087–1089.

Ranvier L (1880a): Nouvelles recherches sur les organes du tact. *Comptes Rendus de l'Académie des Sciences 91*: 1087–1089.

Ranvier L (1880b): On the terminations of nerves in the epidermis. *Quarterly Journal of Microscopical Science 20*: 456–459.

Ranvier L (1881): Terminaisons nerveuses sensitives; cornée. In: *Leçons d'anatomie générale faites au Collège de France*. Paris, Baillière.

Robin, CP (1849): *Du Microscope et des injections dans leurs applications à l'anatomie et à la pathologie*. Paris, Baillière.

Robin, CP (1854): *Sur un nouveau microscope approprié aux besoins des démonstrations anatomiques et permettant à plusieurs personnes d'observer ensemble*. Paris, Thunot.

Robin, CP (1856): *Mémoire sur les objets qui peuvent être conservés en préparations microscopiques transparentes et opaques, classés d'après les divisions naturelles des trois règnes de la nature*. Paris, Baillière.

Shepherd GM (1991): *Foundation of the neuron doctrine*. Oxford, Oxford University Press.

Sherman DL, Brophy PJ (2005): Mechanisms of axon ensheathment and myelin growth. *Nature Reviews Neuroscience 6*: 683–690.

Tello JF (1877–1887): Cajal y su labor histológica. In: DeFelipe J & Jones EG (1991), eds., *Cajal's Degeneration and regeneration of the Nervous System*. Oxford, Oxford University Press.

Van Gehuchten A (1897): *Anatomie du système nerveux de l'homme: leçons professées à l'université de Louvain*. Louvain, Uystpruyst-Dieudonné.

Virchow R (1858): *Die Cellularpathologie in ihrer Begründung auf physiologische und pathologische Gewebelehre*. Berlin, Hirschwald.