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Louis Antoine Ranvier (1835–1922)

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Louis Antoine Ranvier was the most prominent French histologist of the late 19th century. He held the chair of General Anatomy at the Collège de France (1875), thanks to his master Claude Bernard. Ranvier's refined histological techniques and precise observations on normal and injured nerve fibres were soon recognised worldwide as classic work. Although Ranvier was not a clinician, nor primarily interested in pathology, his *"Traité technique d'histologie"* (1875) [1] and observations on fibre nodes and the degeneration and regeneration of cut fibres had a great influence on Parisian neurology at the Salpêtrière.

Ranvier was born in Lyon and obtained the 'internat' of Parisian hospitals with his friend Victor André Cornil (1837–1908). They gave private histopathology lessons in the rue Christine in Paris, which were later published as a *"Manuel d'histologie pathologique"* (1869, 1873, 1876) [2]. Ranvier abandoned pathological studies, when in 1867 he became an assistant of Claude Bernard (1813–1878). The discovery of gaps in sheaths of nerve fibres (soon afterwards called nodes of Ranvier), in the context of Bernard's physiology, led Ranvier to careful histological examination of myelin sheaths and Schwann cells [3]. However, besides his major research interests, Ranvier occasionally collaborated with colleagues (such as L. T. J. Landouzy) on autopsies and histological observations of tumours and injured tissues. In 1872–1873, Ranvier combined both subjects, when he provided a precise description of the degeneration of cut fibres. Ramón y Cajal later thus commented on the scientific and technical contributions of Ranvier: *"It is only the talent of such men as Waller and Ranvier that has been able to overcome the methodological deficiencies (to show the genesis, growth and evolution of the axons)"* [4].

Ranvier confirmed the findings of Augustus Waller (1816–1870) on the degeneration of nerve fibres separated from the centre, but refuted those of Vulpian on the autogenous repair of cut peripheral fibre endings. Félix Alfred Vulpian (1826–1887), a former student of Jean-Pierre Marie Flourens (1794–1867), was an anatomopathologist, clinician and experimenter at the Salpêtrière, with the clinician Jean-Martin Charcot (1825–1893). In his experiments Vulpian observed the development of frog embryo tails isolated from the body and he regarded nutrition, multiplication and differentiation of cellular elements as vital phenomena that were preserved in injured and isolated tissues. Ranvier's studies on the degeneration of nerve fibres (1872–1873) led Vulpian to change his views after

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1873 [5, 6], especially in the interpretation of a gain of motor function of a cut nerve, which he then explained by an anastomosis with adjacent nerves. Although Vulpian adopted most of the views of Ranvier, he persuaded his assistant Joseph Jules Dejerine (1849–1917) to re-examine the role of nuclear swelling of Schwann cells with nerve fibre loss of function [7]. In this matter, Dejerine was able to refute Ranvier's hypothesis using Ranvier's own techniques to show that a direct histochemical modification in the molecular substance of the axon was involved. This study clearly showed the interest of the Sâlpétrière group in Ranvier's studies at the Collège de France.

Charcot and Vulpian's histological observations led to the description of multiple sclerosis ('sclérose en plaques'). This also contradicted Waller's law, since nerve fibre lesions were not associated with anterograde nerve fibre degeneration. Again, Vulpian persuaded a young assistant, Joseph Jules Babinski (1857–1932), to re-examine this problem with Ranvier's techniques, in Cornil's laboratory, after Cornil had replaced Charcot in the chair of pathological anatomy at the Faculté de Médecine in 1882. Babinski demonstrated that multiple sclerosis could not be taken as an exception to Waller's law, because demyelination did not involve a major loss of axons' integrity [8]. Ranvier's observations also led Babinski to contradict Charcot's theory on the genesis of sclerosis. Charcot explained myelin loss, first demonstrated by Frommann (1864), as a passive process, with inflammatory neuroglia exerting pressure on myelin. However, Babinski noticed myelin fragmentation was similar to that observed by Ranvier in the proximal stump of cut fibres, and involved lymphatic cells absorbing myelin particles. In other forms of sclerosis ('sclérose systématique'), Babinski noticed secondary degeneration and histological characteristics identical to those described by Ranvier, in the peripheral segment of cut fibres. Similarly, Babinski unequivocally adopted Ranvier's view on regeneration: *"The sprouting of central axon-cylinders was demonstrated by Ranvier with indisputable proof and the subject bears no discussion"* [8].

Ranvier's influence on neuropathology at the Sâlpétrière is unquestionable. When Vulpian and Charcot began their anatomopathological studies (1862), histological observations on fresh and fixed tissues were rather unsophisticated. The first chair of histology in France was created for Charles Robin (1821–1885) in the same year, at the Faculté de Médecine of Paris. Histology was not a technique beloved by French medical scholars and any role in the definition of diseases was highly suspect. However, a small histological laboratory was established in a disused kitchen at the Sâlpétrière, around 1875. Dejerine and Babinski recognised the limits of histological techniques used by Charcot and Vulpian. In this context, Ranvier's papers were highly praised, including numerous technical notes in *'Les Archives de Physiologie'*, created (1868) and edited by Brown-Séquard, Charcot, and Vulpian. His technical improvements were rapidly adopted by young histopathologists looking for novel interpretations of previously described diseases.

Nevertheless, as mentioned earlier, Ranvier first opposed the views of Charcot and Vulpian about the degeneration and regeneration of nerve fibres. Although Vulpian's respectful pupil Dejerine rarely quoted Ranvier's work, in his paper refuting one of Ranvier's observations, he attached great value to Ranvier's findings [7]. Cornil, one of Charcot's first interns and lifelong friend, played a major role in diffusing Ranvier's techniques and probably influenced Babinski's adoption of them in his thesis on multiple sclerosis (1885) [8]. When in 1894 Babinski wrote a chapter on *'Névrites'* in the *'Traité de médecine'*, edited by Charcot, Bouchard and Brissaud [9], the first part was devoted to experimental neuritis, where Ranvier's observations played a major role. In this sense, Ranvier's career forms part of French neurology at the Sâlpétrière. His work on injured fibres formed the basis of many subsequent observations and progress in understanding nerve fibre lesions, in a variety of diseases. While French neurology may not have shared the histological tradition developed in Germany and England, Ranvier's influence helped to make up for lost time.

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