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Interplay between scientific theories and researches on the diseases of the nervous system in the nineteenth-century, Paris

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Abstract
In this paper, my aim is to understand the origin of experimental and scientific models of pathogeny of the diseases of the nervous system in the Salpêtrière (Paris). I will analyse the role of the contexts of cell theory, microscopy and the advances in histological techniques in the creation of various pathogenic models, based on the concept of the cell, the Wallerian degeneration and the neurone concept. I argue that, as medicine and pathology remain autonomous in their methods and goals, because of the evident degree of complexity of diseases, close and reciprocal interactions with sciences, their practices and theories, make it possible to establish convergences between clinical observations, pathological data and those from the experimental models of pathologies. The search for pathogenic models behaves like an engine, which is efficient in assembling facts, in testing pathogeneses and reforming nosologies, combined with the breakthroughs in biology. This paper is a case study showing the emergence of such interactions in the last decades of the nineteenth-century in Paris.

Key words: pathogenic model, nosology, nosography, Wallerian degeneration, Charcot, Vulpian.

Introduction

In the past decades, with the historiographic turn in the history of sciences, studies moved away from single disciplinary approaches or studies on simple interactions between two disciplines based on the history of ideas. The new works escaped the basic concepts of "discovery", "precursors" and "Kuhnian paradigms". The history of sciences created more complex narratives on the emergence of new scientific domains involving interactions between different, and often

distant places, each creating particular concepts and theories by using its own instruments and procedures. This was generally achieved in a broad epistemological and sociological perspective within large scientific and socio-political contexts, where continuities were more easily noticeable (see ref. in Stahnisch, 2009).

My recent contribution to the shift has been to unravel the two aspects of the creation of scientific knowledge in the case study of the neurone concept in the twentieth century (Barbara, 2010). First, synchronous conceptions created in distant places by different disciplines, or subdisciplines, may converge in the constitution of objects and explanatory models. Second, such syntheses, either local or more global, may fertilize distant research domains and contribute to the emergence of new ones, or modify the boundaries between existing ones. This is the way I have envisaged the creation of the neurone concept from a physiological perspective in the twentieth century and described its constitution as a scientific object (Barbara, 2006a).

In the present article, this same approach was devised to understand those two aspects of the creation of knowledge in the field of the diseases of the nervous system, in the second half of the nineteenth century, when the field of the clinic of nervous diseases emerged in Paris. I have distinguished three types of places of knowledge production collaborating in the definition of diseases, the laboratories devoted to basic anatomy and/or physiology, the laboratories involved in the study of animal pathological models and the laboratories and clinical departments of hospitals. I wish to demonstrate the different aspects of the circulation of theories, concepts and technical procedures between those places, in the elaboration of explanatory models common to physiology and pathology. The endproducts of these circulations rely on the creation of pathogenic models of diseases, derived from physiological laws, which explain the genesis and early developments of nervous pathologies and help classify them in nosologies. The search for such pathogenic models reveals epistemological search engines circulating different kinds of knowledge (physiological laws, technical procedures, clinical observations, *post-mortem* anatomopathological data) converging in the mechanistic explanatory models of the pathogenies of diseases.

Such a perspective was adopted in some previous studies, in particular those describing the relations between, on the one hand, the anatomical observations of the degenerating brain and the theories of degeneration, and, on the other hand, the diseases of the nervous system within wide sociopolitical and cultural contexts (Hagner, 2001; Roelcke, 2001; Stahnisch, 2008, 2009). The examination of the fruitful collaborations between the research programmes of anatomy, physiology, pathological physiology and medicine was also part of the historiographic shift of the past decades, in contrast with the former views of Ackerknecht who considered these domains more distant (Lesch, 1984, p. 167). Contrary to many previous studies, my analyses are set in the early stages of knowledge production concerning nervous diseases by local circulations of practices, theories, laws and concepts between laboratories more or less distant from the clinic. The epistemological engines at stake are analysed at the level of individual scientists and physicians in direct interaction in the city of Paris, with no mention of societal or political aspects which were however necessary for their development.

My main focus is the study of the interactions between disciplines in knowledge production. Experimental researches on the causes of nervous diseases enabled to establish closer relations between clinic, scientific theories and their associated practices. Such interactions between medicine and sciences appeared in the Parisian medical school of the Salpêtrière in the nineteenth century, in the vast context of the school of Morgagni (1682–1771), the rise of cell theory and the French reception of the works of Rudolf Virchow (1821–1902). With the emergence of the laboratory revolution in medicine (Cunningham and Williams 2002; see also ref. in Stahnisch, 2009), a radical change occurs in the ways the medical community views the causes of diseases, with the use of experimental physiology and the current advances in microscopy. In the field of neurology, those developments are best exemplified by the studies

of Jean-Martin Charcot (1825–1893) and Alfred Vulpian (1826–1887), at the Salpêtrière, which led to the creation of the first chair in the world dedicated to nervous diseases (*chaire des maladies du système nerveux*, 1882).

The interest of these scientists in the understanding of the proximal causes of diseases was not new. In fact, Jean-Pierre Falret (1794–1870), appointed *Chef de l'hospice de la Salpêtrière* in 1831, urged a similar change when he advocated pathogeny as a new trend in medical research, especially for the reform of the nosography of mental diseases (Falret 1864, p. xxxii). However, this approach was extended to general pathology when Virchow put it in practice in the framework of cell theory. In the 1850s, Charcot did not yet work in this direction. However, this medical trend was progressively adopted at the Salpêtrière, after younger physicians, such as Charcot, Vulpian, Ranvier and Cornil studied the works of Virchow and attempted to replicate his methods in a similar theoretical perspective. Later on, Jules Dejerine (1849–1917) advocated it as the new means of nosography. Accordingly, clinical investigation and differential diagnosis were no longer sufficient to study the symptoms and the laws of the evolutions of the diseases of the nervous system. If this methodology was used in isolation, Dejerine commented that nosographies would lead to endless classifications. He hoped that a novel rationality would emerge from those classifications, if they were associated with experimental work and refined laboratory techniques: "Science assembles facts into categories first by analogy, then by analyses. Each process of clinical or anatomo-pathological investigation becomes the starting point of new differentiations […] If this study were carried on indefinitely, medical science would only contain particular facts differing from each other by clinical traits" (Dejerine, 1911, n. 1). The old methodology of making nosographies was still in use, but interdisciplinary researches on the causes of diseases were now being carried out in the laboratory as well and were giving rise to new epistemological engines based on interacting disciplines.

The use of new experimental tools, such as modern microscopes, developed in the context of scientific theories and provided theoretical schemata for the interpretation of the causes of diseases. At the same time, the nature of the relations between theories and medicine was questioned. Claude Bernard (1813–1878) and Virchow championed the physiological understanding of diseases by means of the concepts of physiological regulations and cell theory, respectively. The main question was to know whether those theoretical perspectives could apply to a great variety of diseases or to small sets of particular cases only. Could pathology be subordinated to physiology? Georges Canguilhem fought against this idea, first developed by François Joseph Vicot Broussais (1772–1838) (Canguilhem 1942, p. 138-142). Canguilhem designates a "professional oblivion" of the autonomy of the clinic in the works of Virchow and Bernard, in spite of Bernard's comment on his refusal to subordinate pathology to physiology. Bernard thought the possibility of reducing the complexity of diseases to physiological explanations unlikely.

Those issues are the general framework of this paper, in which I will study how cell theory, Wallerian degeneration studies and the neurone theory changed the nosography of nervous diseases by the creation of new ways of knowledge circulations between disciplines. I will analyse how convergences occurred, as well as how particular diseases were seen as exceptions to physiological laws. Recurring discussions between sciences and medicine enabled not only to refine nosographies, but also to broaden the scope of physiological investigations and to consolidate the connections between biological and pathological knowledge.

Cell theory and medicine

The cell theory is the starting point of my investigation, since both the Wallerian model and the neurone theory are "cellular" theories devoted to the nervous system and both connected to it.

Waller, Waldeyer, Ramón y Cajal were interested in the cellular aspects of nervous elements. First, Waller demonstrated a physical link between nerve fibres and nervous cells which was necessary to maintain the integrity of the nerves, and, more broadly speaking, the integrity of the "fibre-nerve cell" couple, which became the object of the neurone theory. There is a continuity in those three theories and their respective role in the search for pathogenic models of nervous diseases can be analysed successively.

How did cell theory modified the production of the pathogenic models of diseases? It is important to understand the relations between the rise of cell theory and the cellular pathology of Virchow. If the cell theory enabled to reform nosologies, it was also beneficial to find new mechanistic pathogenies and that resulted in the adoption of the cell theory itself and the adage of Virchow "*Omnis cellula e cellula*". In a sense, this collusion strengthened the conception of the disease as a quantitative deviation from physiological mechanisms, since pathological elements remained cells, although modified in specific pathological conditions. Therefore, the adoption of cell theory was associated with its heuristic use in pathology and its value in reforming nosologies. It is thus possible to analyse how the cell theory provided an epistemological engine to search for new pathogenies of diseases. In order to illustrate this point, I will study the case of the pathogenic model of inflammation by Jean Cruveilhier (1791–1874) and its reversal by Virchow (Duchesneau 1987).

The dogma of Cruveilhier asserts phlebitis dominates all pathology and represents a cause of inflammation associated with a thrombus (Duchesneau 1987, p. 294). The microscopical investigations of Virchow showed that the clot was made up of fibrinous corpuscles. Virchow reproduced the formation of thrombi experimentally with acid injections in blood vessels, leading to an analogous inflammation of the vessel walls. He could also describe the formation of similar clots and investigate the mechanisms of their production. Virchow explained inflammatory epithelial cells were formed after acid injection. They seemed to produce the thrombus, which meant it was not a side effect of the inflammation, but a cause of it (Malone and Agutter 2008). The researches of Virchow value the study of the physiological conditions of pathological states and the use of experimental pathology with microscopy, in the perspective of cell theory. The disease was recreated with alterations of the relevant physical factors in pathological conditions.

This case study illustrates how Virchow made use of the cell theory to create a new pathogenic model based on a new pathological cell species, the pathological epithelial cell, as observed in experimental models and humans. The cell was created in animal models with physiological tools, in order to understand the conditions of its production and the mechanisms involved. Where Cruveilhier described a correlation between phlebitis, inflammation and thrombus, and where he decided inflammation was first on a rather speculative ground, Virchow showed that pathological epithelial cells were formed upon blood injection of acid, causing the thrombus and inflammation. The benefit of cell theory in producing such a pathogenic scenario confirmed its adoption in medical circles and enabled its circulation in other experimental models of pathologies, and in clinical and anatomopathological hospital departments. The result was the description of new pathological cellular entities both in experimental models and humans and the convergence of these data in the production of pathogenic mechanisms. Therefore, the search for pathogenies in the context of cell theory behaved as an epistemological engine effective between physiology, pathological physiology and pathology.

In the domain of nervous diseases, Virchow also exploited the pathogeny of vascular obstruction. As a result, the nosological category of encephalitis, thought to be caused by intrinsic inflammation only, disappeared, as noted by Dejerine (1911). The reception of such reforms of nosological classifications supported the acceptance of cellular pathology as a whole. It inspired researches by Vulpian and Charcot, their investigations on the alterations of blood

granules, corpuscles and crystals, studies on the role of fibrinous deposits in embolism and works on intermittent claudication after obstruction of the iliac artery (Charcot 1858).

Thus, during the 1850s, novel pathogenic models appeared in parallel with the extended reception of cell theory in medical circles and the general use of microscopy in medical training and hospital laboratories (La Berge 1994, 2004). In return, scientific theories and their related practices were amended as nosologies were reformed. Pathogenic models were not fixed, but often criticized and corrected in particular cases. For example, Charcot rejected the generality of the interpretation of Virchow, when he ascribed a role to vascular walls in the formation of thrombus. Theoretical pathogenic models introduced new explanatory systems. Experimental and clinical investigations lent credence to their extension, with possible corrections in the formulations of the physiological laws of pathogeny. Conversely, new laws could come out from clinical research and experimental pathology.

Wallerian degeneration and nervous diseases

In the domain of the nervous system, cell theory not only enabled the description of new pathological entities, but it revolutionised the degeneration theory as described by Morel (1857/1858). In such a perspective, the pathogenic reform of Virchow opened a research programme devoted to the degenerating cellular species found in the nervous system. It was natural to first think of degenerating nerve fibres, and to develop experimental models of nerve fibre degenerations, since the dominant object of nervous physiology was not the nervous cell but nerves and intricate fibre nets. The first experimental models used were those of Waller, in which degeneration was induced with a simple section of nerve fibres.

Augustus Volney Waller (1816–1870) was an early microscopist trained in the circle of Alfred Donné (1801–1878), one of the first Parisian physicians to use microscopy in pathology. The work on the degenerative processes in cut nerves that Waller performed in the late 1840s set up a powerful physiological model for nervous diseases. His experimental model of the tongue of the frog was well suited to describe the cellular modifications resulting from the section of small nerve fibres. The transparency of the tissue made it possible to achieve careful examinations of the degeneration of individual fibres. In particular, Waller described how nervous fibres degenerated when they were separated from their cell body. After 1852, he investigated a new methodology to discover the location of the cell body region of a cut degenerated nerve, with the combination of various histological sections (Sykes 2004). The law of the Wallerian degeneration expressed the fact that a nerve fibre degenerated in the proximal stump in the direction of its cell body. When the degenerative process was complete, histological sections could locate degenerated fibres of a nerve between the location of the lesion and its cell body region. Different sections were tested from the periphery towards the centre. When no degenerated fibres could be seen in any sections, it indicated that the section had been made over the cell body region, along the axis of the nerve from the periphery towards its centre. The centre could then be located between this section and the previous section leading to some degenerated fibres.

A cellular mechanism was introduced in the Wallerian model as a physiological law explaining the degeneration of the nerve fibres. The law stated that nerve fibres degenerated when they were physically separated from their centre, and this centre was therefore termed a “trophic centre”, since its function was interpreted as nutritive in maintaining the integrity of the fibres.

In principle, this law could be used in pathology to discover the locations of injured nerve centres leading to the degeneration of their output nerve fibres. Various theoretical discussions came forth on the processes of degeneration and regeneration of nerves, before and after the neurone theory appeared, in the domain of general histology, but also in the pathological

framework of utmost importance associated with the law of Waller, raising much enthusiasm and conflict, especially in the works of Charcot and Vulpian.

All discussions relating to this model of pathogeny dealt with a central issue: is a peripheral pathological degenerative locus always associated with a primitive lesion in a centre of the nervous system? Can a peripheral pathological degenerative locus appear without any lesion in a centre of the nervous system? Can a peripheral pathological degeneration be a primitive process? Those questions addressed the generality of the law of Waller in pathology, and asked whether this law was absolute, or if degeneration could also occur without central lesions.

The answer to such questions concerned both present and past data. The law of Waller was derived from minute histological investigations. Nonetheless, it was also supported by earlier eighteenth-century pathological observations, which seemed to fit current clinical knowledge. Secondary peripheral nerve degenerations had been described in the case of central lesions after a stroke or a softening of the brain, during an infection for example. Thus, the law of Waller seemed to apply to nervous diseases and pathological microscopy became a means of investigating the possible causes involved. Virchow described amyloid corpuscles in degenerative centres, later observed by Jules Luys (1828–1897), a physician trained in histology and collaborating with Charcot (Luys and Hillairet 1859, Charcot and Luys 1859). Such researches attempted to explain secondary degenerations occurring after a primitive degenerative process.

The papers by Luys were presented at the *Société de Biologie* in Paris, where the works of Waller had already been presented and discussed, especially by pathologists, and where they had received a warm reception. Adolphe Gubler (1821–1879) was one of the first members of the society to work in this field. In 1859, he made a report and concluded: "In the future, secondary lesions should be searched for […] in all cases of prolonged diseases of the brain [where primitive brain lesions occur]. The anatomist will gain much insight on the direction of sensitive and motor nerve bundles of the brain from the study of softened nervous tracks, after retrograde alterations similar to those seen in foetuses died in mother" (Gubler 1859). This research programme was reversed compared to that of pathology, since central lesions were analysed to gain insight into the physiology of brain nerves, by tracing their paths from the brain to the periphery.

Such research programmes were conducted in France by two physicians, Vulpian and Charcot, who were also members of the *Société de Biologie*. In 1862, they became *chefs de service* at the Salpêtrière hospital and started collaborating. They first established a complete inventory of their female patients with chronic incurable diseases at the *Vieillesse-Femmes hospice* (Old-women hospice of the Salpêtrière). Living conditions were terrible and criticized by the physicians who progressively understood they were involved in the poor health of the patients. At the same time, those patients formed a sort of "anatomo-pathological museum" of great interest for the study of the pathogeny of the chronic nervous diseases left to young clinicians (Charcot 1887, p. 5). This context explains why Vulpian and Charcot focussed on the study of the chronic diseases of the nervous system. However, other reasons can further explain the choices of Vulpian: in his thesis, he had studied the origin of the nerves of the head (Vulpian 1853), and the experimental pathology of nerve compression and section, degeneration and regeneration in the laboratory of Pierre Flourens (1794–1867) at the *Muséum d'Histoire Naturelle*.

From the beginning of the 1860s, common studies by Vulpian and Charcot made a greater use of histological techniques in autopsies. It should be noted that these techniques were still rather unreliable although they had led to isolated observations, such as the primitive fibre of Remak (1815–1868) or the nervous cells described by Jan Evangelista Purkinje (1787–1869).

In their studies on spinal cord scleroses from posterior columns, Vulpian and Charcot were experiencing the novel pathogenic framework developed after the law of Waller (Charcot and Vulpian 1861). In 1862, they came across an exception to the law, with the description of a case of altered posterior columns, without any sign of degeneration of dorsal root ganglia. In the associated experimental model of Waller, the lesions of these ganglia lead to the degeneration of the posterior roots (Charcot and Vulpian 1862). Charcot and Vulpian concluded without being unduly upset: "One of our findings supports the doctrine of Waller adopted by most physiologists […] But, on the other hand, it is ruined out by another of our observations" (Charcot and Vulpian 1862). Charcot and Vulpian saw physiologists and pathologists as opponents. They seemed to advocate an epistemological position according to which experimental pathology has no central and necessary role in the pathogeny of diseases (Goetz et al. 1995, p. 71). So, an exception to the law of Waller may not be a false observation; it may rather confirm that pathological states can follow their own laws.

Therefore, soon after its reception, the law of Waller was at variance with clinical and pathological investigations. However, it constituted a powerful pathogenic model, which urged pathologists to search for primitive nerve and central lesions, as well as secondary degenerative areas. Pathological histology was able to reconstruct the history of nervous lesions paralleling the clinical history of patients. Clinical and post-mortem histological investigations could correlate paralyses and the various symptoms of the patient with the progression of degenerative processes. This common theoretical and clinical framework permitted interdisciplinary work involving histology and clinic, laboratory procedures on cadavers and the personal history of patients collected year after year by the clinicians of the Salpêtrière.

Although its explanatory power was limited from the very beginning of its application to pathology, the Wallerian model settled an engine to search for pathogenies of nervous diseases. It provided two morbid entities, the degenerating centres (primitive lesion) and the degenerating nerve fibres (secondary lesions). Moreover, the model insisted on the chronological succession of these lesions. It became obvious that the model could be tested on various experimental models of pathologies, but also, with clinical and *post-mortem* anatomopathological data, where central lesions were found in the nerve centres of patients with peripheral functional deficits. This pathogenic model paved the way to a novel regime of the circulation of the law of Waller, its associated histological techniques (silver nitrate staining, Marchi method) and parallel sets of data from physiology, clinic and anatomopathology. In a similar way as in the cellular pathogenic models of Virchow, the Wallerian model behaved as a fruitful search engine in the production of mechanistic explanatory models relying on histological investigations of cellular elements.

The advances in histological techniques and the generalisation of the Wallerian pathogenic model

The Wallerian model was not initially seen as applying to the bulk of nervous diseases, because of the great complexity of pathological conditions and numerous possible exceptions to the law of Waller. Its validity in some experimental pathological models was not sufficient a condition for its extensive application in pathology. Vulpian and Charcot interpreted exceptions to the law in the defence of the autonomy of pathology *versus* physiology, according to a common idea. However, this view could be adopted, once it was made sure that experimental models of pathologies and patients were studied with similar techniques. Only on that condition, the data sets produced were of similar quality in order to be compared. This was not the case at the Salpêtrière in the 1860s, where central lesions were still often observed with the naked eye. The insufficient histological techniques used caused some hindrance to the pathological application of the law of Waller. This fact was made apparent by the progress of the histological techniques

later used at the Salpêtrière in the 1880s and 1890s, after new procedures were imported from outside laboratories.

In Paris, Louis Antoine Ranvier (1835–1922) made much progress in the histological techniques used for nervous tissues. His work exemplifies the improvement of microscopic techniques applied to nervous tissues in the best possible way. Ranvier refuted the ideas of Vulpian on the regeneration of nerves after section, and he developed a new physiological framework for the interpretation of degenerative and regenerative cellular processes involved in the alteration and repair of nerves (Barbara 2007a). The results of Ranvier confirmed the law of Waller and provided precise cellular norms, such as the number of Schwann cells *per* interannular segments in both healthy and degenerating nerve fibres.

Ranvier is known for his description of the *nœud de Ranvier* (Ranvier's node), a minute interruption of the myelin sheath of fibres that he held responsible for nutrient exchanges with the extracellular milieu (Ranvier 1871). Ranvier was faithful to Claude Bernard's general guidelines when he studied small "anatomical elements" involved in the nutrition of the nervous tissue (Barbara 2007a). In the cellular perspective of Virchow, whom he respected and followed, Ranvier established that a single Schwann cell nucleus only was stained between two nodes. This anatomical norm became a necessary condition for the normal functioning of nerves. Alternatively, in the altered nerve, the multiplication of Schwann cell nuclei occurred in parallel with the loss of function of the nerve and their number was back to normal after the repair of the nerve (Ranvier 1873). These observations by Ranvier refuted the past interpretations of Vulpian (Philipeaux and Vulpian 1859a, 1859b) and paid tribute to the value of the law of Waller in explaining degenerative processes.

The work of Ranvier enabled to provide more refined pathogenic models derived from the law of Waller. New norms for normal and degenerating fibres were defined. It was possible to further describe the pathological mechanisms involved and to follow them in models of experimental pathology.

The revised model of Ranvier was introduced at the Salpêtrière by Jules Dejerine and Joseph Babinski (1857–1932), two students of Vulpian, who joined in this field of research, taking advantage of the new histological techniques of Ranvier, based on silver nitrate and chromic acid. Dejerine was in charge of repeating and criticizing the experiments of Ranvier on the degeneration of nerves, in the light of the erroneous interpretations of Vulpian who admitted his errors in 1873 (Dejerine 1875). Dejerine quickly mastered the techniques of Ranvier and he could correlate the multiplication of the nuclei of Schwann cells with the loss of function of the nerve, three days after section, thereby refuting a mechanical interpretation of the loss of function of the nerve by Ranvier (Barbara, 2006b). The law of Waller was thus central to the interpretation of nervous degenerations in experimental pathological animal models. Such circulation of techniques and procedures was necessary for the maximal extension of the law of Waller in providing pathogenic explanations of experimental models of pathologies.

The model was further tested on human pathologies by Babinski then head of clinic of Charcot. He took a similar path when he too adopted the techniques of Ranvier. Babinski also could recognise the value of the law of Waller in pathology, when he corrected Charcot on his interpretation of a clinical observation viewed as an exception to this law. Charcot had described central lesions in multiple sclerosis without anterograde nervous degeneration, as expected by the law of Waller. Charcot explained: "There is a black spot in our general views. I mean the well-known exception to the law of Waller: the extended lesions seen in multiple sclerosis do not yield to secondary degenerations. In the past, I made the hypothesis this was due to the longer persistence of axon cylinders in the multiple centres of sclerosis […]" (Charcot 1876) But Charcot was wrong, because his histological techniques were defective; Babinski demonstrated secondary degeneration did not occur because in this case axons were not altered (Babinski 1885). The work of Babinski extended the validity of the law of Waller and of the experimental

model of Ranvier to two other fundamental pathologies: multiple sclerosis and systemic sclerosis. In multiple sclerosis, the myelin fragmentation is similar to that observed in the central stump of the cut nerve. In systemic sclerosis, secondary degenerations resemble those of the distal stump. Thanks to the work of Ranvier and his followers in the Salpêtrière school of Vulpian and Charcot, the experimental model of nerve degeneration seemed to provide a general physiological and pathological law guiding the reforms of nosologies with proper general principles.

Therefore, the combined use of the cell theory, of the law of Waller, of the Wallerian model of the cut degenerating nerve fibre and their associated techniques revealing normal and pathological fibres allowed the production of a novel type of engine searching for the pathogenies of nervous diseases. Two distinct components can be distinguished here. One links physiological laws, theories and techniques to the anatomical and physiological procedures applied to the study of experimental models of pathologies. Another establishes connections between, one the one hand, mechanistic models and cellular pathological elements and, on the other hand, the clinical and *post-mortem* anatomopathological data.

This search engine was considered highly prolific when it was extensively applied to a larger bulk of nervous diseases, and virtually to all of them. However, the validity of the model used in pathology reached its limits and physicians were tempted to go beyond, as judged by current knowledge. Thus, any pathogenic model has a limited extension in pathology. A short analysis of various studies by Dejerine will now be presented in order to show how he came to realise he had gone too far in applying the model to diseases which could not be explained in that way. The basic strategy Dejerine used was the understanding of the topography of central lesions in the brain, bulb, spinal cord and ganglia, and that of nervous lesions in spinal roots, peripheral nerves and end organs in skin and muscle. This allowed him to make interpretations of primary and secondary lesions. Dejerine used the most sophisticated techniques of Ranvier and counted Schwann cells nuclei systematically. For example, Dejerine searched for limited central alterations in the spinal cord in his study of congenital clubfoot (*pied bot équin*): "since a cellular atrophy of anterior horns of spinal cord was demonstrated in infantile paralysis (1865) […] various analogous facts were published […] the precise limitation of this process to the anterior part of the lateral column engages us to publish this particular case" (Dejerine 1875, p. 256).

Dejerine extended the Wallerian pathogenic model to the ascending acute paralysis (*paralysie ascendante aiguë*) studied between 1876 and 1879 (Dejerine 1879). Macroscopic histological investigations failed to uncover central lesions of the spinal cord. However, the question whether the Wallerian pathogenic model applied here or not, remained open. Dejerine thought microscopy was essential to the answer: "Ascending acute paralysis would be explained in a rational manner, if alterations of anterior horn (of spinal cord) were found" (Dejerine 1876, p. 317).

In 1878, Dejerine could study two new cases of this same pathology and he described them in his doctorate (Dejerine 1879). The norms of Ranvier concerning the number of Schwann cell nuclei applied to the lesions that Dejerine found in the anterior horns. Dejerine seemed to have succeeded in applying the Wallerian pathogenic model to this pathology. However, André Victor Cornil (1837–1908), a friend and colleague of Ranvier's and Charcot's, pointed out that the lesions found by Dejerine seemed too tenuous to explain the severe clinical deficits of the cases of Dejerine (Cornil 1869).

In this case, Dejerine later recognised that he had generalised the Wallerian pathogenic model too rapidly. Before that, Dejerine had applied the model to three categories of pathologies: cutaneous diseases of nervous origin, various paralyses and various muscular atrophies. In a later study, Dejerine finally defined the Wallerian pathogeny and its norm: "the alteration of nerves produced by a central lesion is necessarily proportional to the number of their nuclei of origin (the nerve cells of the nerve fibres)" (Dejerine 1883, p. 208).

However, in that same study, Dejerine encountered curious facts, i.e. nervous lesions observed at various locations of a nerve, without any lesion of its centre of origin. After an extended generalisation of the Wallerian model to pathogeny, Dejerine finally found himself confronted with serious exceptions to the law of Waller, as Charcot had been in the past.

Dejerine progressively found a large number of other cases. Hence, he urged his colleagues to study with great care the nervous degenerations that seemed independent of central lesions (Dejerine 1890a). Dejerine described different types of nervous degenerations, the Wallerian type, and others, such as the retrograde degeneration (Dejerine 1896), the ascending degeneration (Dejerine and Sottas 1895), the focal, and multiple primitive scleroses (Dejerine 1895). Not all those degenerations seemed comparable to the experimental model of sectioned degenerative nerves (Dejerine 1890b).

Hence, Dejerine finally came across many types of nervous diseases which could not be understood by means of the Wallerian pathogenic model. This was a natural consequence of the multiplication of attempts to apply the model to new diseases. From then on, the Wallerian model and the associated pathology could not legitimate any longer in a mutual manner. The model failed to provide pathogenic models of some diseases. Consequently, the power of the law of Waller could not be consolidated anymore. This co-constitution of the law of Waller and the Wallerian pathogenic model of nervous diseases was put to a stop, as was the search engine for those models. A crisis occurred and a new theory was therefore awaited.

At that time, the neurone theory appeared well suited to overcome those difficulties. This shift can be referred to what I called the passage from the nervous paradigm to the neuronal paradigm (Barbara, 2010a, 2010b). This notion does not pertain to the Kuhnian paradigm shift or scientific revolutions. Rather, the neuronal paradigm describes a change of viewpoint by drawing all the inferences from the cell theory in the study of the nervous system in the twentieth century, in connection with past science since antiquity. The neuronal paradigm is characterized by large continuities between its novels forms of knowledge and that of the nervous paradigm; however, it also creates a new object and knowledge irreducible to previous concepts. Indeed, the neurone theory did not solve the problems raised by the application of the law of Waller in the studies of degenerating nerve fibres, but it did get around those questions, which then became secondary. In fact, the chief issue was no longer to determine if a peripheral lesion was primitive or secondary. What mattered was to locate, not the injured centres or nervous fibres, but ensembles of fibres and nervous cells, defining a new cellular morbid element, the neurone. Hence, the question whether a neurone degenerated first at the level of the soma or the axon was of lesser importance than the definition of degenerating neuronal types indicating new pathogenic models and the novel nosological categories of the nervous system.

The etiological turn (1880-1890)

Those researches devoted to nervous diseases emphasize the search for proximal causes involved in the morbid processes within a mechanistic framework. This was a consequence of the heuristic engines devoted to build pathogenies. Goetz has named this new trend the “etiological turn” (1995). I would like to place it in a broader epistemological perspective.

Etiology, the study of distant and proximal causes of diseases, was systematically replaced in the period 1880-1890, although not entirely, by pathogeny, the search for the mechanisms of pathogenesis in various theoretical frameworks (Goetz et al. 1995). This was made possible by the advances in histological techniques and the systematic anatomo-pathological microscopic investigations of particular clinical cases. However, those works were most often single-case studies approving, ruining out or refining pathogenic models whose degree of generalisation had to be further tested.

Claude Bernard defined pathogeny as the explanation of the production of diseases (Bernard 1947, p. 297). In the 1930s, it was defined differently, i.e. as the mechanism by which morbid causes determine diseases. A gap remained between the causes, as defined by Bernard, and the mechanisms referred to in the later definition and which remained to be found.

Pathological models enabled to define the etiology of diseases along with the clarification of the determining causes of various degrees of proximity to the diseases. Before the 1880-1890 period, Etienne-Jean Georget (1795–1828) distinguished influential causes of madness and efficient causes, direct or indirect (Georget 1820, chapter 2). In the 1870s, etiology and pathogeny were brought closer, as it can be seen in the works of Charcot. Charcot described a rather classical etiology for articulary rheumatism and gout, with a role for heredity, age, sex, humidity, food and relations to other diseases (Charcot 1874, lessons 8th and 17th). In his lessons on the diseases of the nervous system (1872–1873), Charcot encouraged an etiological turn, as he commented that the theory of congestion did not explain the current pathogeny of apoplectic stroke (Charcot 1873, lesson 8th). In the same lessons, Charcot was able to consider a new pathogeny for multiple sclerosis as a novel "succession of lesions" (Charcot 1873, lesson 6th). The explanation used by Charcot is somewhat mechanistic: "the morbid process is fully active: the medullar cylinder [of the nerve fibre] is compressed and becomes thinner until it disappears" (Charcot 1873, lesson 6th, p. 192). Charcot offered new pathogeneses for an increasing number of diseases during the 1880s and 1890s. For example, in 1893, he attempted to explain ophtalmic migraine (Charcot 1893, p. 70). Thus, pathogeny progressively became essential to the study of diseases between anatomopathology and etiology. A deterministic view appeared in the description of the evolutions of diseases, involving "constant" lesions, with proper histories, in accords with the clinical history of the patients.

Therefore, morbid processes were not described in terms of physiological mechanisms only, but they seemed relevant to proper pathological determinisms. Thus, pathogeny was defined as a distinct domain of nosology, as Charcot mentioned it in the opening lecture to his chair in 1882 (Charcot 1887, volume III).

One can ask how the search engines of pathogenies can work from an epistemological point of view, by the interaction of the two loops which I have previously described. What circulates in these loops have very different epistemological values. An anatomical or physiological theory does not share the same status as a generalisation of clinical or pathological data. In this latter case, generalisation is hampered by the diversity of individual diseases, whereas biology deals with simple, standardised and reduced models, allowing an experimentally maximized determinism.

The search engines I describe rely on complex circulations of knowledge between disciplines. They do not refer to the notion of engines of discovery as simple monodisciplinary procedures (Hacking, 2006), which I see as more local procedures leading to specific modes of objectivization of concepts. The function of my epistemological engines is to bring together those modes of objectivization and to circulate their scientific norms between disciplines. For example, Ranvier's norms of the number of Schwann cells per interannular segment of the healthy and degenerating nerve fibres were finally accepted in physiology, experimental physiology and pathology.

As far as techniques and manipulations are concerned, biological models and dead or alive patients cannot however be studied in the same ways. Nevertheless, some convergences may appear when homologies between entities and basic cellular mechanisms are found in groups of pathologies, and when they are further established in experimental models of pathologies. What is at stake here is the homology between the degenerating fibres (or neurones) after an experimental section (or degeneration) and those identified *post-mortem* in a patient with peripheral nervous disorders, in such a way that convergences can be found at the level of basic pathogenic mechanisms by pathogeny search engines. This is the kind of engine still searched for

today in Alzheimer's disease, with the open question whether amyloid plaques are a cause of the functional disorders or a secondary consequence of an unknown primitive process. Hence, I argue that the circulations of knowledge between basic biology and experimental pathology, and between experimental pathology and clinic and anatomopathology enable convergences of knowledge, at the level of basic pathological mechanisms close to physiological processes at the commencement of diseases.

The neurone theory and the nosography of nervous diseases

Resorting to the neurone theory, the old Wallerian pathogenic model was changed completely, as well as the nosographies of nervous diseases. However, this shift needs a careful historical study applied to our case study of Paris, in an epistemological perspective. As for the cell theory and its relation to pathology, the neurone theory gave rise to novel pathogenic models, while physicians were simultaneously involved in its defence. The relations between physicians of the Salpêtrière and Ramón y Cajal can be interpreted in this way.

The studies of Ramón y Cajal and the rise of the neurone theory interfered with the etiological turn in Paris described above. Cajal introduced himself on the international scene, first at the German Anatomical Society, where he demonstrated his microscopic slides to Rudolf Albert von Kölliker (1817–1905). One path for the French reception of the staining procedures of Cajal was the Belgian physician Arthur van Gehuchten (1861–1914), professor of anatomy and neurology at the catholic university of Leuven. He reproduced the Cajal's slides he had seen in Berlin and he published his results in the French journal *La Cellule* (Van Gehuchten 1890, Van Gehuchten 1897, preface). The following year, Gehuchten and Cajal published articles in the same issue of that journal (Van Gehuchten 1891, Ramón y Cajal 1891). Consequently, Léon Azoulay, a French physician, undertook the first systematic researches with the Golgi technique in France. In 1894, he published seven papers in the *Comptes rendus de la Société de Biologie* relating his observations performed on human material.

Actually, the Golgi technique was introduced in Germany and France much earlier (Barbara 2007b). As early as 1875, Ranvier praised its quality, despite the unreliable character of the technique, in the lessons at the Collège de France (Ranvier 1875, Barbara, 2007a). Earlier than 1895, the laboratory of Dejerine was experiencing the technique at the Salpêtrière. The wife of Dejerine, Augusta Dejerine-Klumpke (1859–1927), had followed the lessons of Ranvier, and she performed her own histological work in that same laboratory, as did the young physician, André Thomas, who was in charge of reproducing the results of Cajal on the cortex (Thomas 1894, DeFelipe and Jones 1988, 2000). In addition, Doctor Cyprien Conil, a student of Mathias Duval, had published a memoir on the olfactory bulb, even earlier, in 1892 (Conil 1892).

Thus, the Golgi technique was used and taught in Paris during this period, especially by Mathias Duval, Edmond Retterer at the faculty of medicine of Paris and Adrien Charpy in Toulouse. Many physicians, such as Azoulay, Duval, Dejerine and Jean Nageotte (1866–1948) became close friends of Cajal's and ardent defenders of the neurone doctrine. The proximity of the medical milieu in Paris to the concept of the neurone differed from its reception at the Collège de France or at the Parisian University of the Sorbonne. The reasons are probably numerous and complex. However, they may be relevant to the mutual benefit of a close interaction between a new theory and the evolution of the clinic and the anatomopathology of the diseases of the nervous system.

Therefore, I will now analyse how the neurone doctrine changed some of the views on the classifications of nervous diseases. Before the neurone concept emerged, the anatomical data used in nosology was based on specific cellular lesions and nervous lesions, either primitive or secondary. In the beginning of the 1890s, the relations between lesions of nervous cells and nervous fibres were highly complex and their understanding was very difficult. Dejerine was now a defender of the "peripherist view", arguing that peripheral nervous lesions could occur

first and alter nervous cells as a secondary process, reversing the conception of the law of Waller. The pathogeny of nervous diseases had reached a point where the questions it asked were rather unsolvable and general knowledge to distinguish the various forms of nervous degenerations was lacking.

In this context, the neurone theory appeared as a fortunate simplification in the field of nosology, while it seemed of no interest to many Parisian anatomists and physiologists, among whom Albert Dastre (1844–1917). In his work on general paralysis, Ernest Coulon summarised how he viewed the neurone concept: "[it is] the biological entity given back to the nerve cell and ignored because of its structural complexity, its strange aspect during development, and the difficulties encountered in its observation." (Coulon, 1896). Fulgence Raymond (1844–1910), the successor of Charcot, described how the concept was profitable to nosology, given the complexity in the degenerative processes of different neuronal parts: "neuropathology is wrong to overuse morbid entities, and when it considers simple syndromes as autonomous, using arbitrary lines of demarcation" (Raymond 1897, 2nd series, p. 41). The neurone theory enabled to localise different types of lesions in a single anatomical and pathological element. The question whether a neuronal lesion began in the soma or the axon became less prominent. Raymond advocated a new point of view : "We must abandon the rigid distinction between nerve cells and nervous fibres: cells and fibres are one, the latter being the prolongation of the axon and the continuation of the cell" (Raymond 1897, 2nd series, p. 42).

The neurone theory represented a theoretical framework, which made the search for the refined history of central and peripheral regions of pathological cases useless. It seemed more interesting to distinguish what types of neurones were injured, whether at their cell soma or their axon, in respect to the particular functions of these neurones. Nosology could identify diseases relative to specific neuronal types and the pathogeny of diseases was simplified accordingly (Dejerine 1914). The causal relations between cellular lesions were no longer the main goal of pathogeny, but instead, the topography of neuronal cell death was studied and correlated with the symptoms of the patients.

Conclusion

I conclude that the first engines devoted to finding pathogenies of nervous diseases were built within the large context of cell theories in a mechanistic perspective based on the acknowledgement of cellular morbid entities. The mechanisms established were further tested on experimental models of pathogenies involved in the circulation of concepts, theories and associated practices between biology (anatomy and physiology) and experimental pathology, but also between this former domain and the clinic and anatomopathology. The first engines were devoted to degenerating nervous fibres from the Wallerian model, and then to injured neurones. In each case, the final result was a reform of the nosologies of nervous diseases.

Convergences occurred within such circulations when basic pathological mechanisms were found and understood as limited deviations from physiological processes. The homologies found between experimental models of pathologies, clinical and anatomopathological data are best understood if pathological mechanisms under study are close to normal physiological mechanisms. This idea of pathology is similar to that of Broussais and Claude Bernard. Canguihem fought against it, when he presented pathology as a state distinct from the normal, with its own particular norms imposing a new way of living. However, I share those two points of view because the pathogeny search engines described here try to find early pathological processes still comparable to the physiology of healthy patients, from which they progressively depart. Beyond a certain degree of duration and complexity of prolonged or chronic diseases, the organism adapts to its novel conditions of life. It seems clear then that the distance increases

between the disease and the physiology, while the disease imposes its novel norms and ways of being to the patient.

Individual patients tend to become unique. It is an illusion to think that simple pathogenic models may subsume all pathologies. In the same way, each cancer is original and can be understood as a complex and unique assembly of gene mutations and environmental factors. Thus pathology remains autonomous. However, local convergences on basic pathological mechanisms require the best cooperation between biological theories, practice, instruments and pathology.

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