

DORSAL COLUMN

Grey Matter

One hundred and fifty years ago Charcot reported multiple sclerosis as a new neurological disease

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Introduction

In May 1868, Jean Martin Charcot (1825–93) (Fig. 1A) delivered a series of major lectures, establishing multiple sclerosis as a novel disease of the nervous system. Delving into the early 19th century medico-scientific literature illustrates how confusions delayed the identification of multiple sclerosis as a single nosological entity. The confusion arose in part from the difficulty to relate polymorph symptoms to the same disease as clinical signs are highly variable during the course of the disease, reflecting either spinal, or cerebrospinal or purely cerebral neurological symptoms. Charcot's merit was to realize, applying his rigorous methodology inherited from Laennec (1781–1826) and Claude Bernard (1813–78), to bring together clinical observation, anatomo-pathology and physiology. This approach, along with detailed observations from others, led to Charcot's proposition that these apparently unrelated symptoms belonged to the same disease, which he named *Sclérose en plaques*, a term that (from 1954) became multiple sclerosis in the English literature. Here I wish to commemorate the 150th anniversary of Charcot's brilliant demonstration and tentatively decipher the reasoning that led Charcot to successfully 'extract the *sclérose en plaques* from the chaos of chronic myelitis'.

Where it all happened

Charcot was 31 when he arrived at La Salpêtrière in 1856, having recently been nominated Hospital physician

(*Médecin des Hôpitaux*). The Salpêtrière Hospice had been built under King Louis XIV shortly after the Thirty Years' War (Treaty of Westphalia 1648) ended. In a letter dated April 1656, the King stated:

'Religion and charity dictate that We provide for the disorders that this war has caused or occasioned...Paris is flooded with an infinite number of tramps and beggars living a licentious life in complete impunity. To prevent this debauchery and at the same time remedy their need, the King creates the "Hospital Général".'

In the same letter the king's orders were: 'that all the poor of any age shall be locked up; that crippled and elderly will receive all the necessary assistance; that those who are able to work should be variously employed; that everyone should be instructed in the duties of devotion'. To obey these orders La Salpêtrière was built and intended primarily for women only. (Men were sent to a nearby hospital, Bicêtre, while wounded soldiers were treated in the Hospital des Invalides.) To be more exact, La Salpêtrière was not a hospital but rather a hospice to house beggars, poor, elderly, crippled and loose women. During the 18th century the hospice had progressively switched to handle also mentally disabled women and in the spirit of the French revolution, in 1795 Philippe Pinel (1745–1826) ensured that psychiatric patients were no longer chained, but were given a 'moral treatment', prefiguring modern psychotherapies.

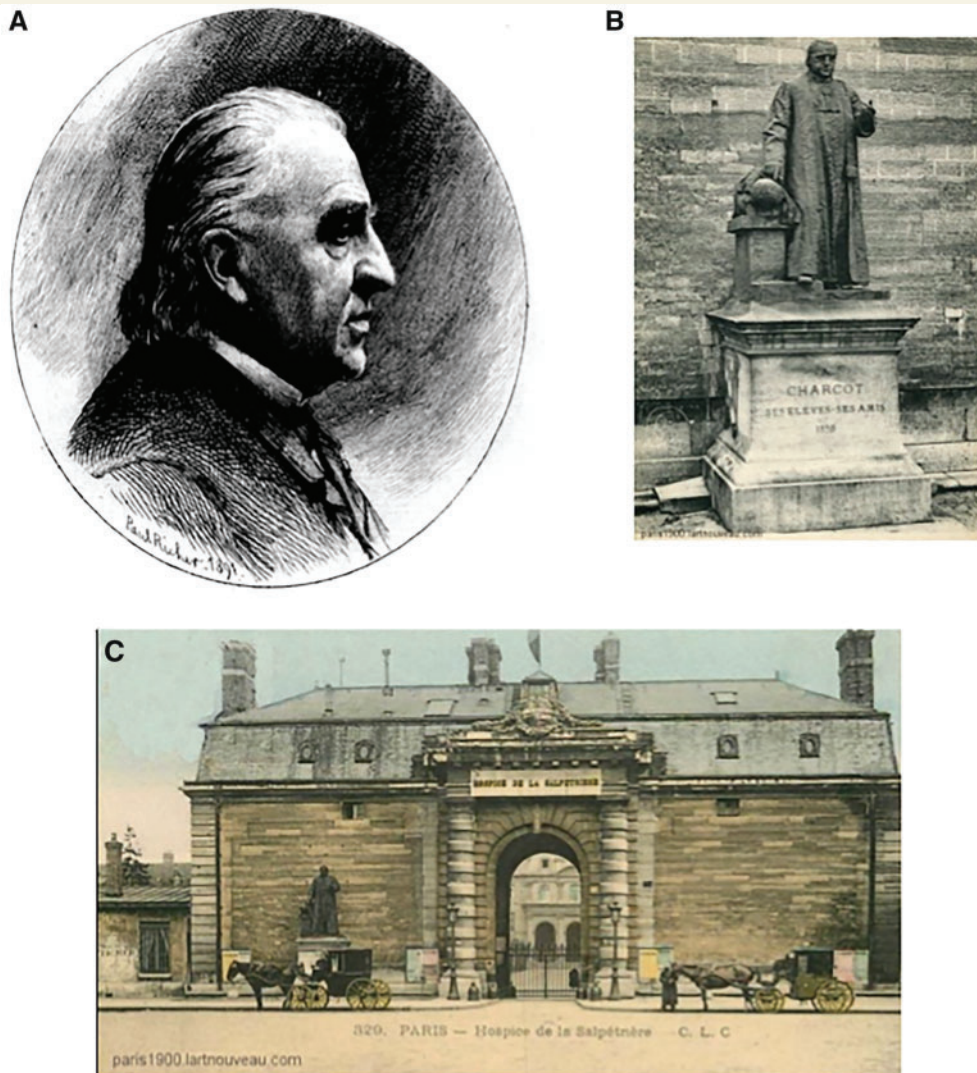


Figure 1 Charcot's tribute paid by his students. (A) Portrait of J.M. Charcot designed and engraved by Dr P. Richer 'one of JM Charcot most distinguished students' on the front page of the sixth edition of '*Oeuvres complètes de JM Charcot*'. The importance of Charcot's international reputation is shown by the fact that, between 1874 and 1882, his '*Leçons cliniques*' were translated into German, Russian, English, Italian, Magyar, and Spanish. (B) Charcot's statue, which was melted down in 1942; the stone pedestal was removed in 1967. (C) Main entrance of the Hospice de la Salpêtrière (c. 1900) showing the statue of Charcot placed on the left. Sources: A: Charcot (1892); B and C: http://paris1900.lartnouveau.com/paris13/lieux/hopital_de_la_salpetriere.htm.

Vulpian and Charcot: a successful collaboration

In November 1861, Charcot and his friend and colleague Alfred Vulpian (1826–87), were promoted head (*Chef de service*) of the two departments of internal medicine of La Salpêtrière. They had known each other since 1848, when they had become interns. This has been the beginning of a long-standing friendship, interrupted only by Vulpian's death in 1887, with Charcot at his bedside. The two colleagues worked together, creating and sharing the same pathological anatomy laboratory. Between 1862 and 1865, they identified a series of clinical traits gathered on three patients (one from Vulpian's ward and two from

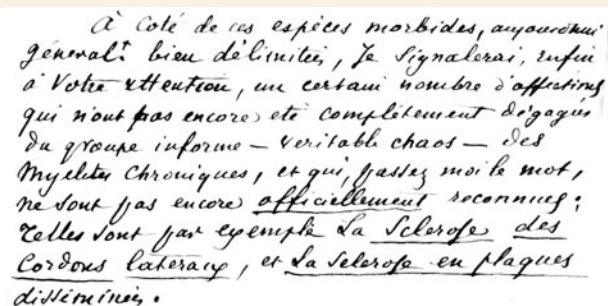
Charcot's) characteristic of a spinal form of multiple sclerosis. The cases were published by Vulpian (1866). Although Vulpian published alone, this was not to deny Charcot's contribution since in this publication he mentioned Charcot 18 times and even opened his communication by recalling a previous communication in *Union Médicale* (25 January 1865) by Charcot (alone) on '*Sclérose des cordons latéraux de la moelle épinière*' and insisted that it is Charcot who gave the name of the disease '*cette Sclérose en Plaques comme la nomme M. Charcot*' (Vulpian, 1866). Similarly, Charcot signed several papers on '*sclérose en plaques*' without Vulpian as co-author, although mentioning Vulpian's name iteratively and in his *Leçons Cliniques* Charcot referred to Vulpian's contribution multiple times. This situation is difficult to understand

as the two friends had numerous publications in common. A possible explanation being that in the years 1865–70, both were trying to obtain a full professorship and to be elected member of the Academy of Medicine and of the Academy of Sciences and I suppose that they could have been asked by their ‘hierarchy’ to publish independently of each other. Nevertheless, the close collaboration between the two was well recognized and in 1872 the correspondent of the British Medical Journal in Paris called them the ‘Castor and Pollux of experimental physiology and pathology’ (quoted in Goetz *et al.*, 1995). It is interesting to note that Vulpian, who is almost forgotten nowadays, had a brilliant, rapid academic career. By 41, he had been nominated to the prestigious Chair of pathological anatomy (1867) (following on from Jean Cruveilhier), then to the Chair of comparative and experimental pathology (1872), being a nominated member of the Academy of Medicine (1869), Academy of Science (1876) and being appointed dean of the Faculty of Medicine at the University of Paris (1875–81). This career contrasts with that of Charcot, whose academic progress was slower and more laborious, being elected to the Academy of Medicine 6 years after Vulpian and having failed three times to be elected to the Academy of Sciences. He succeeded Vulpian to the Chair of pathological anatomy in 1872, after having failed to be given a full professorship position in 1867. In several instances, Charcot had to seek Vulpian’s support to obtain academic appointments (Bogousslavsky *et al.*, 2011). However, by creating within La Salpêtrière a large clinical department and by interacting with numerous collaborators and students, including numerous fellows from all over the world, and obtaining in 1882 the first Chair of the nervous system diseases (*Chaire des maladies du système nerveux*), Charcot gained international recognition as the ‘father of modern neurology’ (Thorburn, 1967). Furthermore, his reputation was sealed as the founder of the ‘School of La Salpêtrière’ (*L’Ecole de la Salpêtrière*), a term introduced by Vulpian (Notice sur les travaux scientifiques de M. A. Vulpian Paris: Martinet, 1876. p.6). In 1898 a bronze statue of Charcot, by Alexandre Falguière, was erected at the main entrance of La Salpêtrière (Fig. 1B and C). Sadly, Charcot’s statue, as with many other bronze memorials, was deliberately melted down during World War II. As Georges Guillain noted (in 1956) quoting Horace ‘*Exegi monumentum ære perennius*’ [I have achieved a monument more durable than bronze; Horace (Odes, III, XXX, 1) quoted in Guillain G., JM Charcot 1825–1993, Sa vie son œuvre, Paris: Masson]. Ironically, the stone monument commemorating Vulpian, on rue Antoine Dubois in Paris, survived the cull.

The historical context

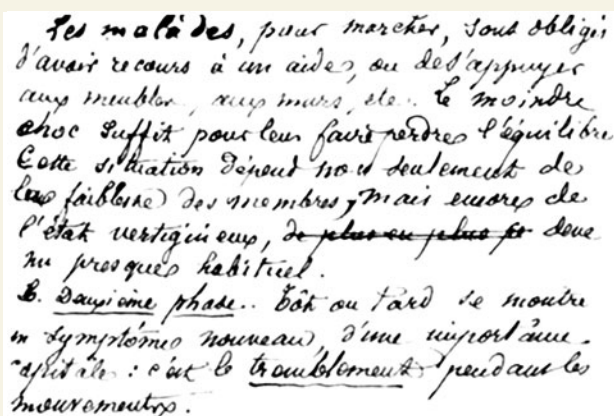
From 1866 Charcot (Fig. 1A) started to deliver his famous lectures, the formal course on Friday and the clinical training

on Tuesday evening. The Friday ‘*Leçons cliniques*’ were very carefully prepared, and we are lucky to have these handwritten manuscripts well preserved (Figs 2 and 3). Charcot began all his lectures with ‘Messieurs’, since in 1868 only men attended his lectures. At some point Augusta Klumpke probably attended Charcot’s lecture, but this was not before 1887, since on the famous painting by Brouillet ‘*Une leçon clinique à La Salpêtrière*’, only three women are shown: Blanche Wittman (the patient), Marguerite Bottard (Chief nurse) and



À côté de ces espèces morbides, aujourd'hui général: bien délimitées, je signalerai, enfin à votre attention, un certain nombre d'affections qui n'ont pas encore été complètement dégagées du groupe informe – véritable chaos – des Myélites Chroniques, et qui, passez moi le mot, ne sont pas encore officiellement reconnues; telles sont par exemple la Sclérose des Cordons latéraux, et la Sclérose en plaques disséminées.

Figure 2 A short extract of J.M. Charcot’s handwritten manuscript of his introductory remarks to the 1868 lectures (*Leçons cliniques*) (Charcot, 1868). ‘Beside these morbid symptoms usually well defined, I will, finally, point your attention to a certain number of diseases, which have not yet been completely cleared from the shapeless group – real chaos- of chronic myelitis, and which, pardon me the word, are not yet officially recognized; such are for example the sclerosis of lateral bundles and multiple sclerosis.’



Les malades, pour marcher, sont obligés d'avoir recours à un aide, ou des appuis sur une meuble, sur une mur, etc. Le moindre choc suffit pour leur faire perdre l'équilibre. Cette situation dépend non seulement de la faiblesse des membres, mais encore de l'état vertigineux, de plus en plus fréquent au presque habituel.
B. Deuxième phase. Bientôt ou tard se montre un symptôme nouveau, d'une importance capitale: c'est le tremblement pendant les mouvements.

Figure 3 Another example of the original handwritten manuscript of J.M. Charcot’s 1868 lesson on multiple sclerosis (Charcot, 1868). ‘To walk, the patients need some external assistance, or to lean on furniture, walls etc . . . The slightest shock is sufficient to knock them off balance. This situation results not only from the weakness of the limbs, but also their vertigo, which is common. The second phase: Sooner or later a novel symptom of crucial importance appears: this is the tremor during movements.’

Mlle Ecary (the nurse), and no women in the audience. Augusta Klumpke was allowed to enter the medical school in 1876 and was the first woman to be admitted as resident in 1887. Each lesson was prepared using a series of notes, including a careful and precise literature search. Charcot was quite fluent in English and German and it is of note that for articles in foreign languages he was copying complete paragraphs of German colleagues (e.g. Carl von Rokitanski or Ludwig Türk) as well as English literature such as papers by William Withey Gull or paragraphs of Brown-Sequart's 'Course of lectures on the physiology and pathology of the CNS' (given at the Royal College of Surgeons of England in May 1858). Then the final version was completely written and was delivered almost word for word, as can be ascertained by comparing the handwritten manuscript and the published version printed from the notes taken by his students or assistants (Charcot, 1872–1873, 1892). Everything was written, nothing being left to improvisation.

As mentioned above, at the end of the 19th century La Salpêtrière was a hospice where between 5000 and at some point, up to 8000 women were locked up. In the introductory remarks to his 1868 '*Leçons cliniques*' Charcot stated

'Sirs, ...those of you who are not familiar with our large hospice will not walk along our wards without being shocked by the considerable number of women of all ages reduced to a more or less advance infirmity stage due to diverse affections of the nervous system'.

Then Charcot mentions that he will focus his series of lectures on some diseases: 'not yet officially recognized as for instance sclerosis of lateral bundles and multiple sclerosis (*sclérose en plaques disséminées*). Those are rather barbarous names, which may hurt for the first time the ears of some of you' (Fig. 2).

Charcot was well aware of the existing scientific and medical literature and gave credit to the authors having published on related topics. He started by quoting the pioneer superb drawings and excellent clinical description by Cruveilhier (1835–42) and the figure in Carswell's Atlas (1838) weakened by the absence of clinical details. Here I need to mention one memorable transcription error: when quoting the two '*livraisons*' related to multiple sclerosis in Cruveilhier's atlas, Charcot correctly noted '#32 & 38' in the handwritten manuscript (p.13), while in the printed collection of 'Oeuvres complètes of JM Charcot' by Bourneville they are quoted '#22 & 23' (p.191). As for the debate on who between Cruveilhier or Carswell had published first, I invite the reader to refer to Alastair Compston's well documented introductory article in *McAlpine's Multiple Sclerosis* (2005). Without opening a dispute with my good friend Alastair, there is no question that he is correct concerning the 'Livraison XXXVIII pl. 1 & 2', since the patient Joséphine Paget was admitted at the Hôpital de la Charité in 1840, i.e. after Carswell's publication in 1838. However, whether 'livraison XXXII pl II, fig. 4' (Patient Dargès) was published before or after 1838,

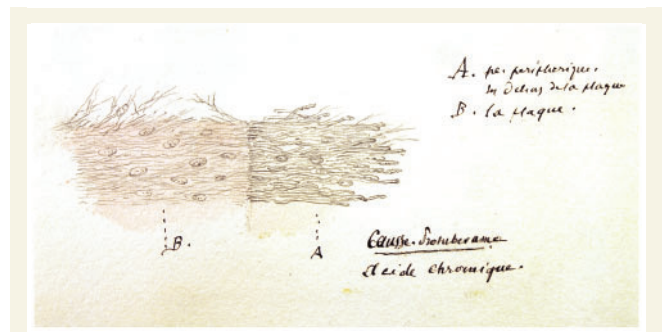


Figure 4 Original drawing from Charcot's notebook illustrating the limit of a lesion in the protuberance. Handwritten legend by Charcot; on the right: A. periphery outside the plaque. B. the plaque. Bottom: Cause [patient's name] Protuberance. Chromic acid. Source: Département de Neuropathologie, Groupe Hospitalier Pitié-Salpêtrière-Charles Foix, Musée de l'Assistance Publique-Hôpitaux de Paris.

the doubt remains. After Cruveilhier and Carswell, for the next 20 years or so, 'this question was left in the cold in France as well as in England, while Germany brought new elements' (Bourneville and Guérard, 1869). This essay is not the place to go through the contributions of the German school. I refer to the most important ones credited by Charcot, which were published between 1855 and 1867 by Ludwig Türk, Carl von Rokitansky, Eduard Rindfleisch, Ernst Leyden, Zenker, and also Karl Fromman, who first described 'greasy' accumulation in the sclerotic lesion (due to demyelination) and finally the two who could have described multiple sclerosis as they had the clinical and anatomic-pathological findings: Friedrich Theodor von Frerichs and his assistant Wilhelm Valentiner, who presented 15 cases in his paper dated 1856. However, as Charcot ironically noted: 'We are allowed to forgive Valentiner, as by grouping these 15 cases he has not proceeded with the most rigorous method...'. He then pursues by demonstrating that only 4 of the 15 cases could 'rigorously' be attributed to multiple sclerosis, two of them being in fact the cases reported by Cruveilhier. In his 1868 lecture Charcot commented: 'It is remarkable to see that a condition presenting with such a characteristic and striking anatomical substratum, and which in addition is not notoriously rare, has escaped for such a long time to clinical analysis' (Charcot *Leçons Cliniques*, May 1868).

Charcot the semiologist

Charcot was a very active physician. He made many astute observations, many of which were published: the correlation of clinical alterations, their physiological substratum with anatomic-pathological post-mortem descriptions. What was the trigger that led Charcot to understand that *La Sclérose en plaques* was a distinct nosological entity from shaking palsy and what permitted his diagnosis of multiple sclerosis

during the patient's life? Vulpian's 1866 publication described only the spinal form of multiple sclerosis, while the cerebral form had initially escaped Charcot and Vulpian's scrutiny. Bourneville, who Charcot considered as his son, relates the story of the discovery that has allowed Charcot to distinguish multiple sclerosis from 'paralysis agitans' (Bourneville and Guérard, 1869): Charcot had a servant named Luc. She suffered from tremors of the head and limbs, initially light, which aggravated progressively. Charcot initially diagnosed shaking palsy. However, Charcot noticed that in contrast to paralysis agitans, Luc's tremor was quiescent at rest, only occurring when carrying out voluntary movements. When no longer able to work, Luc was admitted at La Salpêtrière where she died in April 1866. Charcot performed the autopsy and observed numerous sclerotic plaques in the brain and spinal cord. These lesions whether in the brain or the spinal cord were similar, if not identical. At this point, Charcot realized that his servant in fact had a cerebrospinal form of multiple sclerosis. Shortly after, Charcot examined another patient whose symptoms were similar to those of Luc. This time he diagnosed multiple sclerosis during the patient's treatment, his diagnosis being confirmed at autopsy. The key to diagnosis was the difference in the semiology of the tremor in multiple sclerosis and the 'parkinsonian' tremor. Charcot mentioned:

'Paralysis agitans is the disease with which this form (cerebral) of *sclérose en plaques* has been most frequently confused. It is for this reason that when we endeavor to differentiate "*sclérose en plaques*" from the chaos of chronic myelitis that we proposed to M. Ordenstein, our student at this time, to oppose in a parallel approach the tremor in this disease from paralysis agitans.'

Ordenstein did so and defended his thesis in December 1867 (Ordenstein, 1868; see also Lehmann *et al.*, 2018).

Ordenstein wisely noted:

'It may appear illogic to establish a parallel between paralysis agitans and multiple sclerosis since in the present stage of our knowledge the former is the expression of a functional disorder while the latter corresponds to a lesion of the nervous system producing an array of symptoms resembling to some extent shaking palsy, ... for which the anatomical alteration is unknown'.

Later in the text Ordenstein wrote (p.51): 'M. Charcot in his lectures and at the patients' bedside has often had the opportunity to speak of this morbid condition, and I admit that these oral communications have been extremely helpful for writing my work'.

Charcot summarized the crucial finding by stating: 'In multiple sclerosis the tremor occurs only during intentional movements or when the patient intends to execute a movement and it never occurs in a resting state' (Fig. 3). Ordenstein thought this quality of the tremor was pathognomonic, while Charcot was more cautious, indicating that a similar type of tremor could also be observed in other conditions, but the key finding was the difference with the tremor observed in shaking palsy, which is present when the limbs are in a

resting state and stops only when the patient is deeply asleep. This feature was the trigger that led Charcot to understand that he was indeed facing two different diseases that could be differentiated from the patients' symptoms and not only at autopsy. In addition it occurred to him that, depending on the areas affected, multiple sclerosis could have a different clinical expression according to whether it was a purely spinal, or purely cerebral, but more often a cerebrospinal pathology.

Charcot the self-confident professor

In May 1868 Charcot felt that sufficient evidence had accumulated to announce, in a series of three outstanding lectures, the anatomo-pathology (sixth lesson), symptomatology (seventh lesson), and different clinical forms, aetiology and treatment (eighth lesson) of *Sclérose en Plaques* (Charcot, 1872–73). Charcot begins:

[in my previous lessons] I have noted some of the characters allowing to distinguish this disease [*paralysis agitans*] from another condition up to now confused with it, "*la sclérose en plaques disséminées*." ...Anatomically multiple sclerosis is a pathological condition clearly determined; clinically, it is another story and from this point of view there are many gaps we will need to fill ...'.

Then after an extensive review of the literature extending between 1835 and 1838, citing Cruveilhier and Carswell and the more recent contributions of the German school (see above), Charcot described the macroscopically visible multiple sclerosis lesions that he and Vulpian had observed, insisting on the fact that they are seen not only in the spine but also in the medulla, cerebellum or brain. Before describing multiple sclerosis lesions at the microscopic level, Charcot reminded the audience of the normal situation using slices given to him by Lockard-Clarke. He insisted on the importance of paying attention to the 'nevroglic' (quoting Virchow) since it is the nevroglic 'which plays a crucial role in some of the alterations of the nervous system'. He also described that the nevroglic is 'composed essentially of star-shaped cells with poor protoplasm and highly ramified thin processes'. Next, Charcot described the microscopic aspect of sclerotic lesions distinguishing three zones: the periphery of the sclerotic lesion, the transition zone and the centre of the lesion. The sharp limit between a lesion and the adjacent normal tissue is shown in Fig. 4. Figures 5 and 6 illustrate two aspects observed in the centre of the lesion: the demyelinated axons and the rarefaction of axons (due to axonal degeneration; Fig. 5) and the presence of myelin debris (greasy droplets; Fig. 6). Charcot commented that these greasy droplets resembled myelin destruction after sectioning a peripheral nerve. (Note that Charcot used the term 'myelin', a name introduced in 1858 by Virchow.) Charcot suggested that the clearing of this myelin debris was by



Figure 5 Original colour drawing from Charcot's notebook illustrating the centre of a sclerotic plaque. In the centre of the preparation is a blood vessel covered with many carmin positive nuclei and on each side are demyelinated axons of different diameter, lightly stained with carmin. In between the axons are thin fibrils, some associated with a nucleus. On the right is Charcot's handwritten legend: Sclérose en plaques—Mr Vulpian 24 April 1868 [indicating that it was Vulpian's patient]—Spinal cord no preparation. Source: Département de Neuropathologie, Groupe Hospitalier Pitié-Salpêtrière-Charles Foix, Musée de l'Assistance Publique-Hôpitaux de Paris.

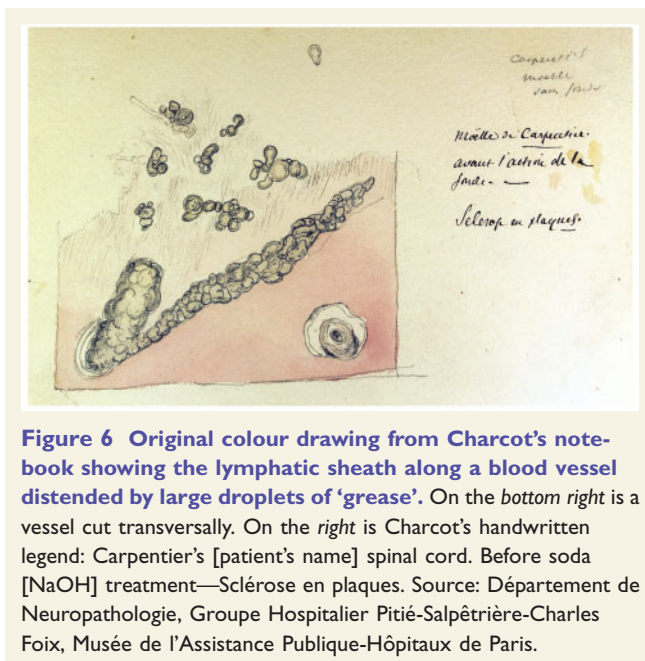


Figure 6 Original colour drawing from Charcot's notebook showing the lymphatic sheath along a blood vessel distended by large droplets of 'grease'. On the bottom right is a vessel cut transversally. On the right is Charcot's handwritten legend: Carpentier's [patient's name] spinal cord. Before soda [NaOH] treatment—Sclérose en plaques. Source: Département de Neuropathologie, Groupe Hospitalier Pitié-Salpêtrière-Charles Foix, Musée de l'Assistance Publique-Hôpitaux de Paris.

infiltration of 'lymphatic sheaths' present along small blood vessels. Charcot concluded his sixth lesson saying: 'Sirs, we are impatient to leave the anatomic-pathology of multiple sclerosis and take it into the clinic'. In chapters 7 and 8

Charcot gave an impressively detailed description of clinical signs of multiple sclerosis, insisting on the variability and versatility of symptoms, amblyopia, diplopia, the classic triad nystagmus, dysarthria, ataxia, the presence of cognitive manifestation, and more characteristic of spinal forms: weakness, spasticity, ankle clonus. Charcot insisted again on the importance of the tremor, in the cerebrospinal and cerebral form, to eliminate any confusion with shaking palsy, and introduced a tentative physiopathological explanation for the amplitude and range of tremor: 'the transmission would still proceed by means of denuded axons cylinder, but carried on irregularly producing oscillations, which disturb the execution of voluntary movements'. And Charcot's pessimistic conclusion:

'The prognosis is extremely severe. We have shown that despite remissions, lasting sometimes for very long period, the disease progresses by aggravation, in the end preventing any movements. We do not know of a single case of healing and one should be aware of complications that may occur during the course of the disease and increase its severity'.

Conclusion

Three factors contributed to Charcot's capacity to define multiple sclerosis: his role as professor at the hospice de La Salpêtrière where more than 5000 women were admitted, the large female/male ratio of patients with multiple sclerosis and his in-depth knowledge of the medico-scientific literature. His capacity for observation allowed him to spot the clinical differences in his servant's tremor as compared to patients with paralysis agitans. Moreover, he complemented his clinical observations with rigorous anatomic-pathologic investigation. Thus, the conditions were ripe for him to synthesize these scientific and empirical data into a new nosological concept: multiple sclerosis. Similar to the apple falling on Newton's head, this illustrates how serendipity, and a creative mind, can lead to major discoveries.

The remarkable series of lessons given 150 years ago illustrates how Charcot envisaged the investigation of diseases, these ideas were formulated in the speech he gave in 1883 when he was, at last, elected member of the French Academy of Sciences: 'I believe with equal conviction that the widely accepted intervention of the anatomical and physiological sciences into medical affairs is essential to further progress in medicine'.

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