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## History of neurology

# 1903 manuscript revived: Cerebral disturbances in multiple sclerosis (*Des troubles cérébraux dans la sclérose en plaques*) by Raymond Cestan (1872–1933) and Claudien Philippe (1866–1903)

## *Un manuscrit de 1903 ressuscité : « Des troubles cérébraux dans la sclérose en plaques » par Raymond Cestan (1872–1933) et Claudien Philippe (1866–1903)*

O. Walusinski (*Médecin de famille*)

20, rue de Chartres, 28160 Brou, France



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### ABSTRACT

Philanthropy aimed at helping medical research has been around for a long time. In the 19th century, cash awards were distributed by the French Academy of Medicine according to criteria determined by each generous donor. It was thus that Mrs. Bernard de Civrieux endowed the Academy each year with the task of supporting one or more laureates whose work furthered understanding of “nervous diseases”. In 1903, Raymond Cestan (1872–1933) and Claudien Philippe (1866–1903) were selected for their dissertation on “cerebral disturbances” during multiple sclerosis with clinical as well as anatomical-pathological effects. Never published, this innovative manuscript, taken from the library of Fulgence Raymond (1844–1910), will be analysed here after a brief biography of each author.

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### R É S U M É

La philanthropie destinée à aider la recherche médicale est ancienne. Au XIX<sup>e</sup> siècle, des prix en numéraires étaient distribués par l'Académie de médecine, suivant des critères déterminés par le généreux donateur. C'est ainsi que madame Bernard de Civrieux souhaitait que, chaque année, l'Académie honore un ou des lauréats œuvrant à l'approfondissement des connaissances « des maladies nerveuses ». En 1903, Raymond Cestan (1872–1933) et Claudien Philippe (1866–1903) sont honorés pour un mémoire consacré « aux troubles cérébraux » survenant au cours de l'évolution de la sclérose en plaques, tant du point de vue clinique qu'anatomopathologique. Jamais publié à ce jour, ce manuscrit novateur, issu de la bibliothèque de Fulgence Raymond (1844–1910), est analysé ici et complété des biographies des auteurs.

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## 1. Introduction

Marie-Élisabeth-Antoinette Bernard de Civrieux (1784–1834) was the wife of Marc-Antoine-Grégoire Michel (1771–1852), a banker and entrepreneur who made his fortune with the sale of Biens-Nationaux. In her will, she bequeathed to the Academy of Medicine a “yearly stipend of one thousand francs” to be used to fund “an annual prize awarded to the author of the best work on the treatment and cure of diseases linked to over-excitation of nervous sensitivity” [1].

In 1901, a committee of academicians including Valentin Magnan (1835–1916), Anatole Chauffard (1855–1932) and Fulgence Raymond (1844–1910), the committee’s rapporteur, proposed as the subject for this prize the study of cerebral disturbances in multiple sclerosis. Only one dissertation was submitted to the Academy, which awarded it the 1903 Prix Civrieux. Raymond praised it very highly to the Academy: “I consider this manuscript of prime importance in resolving the question posed” [2]. It would have been strange had he not praised the work, as it was prepared by two of his favourite students, both former *internes* (house officers) in his department in the positions of *chef de clinique* and laboratory director: Raymond Cestan (1872–1933) and Claudien Philippe (1865–1903). Raymond was certainly very attached to this never-published manuscript, which was nonetheless registered by the Academy, as the stamps on the cover attest. Raymond kept it in his personal library; he probably never brought it back to the Academy library. The path it followed as it was passed down to his heirs after the library was dismantled is unknown to us. In 2012, we acquired it through a Parisian bookseller. This original 113-pages manuscript, which includes four histological drawings in coloured ink, will be analysed below, within the context of what was known about multiple sclerosis at the time. The author’s biographies will also be presented. We have made the manuscript freely available as a typed transcription for ease of reading, accompanied by its magnificent iconography, at this address: [http://walusinski.com/data/cestan\\_philippe\\_1903.pdf](http://walusinski.com/data/cestan_philippe_1903.pdf).

This dissertation is referenced in the thesis of Armand Geay, defended in Lyon in 1903, according to the correspondence of Raymond with the Academy [3]. In 1903, Ernest Dupré

(1862–1930), in *Traité de pathologie mentale* directed by Gilbert Ballet (1853–1916), based his work on the thesis of Achille Souques (1860–1944) to describe the behavioural problems associated with certain cases of multiple sclerosis; he also extensively cited the conclusions of the work of Cestan and Philippe in suggesting an aetiology [4,5].

## 2. Raymond Cestan (1872–1933)

(Étienne Jacques Marie) Raymond Cestan (Fig. 1) was born on 6th April 1872 in Gaillac in the Tarn region of France where his father, a former *externe* (non-resident student) under Armand Trousseau (1801–1867), had practised medicine for 50 years. After secondary studies in Toulouse, he studied medicine in Paris, ranked 19th on the *externe* competitive entry exam in 1892, and 54th on the *interne* competitive entry exam in 1894. He was a student of Charles Féré (1852–1907) and Georges Thibierge (1856–1926), the latter noting in his file: “Good *interne* with whom I’ve had only very agreeable relations. Takes consistent care of the department while at the same time conducting laboratory work. Studies with a predilection for nervous diseases which he knows well.” He also studied under Fulgence Raymond (1844–1910) and finally Joseph Babiński (1857–1932), who noted: “I was extremely satisfied with Mr. Cestan who fulfilled his functions of *interne* with zeal and intelligence throughout the year.” In contrast are the administrative annotations in his file at the Public Assistance Offices: “Difficult character, very disagreeable relations, but hard-working”; a warning was addressed to him on 20th October 1898 for interpersonal difficulties with the hospital administration hierarchy, but no further details are available [6]. Among his contemporaries interested in biographical details, an anecdote circulated that might explain this. When he was working nights, Cestan discovered a gong in an attic of the La Salpêtrière Hospital. He began to bang on it, awakening the patients. One of them, already hospitalized at the time of Jean-Martin Charcot (1825–1893), “fell into a catalepsy. She had been one of the stars of the Tuesday lessons, and responded as docilely as she had to the old miracle-worker” [7].

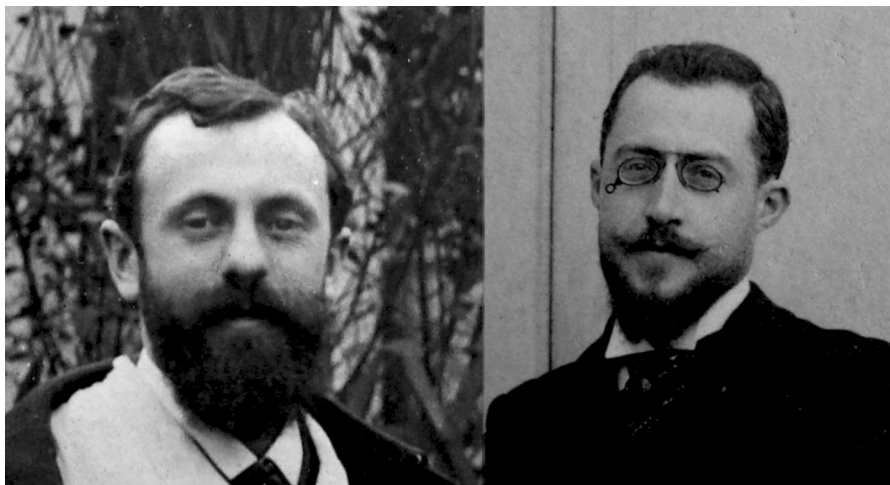


Fig. 1 – Left: Raymond Cestan in 1902; right: Claudien Philippe in 1899.

In 1899, Cestan defended his thesis, presided over by his teacher Raymond and covering Little syndrome [8]. Raymond made him his *chef de clinique* in 1899, then head of his laboratory in 1902. In the second half of the 19th century, further to descriptions given by Jean-Baptiste Cazauielth (1802–1849) in France and by the orthopaedist William John Little (1810–1894) in England, Charcot directed several student theses, for example “congenital cerebral atrophy” by Jules Cotard (1840–1889), in 1868, and a clinical study of athetosis occurring in “infantile cerebral hemiplegia” by Paul Oulmont (1849–1917), in 1878 [9–13]. Continuing along this path, Cestan reviewed all publications covering what was then called Little syndrome, to establish a unique pathogenesis for paralysis originating in the brain (Cazauielth and Cotard) and in the spine by Le Meigen in 1897 [14]. He based his work on cases gathered by his friend Maurice Lorrain (1867–?) at Bicêtre Hospital, in the department of Désiré-Magloire Bourneville (1840–1909), which he compared to the work of Sigmund Freud (1856–1939) [15,16]. Furthermore, he aimed to use this pathogenic model to provide a pathophysiological explanation for pyramidal contracture: “Is spasticity dependent on the absence of the pyramidal tract? What was thus the relationship between permanent spasmodic contracture and sclerosis in the motor tract?” Drawing on the work of Babiński and Raymond, he concluded that contracture is not always a function of pyramidal sclerosis. Cestan studied the fetal development of the pyramidal tract and also took an interest in the difficulties of eliciting the Babiński reflex in newborns. Furthermore, he established a distinction between premature births, neonatal asphyxiations, and cervical spine trauma in newborns during dystocia. “Pathological anatomy has recently proven that the clinical failure to show that lesion localisation determines all symptomatology, that localisation in the motor region determines motor disturbances, and that localization in frontal circumvolutions determines intellectual problems.” He reviewed all the theories concerning a pathophysiology for pyramidal contracture. He did not adhere to the concept developed by Charcot, Alfred Vulpian (1826–1887) and Paul Blocq (1860–1896) whereby the loss of an inhibitory function liberates pyramidal hyperactivity, preferring instead the theory of Constantin von Monakow (1853–1930) that postulates hyperactivity in the subcortical centres. Armed with this pathophysiology for cerebral or spinal neonatal paralyses, Cestan identified several aetiologies, notably prematurity and anoxia during dystocia, which led him to propose the concept of Little syndrome rather than Little disease [17].

Cestan lectured on the semiology of the nervous system at Clinique Charcot from 1899 to 1903. He passed the *agrégation* (competitive exam) in 1904. He went on to publish research conducted in the La Salpêtrière laboratory with Philippe under the title “Principales formes et histogénèse de la myélite tuberculeuse” in *La Revue Neurologique* in 1899, and “Sarcomes et sarcomatose du système nerveux” as well as “La neurofibromatose” in *La Revue Neurologique* in 1900. Along with Louis Le Sourd (1873–1961), in 1899 he played a role in disseminating and validating the “Babiński reflex”, proposed in 1896 and still subject to controversy [18]. With Paul-Edouard Lejonne (1872–?), Cestan tried to establish a semiology for behavioural problems in frontal lobe tumours [19]. Under Raymond’s

influence, he took an interest in familial myopathies [20]. With Ernest Huet (1858–1917), Cestan described the topography of muscular atrophies secondary to spinal pathologies, syringomyelia and poliomyelitis [21].

His name remains associated with that of his teacher in the description of antero-medial pontine syndrome or Raymond-Cestan syndrome, and with his colleague Chenais (1872–1950) for Cestan-Chenais syndrome, which corresponds to Babiński-Nageotte syndrome with additional damage to the nucleus ambiguus, responsible for a homolateral paralysis of the soft palate and one vocal cord [22–25].

Encouraged by Babiński, Cestan, with Louis Dupuy-Dutemps (1871–1946) confirmed a finding that Babiński had propounded since 1889. They published it in a general review under the title “Le signe pupillaire d’Argyll Robertson; sa valeur sémiologique; ses relations avec la syphilis”; more specifically he held that the loss of the reflex is not exclusively caused by tabes but is a pathognomonic sign of syphilis regardless of apparent symptomatology [26,27].

## 2.1. Career at Toulouse

His eldest brother, Étienne Cestan (1867–1912), a former *interne* in Paris as well as an urologist and professor of surgery in Toulouse, asked Raymond to join him in Toulouse in 1904. Cestan was a hospital physician in Toulouse starting in 1905, and was attributed the nervous and mental diseases chair in 1915. In his inaugural lesson, he declared: “Medicine is the least exact of the sciences; I would call it the most mobile”; this to explain that he intended to give medicine a solid foundation by dint of his heightened observational skills and an exceptional memory. During World War I, Cestan directed a wartime neurology centre in Toulouse, as did other neurologists throughout France in those days. He can indeed be said to have founded the Toulouse neurology school. His student Marcel-Marie Riser (1891–1975) took over his neurology chair when Cestan, in a very uncharacteristic move, took the clinical medicine chair and devoted himself to haematology work. He also sought to understand the mechanisms of visceral pain (angina, colic), linking neurophysiology, clinical medicine and humanist concepts. As he said: “In order to know much about one thing, it is necessary to know enough about everything” [28]. Another of Cestan’s activities was the local medical journal he directed, *Toulouse Médical*. In company of Albert Pitres’ student in Bordeaux, Henri Vigne (1873–1930), he wrote the fourth volume of *Précis de pathologie interne* directed by Victor Balthazard (1872–1950), which focused on the nervous system, and whose positive reception led to three successive editions from 1906 to 1912 [29]. He completed several works on the predictive value of diagnosing neurosyphilis in which he made references to the reactions of August von Wassermann (1866–1925) and the colloidal benzoin of Georges Guillain (1876–1961) in the CSF [30,31]. Apparently unaware of the work of Constantin von Economo (1876–1931), Cestan discussed in 1929 the encephalitis lethargic epidemic (during which cases of agrypnia occurred) and the usefulness of the disease for identifying hypnic brain centres; he was not, however, successful in this endeavour [32]. In Cestan’s last publication in 1934, Cestan and Riser rejected, once again premonitorily, any relation between neuromyelitis optica or Devic disease

(Eugène Devic, 1858–1930) and multiple sclerosis, based on anatomical-pathological arguments. They regretted “the absence of biological tools allowing an exact aetiological diagnostic”; such tools would not come of age until 2004 [33–36].

Briefly stricken with aphasia in 1933, he knew his days were counted. One year later, he died rapidly following a stroke.

### 3. Claudien Philippe (1866–1903)

Claudien Philippe (1866–1903), usually known as Claude Philippe (Fig. 1), born in Charolles (Saône et Loire region), started his house officership (*internat*) in Lyon in 1888, in the “department for incurable epileptics and the elderly” at the Hospice du Perron. In response to a serious diphtheria epidemic, he studied anatomical-pathology of the “diphtheritic acute interstitial myocarditis” with François Rabot [37]. In 1891, he ranked 38th on the *externe* competitive exam for the Hospitals of Paris, and worked for one year under Auguste Voisin (1829–1898) at La Salpêtrière. The following year, in 1892, he ranked 26th on the *interne* competitive exam. He was trained in nervous system anatomical-pathology by Albert Gombault (1844–1904), who considered him “excellent”; Chauffard considered him “a first-rate *interne*, absolutely devoted, very knowledgeable, and exceptionally valuable in all respects”. He continued his *internat* with Fulgence Raymond, Jacques-Joseph Grancher (1843–1907), Pierre Merklen (1852–1906) and Charles Féré (1852–1907) [38]. In 1897, Raymond presided over his thesis “Contribution à l’étude anatomique et clinique du tabès dorsalis”, defended before Georges Debove (1845–1920), André Chantemesse (1851–1919) and Antonin Marfan (1858–1942) [39]. Philippe first presented an anatomical-pathological history of locomotor ataxia, starting with the work Hippolyte Bourdon (1814–1892) and Jules Luys (1828–1897) and continuing through to that of Antoine-Auguste Pierret (1845–1920), Ernest de Massary (1866–1955) and Victor Babes (1854–1926). Aligning himself with the thesis of Jean Nageotte (1866–1948), Philippe employed the term *tabes*, which encompasses general paralysis and syphilitic locomotor ataxia. He also innovated “by drawing on old facts which are interesting but poorly interpreted”. Assisted by the research of his teacher Gombault, he described a new and more exact anatomy of the dorsal cords which he “studied using the most recent techniques”, i.e. with new dyes developed by Paul Ehrlich (1854–1915), Franz Nissl (1860–1919) and Camillo Golgi (1843–1926), whose work was considerably enriched by the very recent neuron theory of Santiago Ramon y Cajal (1852–1934) [40–43].

While he was still in his last year as an *interne*, Raymond named him “Head of pathological anatomy work at La Salpêtrière”, a position which Philippe held for seven years. He published a very large number of articles on aphasia, *tabes*, syringomyelia and acute encephalitis, notably in children (work completed with Bourneville), as well articles on nervous system sarcomatosis with Guillain, etc. [44–47]. His name remains associated with that of Gombault in the description of the “associative tract at the posterior spinal commissure” or “triangular tract of Gombault and Philippe” and in the description of “the periaxial segmental neuritis of Gombault and Philippe” [48].

Claudien Philippe suffered what was likely a sudden aneurism of a cerebral artery, at the age of 38, when he was taking the *agrégation* [49]. Philippe died a few days after being awarded the Civrieux prize; was he aware that he had been a laureate?

### 4. Vulpian and Charcot describe multiple sclerosis

Pierre Marie (1853–1940), in his lesson on spinal diseases given in 1891, summed things up as follows: “Charcot and Vulpian are deserving of credit for raising multiple sclerosis to the dignity of an anatomical-clinical entity, starting in 1866, by masterfully tracing the clinical picture of symptoms and defining the anatomical-pathological characteristics. The thesis of Ordenstein, inspired by Charcot, dates from 1867, and in 1869 the dissertation of Bourneville and Guérard was published, a monograph of genuine worth; since then multiple sclerosis has had its own existence.” [50–53]. Vulpian spoke of multiple sclerosis on 19th May 1866 in his address to the Medical Society of Paris Hospitals, in which he presented three observations, two of which were compiled by Charcot, accompanied by a complete histological study: “The histological study of the damaged parts revealed that the axial filaments and the exterior sheaths of the nerve fibres remained intact, which is not the case ordinarily, or at least not to that degree, especially for axial filaments, in cases of spinal tract atrophy, in the disease known as locomotor ataxia, for example. The existence of multiple sclerosis seemed to me to be potentially profitable for physiological research (...). We have observed in these cases a few interesting particularities, such as the existence of sclerotic plaques in the white and grey parts of the brain itself, and the same sort of plaques on the optical nerves” [54]. Charcot attributed the paternity of the initial anatomical descriptions in 1835 to Cruveilhier in France and to Robert Carswell (1793–1857) in England, even though this research was unable to establish anatomical-clinical correlations [55–57]. In 1868, Charcot published the disease complete clinical picture: shaking, diplopia, amblyopia, nystagmus, vertigo, parietic state with rigidity, early onset in young adults, and irregular progression with periods of remission. He was aware that the aetiology was still unknown and that young women are more often affected than men [58–60].

### 5. Analysis of the work of Cestan and Philippe

“In this work, we shall study the cerebral manifestation of multiple sclerosis. From this point of view, the word ‘cerebral’ has received various interpretations according to the author [...]. We will study any sign that may result from damage to the cerebral cortex, the semioval centre, the internal capsule and the central basal ganglia.” The presentation of Cestan and Philippe includes an initial part with “anatomical-pathological data” followed by a “clinical data” part. They cite the following words of Charcot: “the plaques of multiple sclerosis are very rarely found in the grey matter of cerebral gyri; the same is true for the cerebral cortex [...]. This opinion was generally

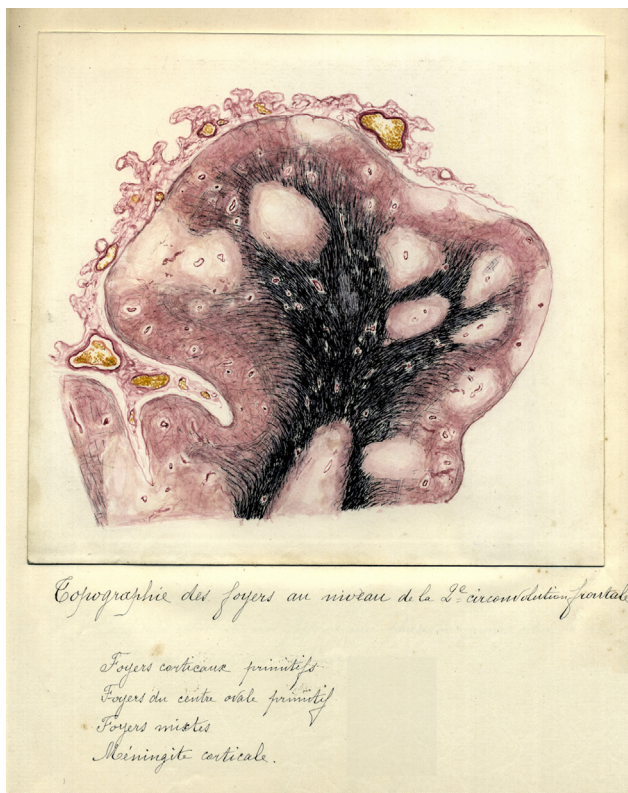


accepted to the point of nearly becoming convention.” In November 1899, Philippe, associated with his colleague René Jonès, had already presented to the French Society of Neurology an anatomical-pathological study of the cerebral cortex in multiple sclerosis. Drawing on this data and recent publications in Germany by E.W. Taylor, part of the laboratory of Hermann Oppenheim (1858–1919) in Berlin, and by Manfred Sander in Frankfurt, Cestan and Philippe agreed that “in reality, all of the brain’s grey matter is susceptible to the very specific pathological process of Charcot and Vulpian disease” [61,62]. They used new dyes, in particular the “Weigert-Pal method”, which entailed “dyes that make it possible to examine, separately, or one by one, so to speak, each element in the central nervous system”, and they developed “from our personal observations a new doctrine which focuses on the frequency of cortical lesions”, indicating that “while the plaques affecting the brain’s grey matter are very frequent in the nerve cells of the cortex and are particularly destructive there, such a pathological process cannot evolve without leading to both somatic and psychological disturbances” (Fig. 2) [63].

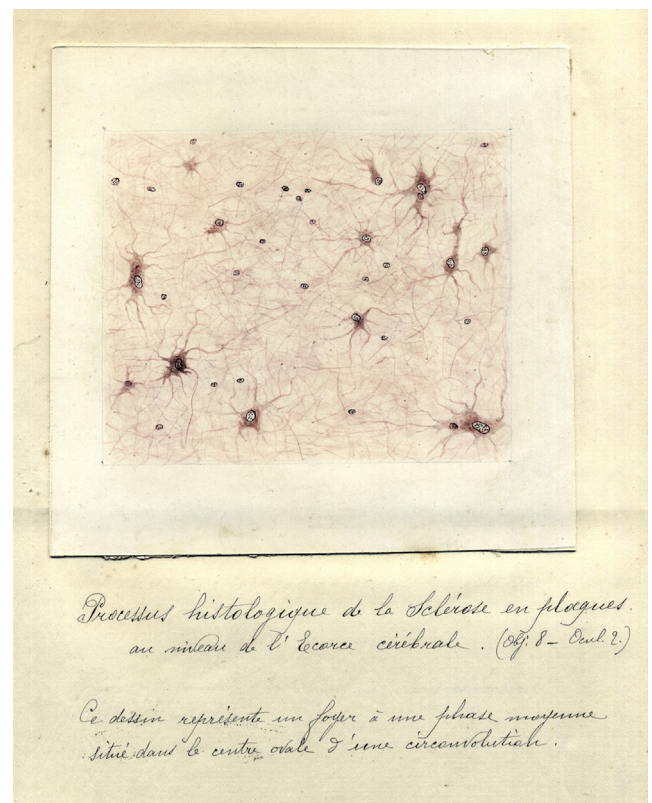
Going into further detail, they note: “Although we can affirm that cerebral cortex plaques are constant in all types of multiple sclerosis based on our personal cases, we must admit that their frequency varies greatly depending on the case.” Their description indicates “purely and simply the early onset of the neuroglia sclerosis from the first plaques in the cortical grey matter; we also think that it would be contrary to the reality of things to consider this sclerosis as a uniquely

secondary lesion, given its early onset and its initial intensity”. Cestan and Philippe give a clear indication of their viewpoint, which opposed the opinion of the time: “Does the nervous cell’s indefinite resistance in response to the sclerotic process in Charcot and Vulpian disease constitute an absolute law? Allow us to say from the start that we do not believe so” (Fig. 3). With what was an innovative concept for their time, they affirmed that “the nervous cells of the cerebral cortex ultimately disappear in relatively large numbers when the sclerotic plaque has existed for a long time”.

Cestan and Philippe go on in this work to present their “clinical data”. An often overlooked fact is that Charcot did not limit multiple sclerosis to sensory-motor problems with a spinal and subcortical origin, but noted early on the existence of cognitive problems during disease progression: “Most patients with multiple sclerosis whom I’ve had the occasion to observe presented quite a specific facies at a certain time during the condition. Their gaze is vague and uncertain; their lips are droopy and half-open. Their features express hebetude and sometimes even stupor. This dominant expression of the physiognomy nearly always corresponds to a mental state that is worth noting. There is a marked weakening of the memory; conceptualisation is slow, and the intellectual and affective faculties are dulled overall. What appears to dominate in these patients is a sort of indifference that is nearly wordless with regard to all things. It is not rare to see them sometimes laugh in a silly manner without any reason, and at other times to do the opposite, that is to burst into tears without any reason” [64].



**Fig. 2 – Topography of focal areas at the second circunvolution. Primitive cortical focal areas. Focal areas of the primitive semioval centre. Composite focal areas. Cortical meningitis.**



**Fig. 3 – Histological process of multiple sclerosis in the cerebral cortex. This sketch represents a focal area at an average stage located in the centre of a circunvolution.**

Neither Babiński nor Edmond Timal (1848–1908) did not describe cognitive disturbances in their thesis whereas Christéa-Stéphane Bouicli (1857–?) had referred to them, not long before, as “the anomalies and mild forms of multiple sclerosis” [65–67].

Cestan and Philippe were perfectly attuned to the psychological state of patients during the progression of their multiple sclerosis: “The intelligence may not undergo any alteration through to the end of the disease, but this is not always the case. The pain caused and perpetuated by the progression of the condition and by the bondage it creates is sufficient to instil over time a permanent sadness, intellectual and moral debilitation, and a sort of dementia. The damage that the disease creates in the brain, when it takes the cerebral-spinal form we are addressing here, is enough to determine the modifications to cerebral faculties. Memory weakens. It must however be said that, even in the cerebral-spinal form of the disease, these intellectual difficulties are far from frequent, or at least they are ordinarily not very marked, unless it is a matter of the last weeks or days of life.”

Cestan and Philippe reported on 30 observations, accompanied in seven cases by the autopsy. They ensure their diagnostic is correct based on clinical criteria: “Onset: after age 15, gait of cerebellar-spasmodic patient, exaggeration of tendon reflexes, plantar reflexes in extension, intentional shaking of the hands, slow and jerky speech, nystagmus, and finally optic neuritis in a few cases.” Taking into consideration education levels, they studied memory, logical reasoning and the psychological state of their patients. “The vast majority of our patients have a normal psychological state [...]. We carried out an autopsy on five of these patients having an absolutely normal psychological state and nonetheless, despite the integrity of their intellectual faculties, we found indubitable lesions from multiple sclerosis in the brain. In 15 patients, the euphoria noted by previous authors was very clearly exhibited. The faculty of memory was well preserved but the patients showed mental puerilism, laughing to the point of tears in response to the slightest antics; this was genuine laughter, lacking any spasmodic or convulsive aspect.” They concluded: “Of the thirty multiple sclerosis cases examined, we observed in 15 cases a specific psychological state, essentially characterized by prolonged crises of laughter or tears, a remarkable euphoria and a state of mental puerilism.”

Cestan and Philippe reviewed numerous previous publications, both French and foreign, for results comparison, despite the difficulty of ensuring the diagnosis of multiple sclerosis was the right one; they went so far to ask themselves if children can be affected by the disease. The following considerations appeared justified: “We cannot avoid noting a similarity between certain types of multiple sclerosis and patients with pseudobulbar paralysis, a condition which is also characterized by laughter and spasmodic tears, but in which it is often impossible to distinguish between mental weakening on one hand, and voluntary involvement of the laughter centre or spasmodic crying on the other, based on the theories of certain authors. Euphoria, temporary melancholia, mental puerilism, weakening of the memory, the tendency to laugh or cry, in a manner made abnormal by the futility of the motive as well as the length of the crisis; in our opinion, these are the most frequent mental disturbances that are truly specific to multiple sclerosis.”

After presenting these personal cases and the literature, they discussed differential diagnostics: “Hence the difficulty, at times extreme, to be certain in diagnosing multiple sclerosis and to differentiate this condition from hysteria, general paralysis and infantile encephalopathies.” They highlight, in these cases, the relevance of lumbar puncture and identifying the Argyll Robertson pupil. Drawing on Souques’ thesis, they seek to eliminate the diagnostic of hysteria by contesting the clinical pertinence “of the new symptom described by Babiński: diadocokinesia, a symptom indicating a change in the cerebellar system”, but they also attest that: “It appears that the clinical problem may be resolved now by examining ocular disturbances and by studying tendon and skin reflexes [...]. Babiński drew attention to the relationship between “spinal trepidation” and hysteria attacks. In his opinion, a hysteria attack does not determine, in and of itself, the exaggeration of tendon reflexes and especially, spinal trepidation [...]. There could no longer be any doubt, according to Babiński, with regard to the plantar reflex, which always occurs in a flexion position in normal individuals and would most often take place in extension with multiple sclerosis” [68,5].

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## 6. Conclusion

This work by Cestan and Philippe contributed new data at the time it was published:

- frequent presence of grey matter plaques, mainly in the cerebral cortex; noted as exceptional by Charcot, but in agreement with more recent works by Taylor in 1892 and Sander in 1898;
- confirmation of mental and psychological disturbances, already noted by Charcot and Bouicli, but ignored by Babiński.

Currently, the results of studies using recent quantitative and functional MRI techniques confirm the data of Cestan and Philippe. They point to diffuse damage in the cerebral cortex, in grey matter as well as white matter, that progresses with time. The evaluation of cortical lesions is corroborated by sensory-motor and cognitive dysfunctions [69,70].

Although undoubtedly very far away from the concepts of Cestan and Philippe, current research still addresses inflammation, only at the molecular level, and is accompanied by the study of apoptosis within microglia and macrophages, giving rise to a concept known as the “inflammasome” [71].

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## Disclosure of interest

The author declares that he has no conflicts of interest concerning this article.

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