



Jean-Martin Charcot and the Conceptual Foundations of Multiple Sclerosis Diagnosis: *From the Anatomo-Clinical Method to Modern Diagnostic Criteria*

(History of Medicine)

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Abstract

Jean-Martin Charcot's work on multiple sclerosis (MS) represents a cornerstone in the history of neurology. By integrating meticulous clinical observation with pathological anatomy, Charcot transformed a heterogeneous constellation of neurological symptoms into a distinct nosological entity. In doing so, he established a conceptual framework grounded in clinical reasoning, dissemination of lesions in space, and the temporal evolution of disease. These principles remain the foundation of modern diagnostic criteria for MS. This article revisits Charcot's original contributions and examines how subsequent diagnostic frameworks—from the Schumacher criteria to the Poser criteria and later the McDonald criteria—have progressively translated Charcot's clinical insights into structured diagnostic tools integrating neuroimaging and biological markers. Although modern technologies have greatly improved diagnostic sensitivity and specificity, the fundamental paradigm introduced by Charcot remains unchanged. Contemporary diagnosis continues to rely on the integration of clinical evaluation, imaging, and laboratory findings, guided by the principle that multiple sclerosis should only be diagnosed when there is no better explanation for the observed findings.

Keywords: Charcot, Jean-Martin; diagnostic criteria; dissemination in space and time; history of neurology; multiple sclerosis

Introduction

Jean-Martin Charcot (1825-1893) was not only a great neurologist but a scientist whose work profoundly shaped the history of multiple sclerosis (MS). MS itself occupies a crucial place in the development of neurology as a discipline. Through Charcot's work, the study of MS became more than a methodological exercise leading to a diagnosis; it established a conceptual foundation that highlighted three fundamental aspects: the importance of the clinical method, the spatial dimension of lesions—forming the basis of the concept of spatial dissemination—and the temporal evolution of the disease, which Charcot described with remarkable precision and which later became the basis of the concept of temporal dissemination.

In his lectures, when introducing the clinical method to younger colleagues, Charcot often emphasized that *the facts are already there; one only needs to know how to see them* (“*Les faits sont là; il faut savoir les voir*”). This remark captures the very essence of the scientific method in neurology: the careful, systematic, and rigorous observation of clinical phenomena. Within this framework, clinical semiology plays a fundamental role, particularly in the observation and interpretation of MS.

Within its historical context, Charcot's contribution addressed a major challenge: that of disease identification. Before Charcot, MS was not recognized as a single pathological entity. The confusion arose from the difficulty of attributing a wide range of polymorphic symptoms to a single disease. Charcot's merit was to apply a rigorous methodological approach inherited from his predecessors—such as René Laennec (1781–1826) and Claude Bernard (1813–78)—integrating clinical observation with pathological anatomy and physiology. Through this work, Charcot transformed a heterogeneous constellation of neurological symptoms into a distinct nosological entity.

Integrating Clinical Observation and Pathological Anatomy

The innovation of Charcot's contribution to MS lay in his systematic combination of clinical observation with post-mortem pathological examination. Through this approach, he identified patterns of disease and recognized that apparently heterogeneous symptoms could arise from a single underlying condition. His work built upon existing knowledge. Earlier anatomopathologists, such as Jean Cruveilhier (1835–42) and Robert Carswell (1793-1857), had already illustrated macroscopic lesions of the central nervous system in their anatomical atlases. However, Charcot went further by integrating these observations within a coherent clinical framework.

Another crucial aspect of Charcot's legacy was the creation of a scientific school. At the Salpêtrière he trained a generation of brilliant students, among them Leopold Ordenstein (1835-1902). Under Charcot's supervision, Ordenstein published a doctoral thesis describing the clinical characteristics of MS, carefully distinguishing its symptoms and early manifestations from those of Parkinson's disease (PD), then known as *paralysis agitans*, that were often confused with it. This work represented one of the first systematic descriptions of MS as a distinct nosological entity. In his thesis, Ordenstein highlighted differences in symptomatology and disease onset, noting in particular the distinction between the resting tremor characteristic of PD and the action tremor observed in MS. Although such distinctions may seem obvious

today, they were groundbreaking observations in the 1860s. The thesis also included anatomopathological descriptions of lesions in both the brain and the spinal cord. Tragically, Ordenstein died prematurely after being murdered, and his contribution was widely commemorated in the French press for its importance in distinguishing *paralysis agitans* from MS.

These developments paved the way for the three lectures that Charcot gave on the topic of MS in 1868 (lessons number 6, 7 and 8). Charcot left nothing to chance: he meticulously prepared his lectures and even produced detailed drawings of pathological anatomy. He described both macroscopic and microscopic lesions in the spinal cord, medulla, cerebellum, and brain. In his seventh lecture he discussed the clinical characteristics of the disease, emphasizing what later became known as Charcot's triad. In the eighth lecture he addressed issues that we might today call phenotyping, as well as the etiology and treatment of the disease, although therapeutic options were extremely limited at the time.

The so-called Charcot triad—nystagmus, dysarthria, and ataxia—became a classical hallmark of MS. Yet Charcot's contribution went far beyond describing this triad. Through his careful analysis of patients' symptoms, he documented a wide range of manifestations, including diplopia and cognitive dysfunction. Remarkably, he was among the first to describe cognitive disturbances in patients with MS. By bringing together this heterogeneous symptomatology under a single clinical framework, he defined what he termed *sclérose en plaques*, now known as MS.

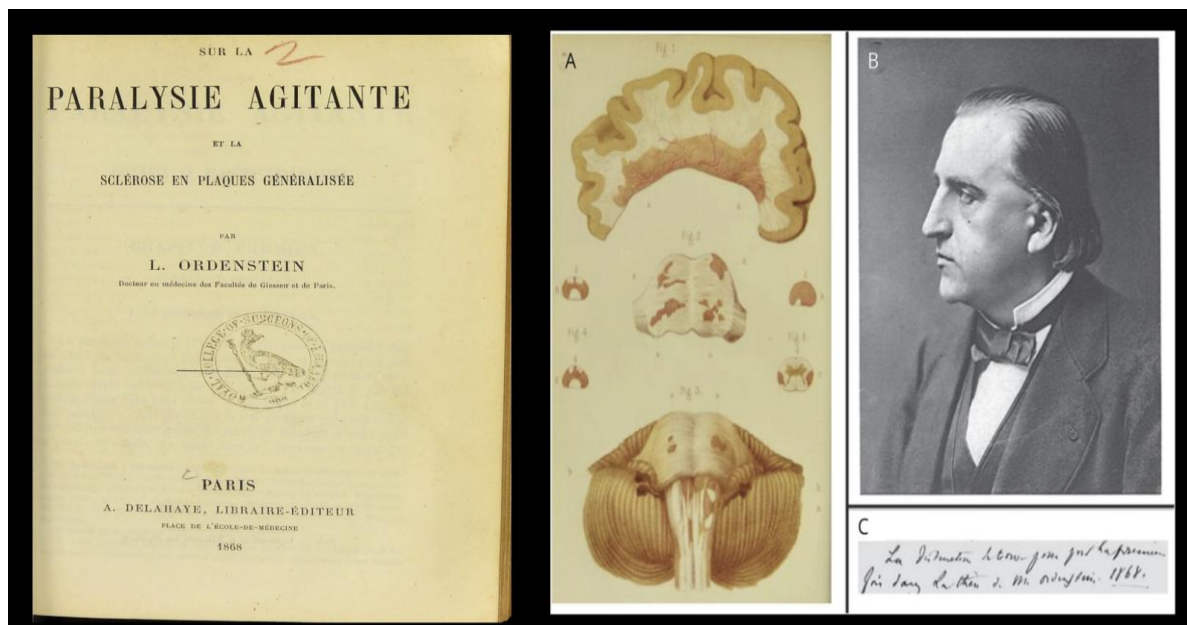


Figure 1. Title page of Leopold Ordenstein's 1868 doctoral thesis *Sur la paralysie agitante et la sclérose en plaques généralisée* (Paris).

Charcot also established a fundamental correlation between clinical manifestations and pathological findings. He clearly distinguished the macroscopic and microscopic features of MS from those observed in other diseases. In PS, for example, pathological changes appeared relatively nonspecific, whereas in MS distinct demyelinating lesions were observed in both the brain and spinal cord.

At the microscopic level, Charcot described characteristic features including demyelinating lesions and the presence of so-called “fatty granulations”—small lipid droplets resulting from the breakdown of myelin—along with inflammatory infiltrates typical of MS. These observations represented an important step forward in microscopic neuropathology. Charcot highlighted several key aspects: the sharply defined borders between lesions and normal tissue; the gradual transition between normal-appearing and pathological white matter; and the central clearing within lesions associated with demyelination and lipid debris. Charcot illustrated these discoveries through detailed drawings.

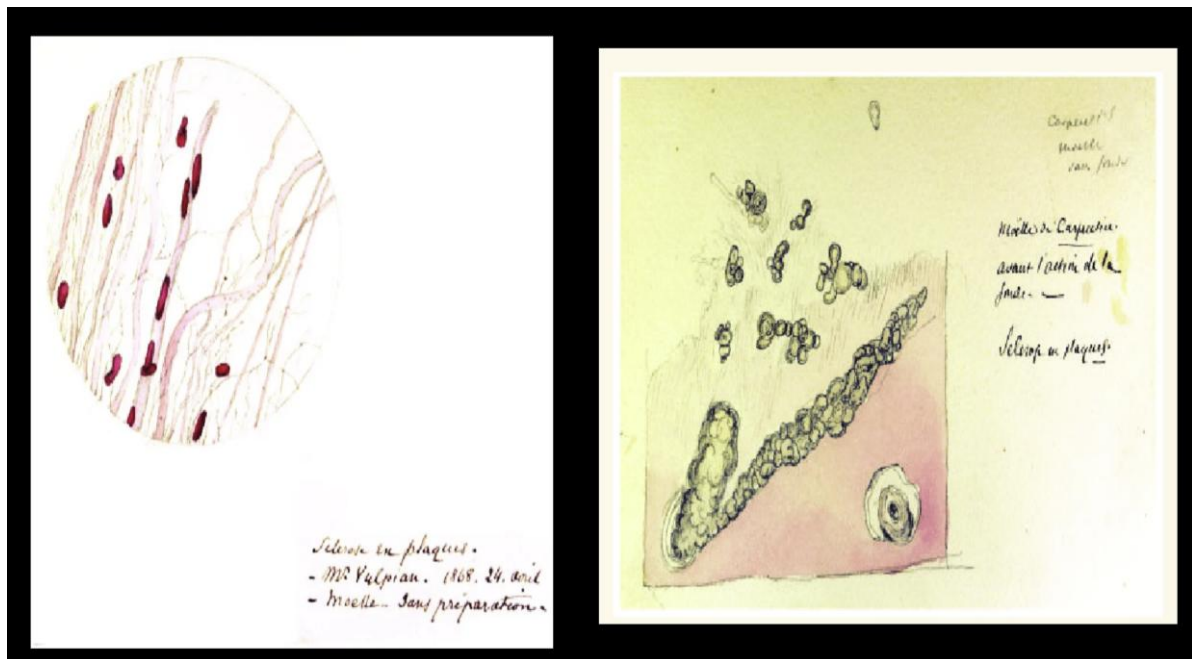


Figure 2. Neuropathological illustration of a sclerotic plaque as described and drawn by Charcot.

The concept of myelin itself had only recently been introduced by Rudolf Virchow (1821-1902) in 1858. Building on this emerging knowledge, Charcot hypothesized that the disease involved the removal of myelin by cells associated with blood vessels and proposed a pathogenic model of MS. In this model, demyelination leads to the destruction of myelin, the accumulation of lipid debris, and the subsequent inflammatory vascular processes responsible for clearing this material. In doing so, Charcot anticipated the modern understanding of MS as an inflammatory demyelinating disease of the central nervous system.

Spatial and Temporal Dissemination: The Conceptual Roots of Modern Diagnosis

Charcot's approach to MS represented not only a nosological achievement but also a fundamental epistemological step. By moving from a constellation of symptoms to a clearly defined disease entity with its own clinical and pathological identity, he established a paradigm that remains central to MS diagnosis today: the concepts of spatial and temporal dissemination, together with a clinical approach aimed at diagnosis and differential diagnosis against disease mimics.

The concept of spatial dissemination, which still underlies modern diagnostic criteria, was already described by Charcot. He observed that lesions were distributed in multiple regions of the central nervous system—supratentorial, infratentorial, and spinal. This was not merely an anatomical observation but a conceptual framework linking lesion distribution to clinical symptomatology. Today, magnetic resonance imaging (MRI) allows us to visualize these lesions with far greater sensitivity. Yet the paradigm itself remains unchanged. MRI did not invent the concept of spatial dissemination; rather, it made visible and objectively demonstrable what Charcot had already inferred through careful clinical and pathological observation in 1868.

The concept of temporal dissemination, which represents a further cornerstone of the diagnostic criteria for MS, was also already implicitly present in Charcot's observations. He described its course as slow and progressive, characterized by phases of clinical worsening alternating with periods of partial improvement. In other words, he recognized the fluctuating yet progressive nature of MS long before formal diagnostic frameworks were developed.

Modern diagnostic criteria gradually translated these clinical observations into structured definitions. In 1965, the Schumacher criteria formalized the clinical diagnosis of MS, relying primarily on clinical evidence of dissemination in time and space. In 1983, the Poser criteria introduced paraclinical parameters, including cerebrospinal fluid analysis, thereby strengthening diagnostic confidence. A major shift occurred with the McDonald criteria introduced in 2001 and subsequently revised several times, most recently in 2024. These criteria incorporated MRI, allowing the demonstration of dissemination in space and time through neuroimaging. In doing so, modern diagnostic frameworks progressively translated Charcot's original clinical insights into structured diagnostic tools integrating neuroimaging and biological markers.

Charcot's Prognostic Insights and the Modern Concepts of Early Diagnosis and Early Treatment

Charcot's own clinical descriptions of the disease were strikingly categorical regarding prognosis. He depicted MS as a severe and relentlessly progressive disease. According to his observations, the illness advanced gradually, leading to increasing neurological impairment and eventually to severe limitations of movement. He emphasized that no cases of true recovery were known and that complications during the disease course often worsened the prognosis. Interestingly, the modern concept of "silent progression", or progression independent of overt relapses, finds a conceptual precursor in Charcot's work. His clinical insight already suggested that MS leads to permanent and lasting alterations in neurological function. In contemporary

terms, this can be interpreted as an early recognition of the neurodegenerative component of the disease. This intuition also provides the rationale for one of the central principles of modern MS management: early therapeutic intervention. If the disease leads to irreversible neurological damage from its early stages, treatment should be initiated as soon as possible to modify the course of the disease and limit long-term disability.

Above all, Charcot gave us the conceptual roots of our current understanding of MS. At the heart of modern MS research and treatment lies the goal of preventing lesion formation and protecting the central nervous system, objectives that resonate strongly with the pathological mechanisms Charcot first described. These conceptual foundations have profoundly influenced modern strategies for diagnosis and treatment. The aim today is to anticipate the diagnosis as early as possible, reducing the interval between the first symptoms and the initiation of therapy, and thereby protecting the nervous system through treatments that limit inflammatory and degenerative processes. The continuous revision of diagnostic criteria reflects this effort.

Historically, the diagnostic timeline was considerably longer. With the Schumacher criteria in 1965, clinicians had to wait for a second clinical relapse before establishing the diagnosis. The Poser criteria in 1983 introduced paraclinical tests, including cerebrospinal fluid analysis, but the time required to reach a diagnosis often remained long—frequently several years. The introduction of the McDonald criteria in 2001, with the integration of MRI, marked a turning point: for the first time, diagnosis could often be made at the very onset of the disease. What fundamentally changed was our ability to observe the disease *in vivo*, rather than only through neuropathological examination after death. MRI now allows the demonstration of both spatial and temporal dissemination, for example through the simultaneous presence of contrast-enhancing and non-enhancing lesions. In this sense, modern neuroimaging has made visible what Charcot had already inferred through clinical-pathological reasoning. Thanks to these developments, the diagnosis of MS has increasingly approached what might be described as a biological diagnosis. Even in the absence of clear clinical symptoms, the presence of MRI features with high sensitivity and specificity may allow the identification of demyelinating disease and the initiation of treatment.

In essence, what we do today remains deeply connected to what Charcot taught us: to recognize demyelinating lesions and interpret their significance. Modern MRI sequences function almost like a form of *biological microscopy*, allowing us to visualize *in vivo* the pathological processes that Charcot once described through anatomical drawings. The implementation of modern diagnostic criteria has dramatically reduced the average time to diagnosis, with important positive consequences for patients. Earlier diagnosis allows earlier treatment, which in turn has translated into improved long-term outcomes. For example, comparisons between patient cohorts diagnosed before 2010—when escalation therapy strategies were more common—and those diagnosed after 2010 show a reduction in the proportion of patients developing severe disability and autonomic dysfunction. In other words, today we are increasingly able to change the course of MS.

At the same time, caution remains essential. Diagnosis cannot rely exclusively on MRI findings. There is a real risk of diagnostic error, as some conditions may present with white matter lesions that satisfy radiological criteria for spatial dissemination but are not due to MS. For this reason, clinicians must consider not only radiological “red flags” but also clinical red flags. Only by integrating imaging findings with careful clinical evaluation can the risk of misdiagnosis be minimized.



Figure 3. *Une leçon clinique à la Salpêtrière* (1887), André Brouillet's painting depicting Charcot teaching at the Salpêtrière Hospital.

Conclusions

Our present—and our future—rest on conceptual foundations laid long before modern technology existed. This is not a matter of academic nostalgia or a ceremonial tribute to historical figures. It is the recognition that many of the principles guiding today's scientific approach were already articulated with remarkable clarity at the Salpêtrière by Charcot. He had no access to MRI, neuroimmunology, cerebrospinal fluid biomarkers, or modern genetics. What he possessed instead was a rigorous methodological mindset, refined clinical semiology, systematic observation, and an extraordinary epidemiological intuition. These intellectual tools enabled him to construct a framework that continues to shape our understanding of MS more than a century later. The intellectual architecture of MS diagnosis—the integration of clinical observation, anatomical reasoning, and temporal evolution—remains fundamentally the one established by Charcot.

Background Bibliography

Charcot JM. 1872. *Leçons sur les maladies du système nerveux faites à la Salpêtrière*. Paris.

Compston A, Coles A. 2008. Multiple sclerosis. *Lancet* 372:1502–1517.

Goetz CG. 1995. *Charcot: Constructing Neurology*. Oxford University Press.

McDonald WI, Compston A, Edan G, Goodkin D, Hartung HP, Lublin FD, McFarland HF, Paty DW, Polman CH, Reingold SC, Sandberg-Wollheim M, Sibley W, Thompson A, van den Noort S,



Weinshenker BY, Wolinsky JS. 2001. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. *Annals of Neurology* 50(1):121–127.

Montalban X, Lebrun-Fréney C, Oh J, Arrambide G, Moccia M, Amato MP, Amezcua L, Banwell B, Bar-Or A, Barkhof F, Butzkueven H, Ciccarelli O, Chataway J, Cohen JA, Comi G, Correale J, Deisenhammer F, Filippi M, Fiol J, Freedman MS, Fujihara K, Granziera C, Green AJ, Hartung HP, Hellwig K, Kappos L, Kimbrough D, Killestein J, Lublin F, Marignier R, Marrie RA, Miller A, Otero-Romero S, Ontaneda D, Ramanathan S, Reich D, Rocca MA, Rovira À, Saidha S, Salter A, Sastre-Garriga J, Saylor D, Solomon AJ, Sormani MP, Stankoff B, Tintore M, Tremlett H, Van der Walt A, Viswanathan S, Wiendl H, Wildemann B, Yamout B, Zaratini P, Calabresi PA, Coetzee T, Thompson AJ. 2025. Diagnosis of multiple sclerosis: 2024 revisions of the McDonald criteria. *Lancet Neurology* 24(10):850–865.

Ordenstein L. 1868. *Sur la paralysie agitante et la sclérose en plaques généralisée*. Paris: Delahaye.

Poser CM, Paty DW, Scheinberg L, McDonald WI, Davis FA, Ebers GC, Johnson KP, Sibley WA, Silberberg DH, Tourtellotte WW. 1983. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. *Annals of Neurology* 13(3):227–231.

Schumacher GA, Beebe G, Kibler RF, Kurland LT, Kurtzke JF, McDowell F, Nagler B, Sibley WA, Tourtellotte WW, Willmon TL. 1965. Problems of experimental trials of therapy in multiple sclerosis: report by the panel on the evaluation of experimental trials of therapy in multiple sclerosis. *Annals of the New York Academy of Sciences* 122:552–568.

Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, Correale J, Fazekas F, Filippi M, Freedman MS, Fujihara K, Galetta SL, Hartung HP, Kappos L, Lublin FD, Marrie RA, Miller AE, Miller DH, Montalban X, Mowry EM, Sorensen PS, Tintore M, Traboulsee AL, Trojano M, Uitdehaag BMJ, Vukusic S, Waubant E, Weinshenker BG, Reingold SC, Cohen JA. 2018. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurology* 17(2):162–173.

Zalc B. One hundred and fifty years ago Charcot reported multiple sclerosis as a new neurological disease. *Brain*. 2018;141(12):3482–3488.

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