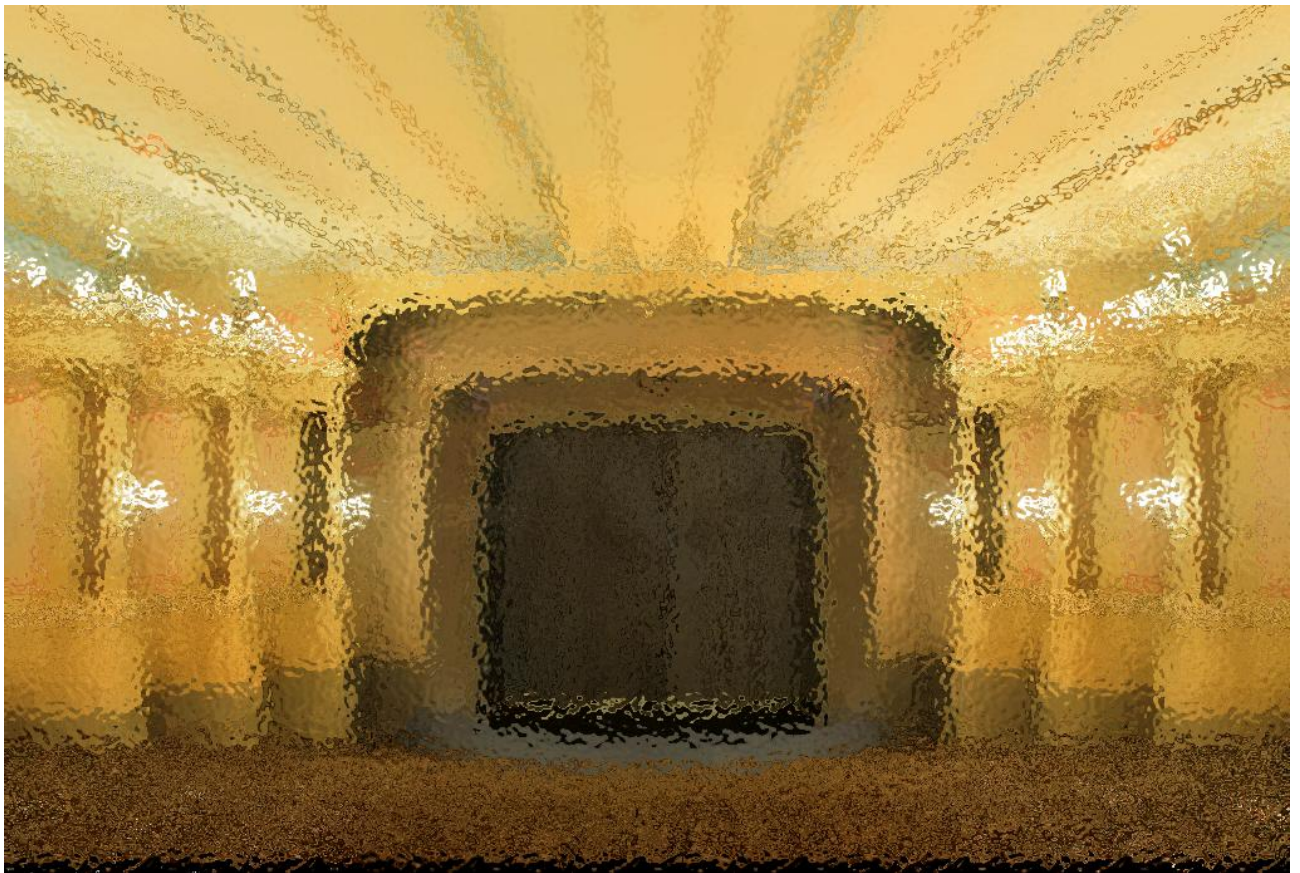


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Cover: Reality or mirage? This blurred image of the *Bayreuth Festspielhaus*—opened in 1876, one hundred and fifty years ago to present Richard Wagner’s operas—looks like a mirage and reflects a nineteenth-century aesthetic aimed at immersing the spectator and momentarily suspending critical distance. In the same year, the first issue of the *Iconographie photographique de la Salpêtrière* was published. At the Salpêtrière, Charcot founded modern neurology on a counter-model of vision: his anatomo-clinical theatre was based on critical distantiation, on the idea that clinical phenomena must be questioned, dissected, described, and organized.

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While several journals currently explore the history of neuroscience, each tends to reflect specific disciplinary orientations. In contrast, *The Charcot Journal* offers a more integrative and dynamic platform—one that fosters dialogue among historians, neuroscientists, clinicians, and scholars from the humanities and social sciences. It is distinguished by its commitment to interdisciplinary inquiry, the inclusion of underrepresented perspectives, and a focus on the evolving cultural and ethical dimensions of neuroscience.

By encouraging cross-disciplinary engagement, this journal aims to illuminate the historical foundations of neurology through critical contributions that bridge medicine, philosophy, cultural studies, psychology, and the history of science.

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Bayreuth and the Salpêtrière 1876-2026: 150 Years of Seeing Differently

(Editorial)

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The year 2026 marks a double anniversary: the 150th year since the first Wagnerian festival in Bayreuth (*Bayreuther Festspiele*), featuring the inaugural complete staging of the *Ring des Nibelungen*, and the publication of the first volume of the *Iconographie photographique de la Salpêtrière* (*Bourneville and Regnard, 1876*). At first glance, these events seem to inhabit entirely separate worlds, one musical, the other medical. Yet a closer look reveals hidden parallels that invite reflection.

Already in 1883, the French newspaper *Le Figaro* drew an unexpected comparison between Richard Wagner (1813-1883) and Jean-Martin Charcot (1825-1893), calling both “great showmen”. The journalist Félix Platel (1832-1888), writing as *Ignotus*, Anonymus, remarked: “Charcot has monopolized hysteria. He astonishes men. He frightens women... He advanced science in the manner of Wagner, the great musical ham [*grand cabotin*]” (*Platel 1883*). At first, the analogy may seem odd, but it captures something essential: both men transformed their respective fields by reshaping the conditions of spectatorship.

A few years later, in 1888, the philosopher Friedrich Nietzsche (1844-1900) published *Der Fall Wagner*, a ferocious critique of the composer. Although writing in German, Nietzsche used a French phrase to deliver his verdict: *Wagner est une névrose* (*Nietzsche 1888*). In this pamphlet, Wagner appears as a hypnotic figure, a sort of snake charmer who captivates his audience and feeds on their emotional energy (*Sommer 2015*). Nietzsche was familiar with Charles Féré’s (1852–1907) research on hysteria and hypnosis, and even without naming the famous French physician, the parallel he draws is unmistakable (*Brigo 2025; Marshall 2025*).

This parallel becomes clearer when we consider Wagner’s radical reconfiguration of theatrical experience. He did not simply compose operas; he reinvented the very conditions of musical perception. In Bayreuth, he designed a theatre for total immersion: the orchestra hidden in the pit, the auditorium darkened, the spectator’s gaze fixed exclusively on the stage (*Spotts 1994*).

This was a dramatic departure from the traditional opera house, which functioned as a social arena as much as an artistic one. Remarkably, with Wagner, architecture changed because the theory of musical drama changed. And it is no coincidence that *theatre* and *theory* share the same Greek root, *theaomai*, “to see.”

Here the connection with Charcot becomes particularly suggestive. Charcot, too, in a sense built a theatre—an anatomico-clinical theatre—where architecture, staging, and the choreography of bodies were all designed to discipline and direct the observer’s gaze. His lectures were theatrical not in terms of aesthetic performance, but because they were structured around the act of seeing (Didi-Huberman 1982). The patient’s body became the stage on which disease manifested itself (Figure 1). As Sigmund Freud (1856-1939) noted, Charcot was a *visuel*, a man of vision (Freud 1893). His demonstrations were not spectacles for their own sake; they served as the visual scaffolding through which he constructed and communicated theory. Once again: theatre and theory.

Continuing along this path of etymological and metalinguistic resonance, the Latin *spectare* (an intensive form of *specio*, “to look”) gives us *speculum* (mirror), *spectaculum* (spectacle), and *spectrum* (spectre) (Principe 2018). The first term reminds us that every act of seeing mirrors the observer’s point of view; vision is never neutral. Charcot’s gaze upon his patients differed profoundly from the medical gaze that preceded him. Much has been written about the spectacular dimension of the Salpêtrière (Didi-Huberman 1982; Marshall 2016; Brigo 2025), yet it is equally revealing to consider the parallel between the anatomical theatre—not as a site for dissecting corpses, but for the *in vivo* dissection of symptoms—and the theatre as an architectural space for artistic performance.

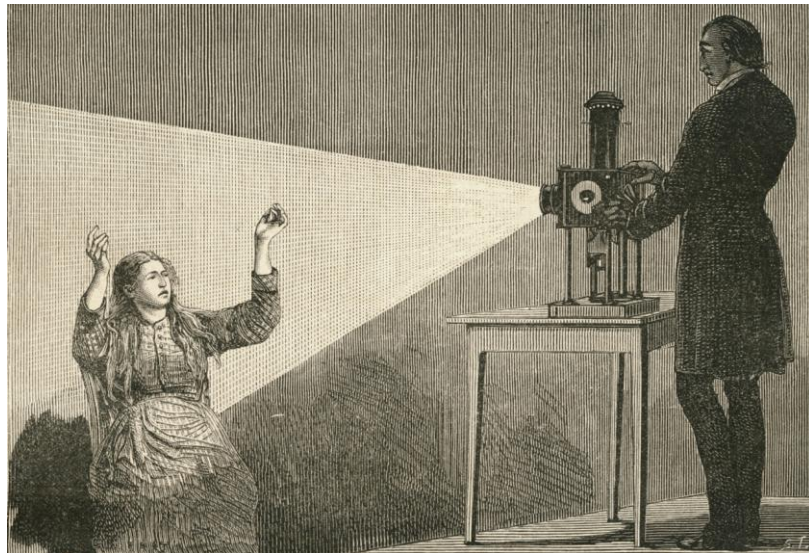


Figure 1. Illustration published in A. Cartaz, *Du somnambulisme et du magnétisme: À propos du cours du Dr Charcot à la Salpêtrière*, *La Nature*, 1879;7(1). The image depicts a Salpêtrière patient in a cataleptic state induced by electric light produced by a projector fitted with an electric source—likely a carbon arc device—during Charcot’s demonstrations on hysteria and hypnosis.

The shared etymology of *spectacle* and *spectre* also illuminates the divergence between Wagner and Charcot. In Wagner's operatic world, the goal was identification between spectator and performer: dissolving the fourth wall through the invisible orchestra and the darkened hall, creating a spectacle that mirrored (*speculum*) reality while enabling what Wagner called *phantasmagoria*, a realm of apparitions (*phantasmata*, spectres) into which the spectator could be drawn, even hypnotized (Wicks 2024). In Nietzsche's reading, Wagner was a sorcerer (Nietzsche 1888).

Charcot the physician, by contrast, did not deal in *phantasmata* but in *phenomena*, a term that shares the same Greek root (*phainomai*, to appear). For Charcot, steeped in positivism, the phenomenon appears like a spectre that must be approached with critical distance. Everything that is seen requires interpretation and explanation, to avoid mistaking a mirage for reality or, in his own words, to "not mistake shadow for the prey" (Charcot 1887), for reality may lie beneath deceptive appearances. If Wagner sought to dissolve the boundary between observer and reality, Charcot sought to preserve it, proposing a mode of looking that, however intrinsically and inevitably subjective, aimed to be objectifying (Veggetti Finzi 1990). Charcot's Salpêtrière became not only a physical space but also a cognitive instrument designed to show, teach and learn by understanding and organizing clinical phenomena.

Hence, Wagner's Bayreuth and Charcot's Salpêtrière reveal two complementary models of modern vision. Wagner transformed theatre into an immersive apparatus that absorbed the viewer into the spectacle; Charcot transformed medicine into a visual discipline that demanded analytical distance. One pursued fusion, the other separation—yet both relied on the same fundamental principle: that seeing is never passive, never innocent, but always epistemologically charged. Every spectacle carries its spectres, every mirror reflects a point of view, and every act of looking shapes the reality it seeks to understand.

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Jean-Martin Charcot: Mapping Epilepsy and Functional Seizures at the Salpêtrière

(History of Neurology)

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Abstract

In the late nineteenth century, Jean-Martin Charcot played a pivotal role in distinguishing epilepsy from functional seizures at a time when both conditions were often conflated under the concept of hystero-epilepsy. Working at the Salpêtrière Hospital in Paris, Charcot developed a rigorous anatomo-clinical method grounded in systematic observation and detailed documentation, helping transform neurology into an empirically based discipline. Through clinical teaching, photographic documentation, and collaboration with colleagues such as Londe and Regnard, he produced some of the earliest visual and descriptive analyses of seizure semiology and functional neurological disorders. Charcot carefully differentiated seizure types, including petit mal and grand mal, and emphasized the clinical importance of brief absence episodes. His school further advanced the understanding of focal epilepsy, particularly through the work of Albert Pitres, who correlated focal motor seizures with cortical lesions identified at autopsy, anticipating modern concepts of epileptogenic localization. At the same time, Charcot investigated “hysteria”, describing the staged semiology of the “grand hysterical attack” and promoting systematic clinical observation rather than sensational interpretation. Contrary to later portrayals that characterized him as misogynistic or as having “invented” hysteria, historical analyses suggest that Charcot maintained a rigorous scientific approach and supported the careers of several women physicians. Toward the end of his career, he also proposed that psychological trauma could produce somatic symptoms beyond conscious control, anticipating later developments in dynamic psychology by Janet and Freud. Charcot’s work ultimately clarified the relationship between epilepsy and functional disorders while highlighting the complex interaction between neurological and psychological processes.

Keywords: Jean-Martin Charcot, Epilepsy, Functional Seizures, Hystero-epilepsy, Seizure Semiology, Salpêtrière Hospital



Introduction

In the late nineteenth century, the neurologist Jean-Martin Charcot (1825-1893) emerged as a central figure in delineating the boundaries between epilepsy and functional (dissociative) seizures (*Hingray et al. 2025*). Today, these conditions can usually be distinguished through careful semiological analysis and, when available, correlation with video-electroencephalographic recordings (*Revajová et al. 2026; Dudley et al. 2024*). In Charcot's era, however, such distinctions were far from straightforward. Clinical observations were complicated by a conceptual overlap between epilepsy and what was then termed hystero-epilepsy, a category that blurred neurological and psychological interpretations of paroxysmal phenomena (*Drouin et al. 2020*). Within this complex clinical and intellectual landscape, Charcot systematically documented seizure disorders, laying the groundwork for modern neurology and shaping the frameworks through which these conditions would subsequently be understood. His meticulous attention to clinical detail and insistence on rigorous observation helped transform neurology from a descriptive field into an empirically grounded discipline.

The Salpêtrière Hospital: Historical and Medical Context

The Salpêtrière Hospital was the stage upon which Charcot made his foundational contributions. It is also remembered for darker chapters of history: during the 1792 September Massacres, many women hospitalized there were killed. Even a century later, the condition of women within medical institutions remained problematic. Charcot worked within a cultural climate shaped by deeply ambiguous-and often misguided-ideas about female illness. These prevailing notions included the belief that women were inherently more susceptible to emotional and neurological disturbances, a bias that influenced diagnosis and treatment throughout Europe.

In the United States, seizure diaries from the late nineteenth century document patients-sometimes labeled hysterical-who in fact experienced frequent epileptic status (*Devinsky 2007*). In Europe, theories such as the "ovarian theory" of hysteria led to therapeutic practices that today seem astonishing: acute compression of the ovaries during a hysterical attack, or chronic compression devices intended to correct presumed organ dysfunction (*Jarrell and Stahnisch 2021*). Another American theory proposed venous hyperemia as the cause of attacks, leading physicians to compress the carotid arteries during seizures, a practice that reflected the era's blending of physiological experimentation with clinical intervention. While these procedures are now obsolete, they would later evolve into experimental explorations of vagal nerve function and, eventually, vagus nerve stimulation-a therapeutic modality still used in epilepsy management today (*Lanska 2002*).

Charcot's Method and School

Charcot introduced a rigorous anatomo-clinical method and trained an extraordinary generation of neurologists who would shape the future of the discipline. Paintings of his famous lectures depict a crowded amphitheater, with clinicians and artists documenting the proceedings.

Lacking video-EEG or motion pictures, Charcot relied on photography to capture the fleeting and complex manifestations of neurological disorders.

One of his principal collaborators was Albert Londe (1858-1917), a pioneering photographer who devised a multi-lens system capable of capturing sequential images—an early form of chronophotography. Through these sequences, he documented the phases of the "grand hysterical attack," including dramatic opisthotonos postures and bizarre contractures, providing an unprecedented visual record of functional disorders. Another major contributor was Paul Regnard (1850-1927), who, with Désiré-Magloire Bourneville (1840-1909), produced a photographic atlas of neurological patients (*Regnard and Bourneville 1880*). Regnard himself had artistic ambitions, exhibiting photographs derived from clinical subjects, blurring the boundary between science and art. These visual records were not merely illustrative; they became essential tools for teaching, research, and the development of semiology.

Charcot and Epilepsy

Jean-Martin Charcot, as a professor of neurology at the Salpêtrière Hospital, delivered a series of dialogue-style case presentations on general neurological disorders between 1887 and 1889, never previously translated into English. These cases provide a first-hand view of Charcot's teaching method and his perspectives on various neurological conditions. One patient, in particular, exhibited bizarre ambulatory spells, likely representing absence status, which Charcot recognized as epilepsy. This otherwise healthy young man, with no history of generalized epilepsy or hysteria, suddenly became unaware of his surroundings during these spells, wandered across Paris and its outskirts, and engaged in complex interactions with others. Charcot traced the patient's movements, analyzing differential diagnosis, treatment, and pathophysiology of these intermittent episodes (*Goetz 1987*).

On January 31, 1888, Charcot devoted a lecture to epilepsy, carefully distinguishing between petit mal and grand mal. He described individuals who suddenly became unconscious, dropped objects, and resumed conversation as if nothing had happened—a phenomenon resembling childhood absence epilepsy but observed in adults. He also noted a "vertiginous" phase, leaving open whether he observed generalized absences or focal impaired-awareness seizures. Charcot recognized that even brief absence seizures could significantly impair quality of life, demonstrating a modern sensitivity to functional impact beyond dramatic clinical presentation (*Charcot 1887*).

In the photographic collections of Regnard and Bourneville, many patients labeled with "partial epilepsy" showed clear motor or neurological deficits, often sequelae of cerebral palsy or stroke. Contrary to common belief, patients with epilepsy were more numerous at the Salpêtrière than those diagnosed with hystero-epilepsy. Some photographic sequences depict a tonic phase with a cry and progressive contracture, consistent with focal epilepsy, though definitive classification remains uncertain.

Albert Pitres (1848-1928), Charcot's pupil, applied the anatomo-clinical method to nearly fifty cases of focal motor seizures with cortical lesions confirmed at autopsy, revealing somatotopic organization and anticipating modern concepts of epileptogenic and symptomatogenic zones in presurgical evaluation. This meticulous correlation between clinical observation and



neuropathology helped establish principles that continue to underpin modern epilepsy surgery (*Brigo 2025*).

The "Myth" of Charcot's Misogyny

Charcot faced criticism from contemporary feminist groups, yet historian Christopher Goetz argues that claims of misogyny lack historical foundation. Women such as Blanche Edwards (1858-1941) and Dr. Augusta Klumpke (1859-1927) thrived under his mentorship, challenging the simplistic image of Charcot as hostile to women. More importantly, he did not view hysteria as exclusively female, recognizing male hysteria as underdiagnosed rather than rare (*Goetz 1999*).

Among Charcot's most famous patients was Louise Augustine Gleizes (born 1861, date of death unknown), known as Augustine. Historical analyses reject any suggestion of inappropriate conduct by Charcot, instead highlighting his scientific rigor in documenting functional disorders. Augustine's case became emblematic of Charcot's method: systematic observation, photographic documentation, and staged demonstrations for educational purposes, without sensationalism or moral judgment (*Walusinski 2013*).

Was the Hysteria of the Salpêtrière "Invented"?

Some claimed that Salpêtrière hysteria was an "invented disease," a narrative recounted by Pierre Marie (1853-1940) in 1925 (*Marie 1925*). Administrative changes separating psychiatric and epileptic/hysterical patients inadvertently exposed functional patients to dramatic epileptic seizures, raising the question of how observation and imitation may have shaped semiology. While some exaggeration or mimicry may have occurred, contemporary scholarship emphasizes that Charcot's patients were genuinely afflicted, and that his systematic classification and documentation reflected scientific precision rather than theatrical invention.

The Semiology of "Grande Hystérie"

Charcot's description of the "grand hysterical attack," as reported in Paul Richer's seminal work on hysterо-epilepsy, unfolds in stages (*Richer 1881*):

- Prodomal Phase: Psychic disturbances, hallucinations, emotional lability, and hysterogenic zones. Patients often reported vague sensations or emotional premonitions preceding the attack.
- Epileptoid Phase: Tonic rigidity, staring gaze, carpopedal spasm, clonic movements; variable and exaggerated compared to stereotyped epileptic seizures.
- Contortion Phase ("Clownism"): Extreme postures including opisthotonos and arc de cercle, often photographed for didactic purposes.

- *Attitudes Passionnelles*: Expressive, theatrical, sometimes ecstatic postures; iconic examples include Augustine.

The sequence could last many minutes, occasionally including hallucinations or residual contractures. Early instruments, such as plethysmographs, attempted to quantify motor patterns, differentiating hystero-epilepsy attacks from tonic-clonic seizures (Table 1). Charcot's attention to these fine-grained motor patterns anticipated modern movement disorder analysis and neurophysiological assessment.

Feature	Hystero-epileptic Attacks	Epileptic Attacks
Aura	None	None
Cry	Repeated, prolonged screams at the beginning and during the clonic period; rarely absent	Inaudible, muffled cry only
General stiffness	Yes	Yes
Limb attitude	Variable	Constant
Cruciform (cross-like) position	Yes	No
Clonic movements	Very extended, highly variable; projecting the thorax, pelvis, torsions, etc.	Limited, momentary clonic shocks
Tympanism (distension of the abdomen)	Present	Absent
Attack termination	Ovarian compression stops the attack	No effect on attacks
Consciousness	Rapid recovery	Prolonged deep sleep, associated with stupor
Delirium	Present	Violent delirium
Cried during attack	Yes	No
Attack duration	Series lasting 4 to 5 hours	Isolated attacks
Other features	Delirium, singing	—

Table 1. Comparison of hystero-epilepsy attacks and epileptic seizures (from Richer P. 1881, modified).



Psychic Trauma and Dynamic Psychology

Toward the end of his career, Charcot proposed that psychic trauma-sometimes manifesting in dreams-could generate somatic symptoms, operating outside conscious control. This anticipation of dynamic psychology bridged his work to that of Pierre Janet (1859-1947) and Sigmund Freud (1856-1939). Charcot's recognition of the mind-body interface demonstrated remarkable prescience: he understood that neurological symptoms could be modulated by psychological states, and conversely, that psychological distress could manifest in physical pathology (Gelfand 2024).

Conclusions

In tracing Charcot's trajectory across epilepsy and hysteria, a coherent intellectual arc emerges. He clarified the distinction between epilepsy and hystero-epilepsy, advanced the idea that psychic trauma can manifest somatically, and laid the groundwork for modern dynamic psychology. Charcot's legacy endures not only in the anatomo-clinical method and semiology of seizures, but in the insight that neurological and psychological phenomena are deeply intertwined-a principle that continues to guide neurology and psychiatry today. His work reminds us that careful observation, rigorous documentation, and an integrative approach to mind and body remain as relevant now as they were in the halls of the Salpêtrière over a century ago.

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Revisiting Charcot's Role in the History of Parkinson's Disease

(History of Neurology)

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Abstract

The history of Parkinson's disease is deeply connected to Jean Martin Charcot. Building on James Parkinson's *Essay on the Shaking Palsy*, Charcot transformed a loosely described disorder into a coherent clinical syndrome, recognizing that "the essential clinical elements of the disease had already been described" by Parkinson. His synthesis of clinical observation, autopsy material, and earlier accounts established a diagnostic framework that remains central to modern teaching. Charcot refined the description of rest tremor, distinguishing it from the tremor observed in multiple sclerosis and cerebellar disorders, and underscored the role of emotional excitation in modulating symptom severity. His descriptions of posture, gait, rigidity, and facial expression remain strikingly accurate. He also used visual media—including clinical illustrations and a commissioned sculpture—to convey the typical Parkinsonian posture. Despite extensive pathological investigations, Charcot and his collaborators could not identify the underlying lesion, a gap later filled by the work of Paul Oscar Blocq (1860-1896), Gheorge Marinescu (1863-1938), and Constantin Tretiakoff (1892-1956) on substantia nigra degeneration. His therapeutic explorations ranged from plant alkaloids with transient benefit to mechanical vibration devices that anticipated later neuromodulatory approaches. Charcot's methodological clarity and clinical precision continue to shape contemporary understanding of Parkinson's disease.

Keywords: Charcot, Jean Martin; Parkinson's disease; History of Neurology; Tremor classification

The history of Parkinson's disease is closely intertwined with the work of Jean-Martin Charcot (1825-1893) and the Parisian neurological school of the late nineteenth century. Speaking about Parkinson's disease inevitably leads to reflecting on the relationship between Charcot and the earlier observations of James Parkinson (1755-1824). Although Parkinson had published his seminal monograph, *An Essay on the Shaking Palsy*, it was Charcot and his students who systematized the condition and gave it the clinical form in which it is recognized today.

One interesting historical point is that Charcot himself refused to name the disease after himself. Instead, he insisted that the disorder should bear Parkinson's name. The reasons for this decision were probably several, but they likely reflected Charcot's cultural and intellectual background. In the small treatise written by Parkinson in 1817, Charcot recognized that the essential clinical elements of the disease had already been described. Many of the symptoms that Charcot later discussed in his lectures were, in fact, derived from Parkinson's original observations.

It is also worth remembering that Parkinson was not only a physician. He was in many respects a naturalist and geologist, and his scientific interests extended well beyond medicine. Indeed, in museums dedicated to geological discoveries, collections associated with Parkinson can still be found. He practiced general medicine, but his scientific curiosity extended across several disciplines. Charcot likely recognized that an observer who was not confined within the strict boundaries of academic medicine could still make an important cultural and scientific contribution to the identification of disease.

Charcot's lasting influence stems not only from his originality but from his ability to synthesize disparate observations into coherent clinical entities. Even in today's environment—defined by instantaneous access to vast digital resources and the growing role of artificial intelligence—the act of synthesis remains essential. Information alone does not produce understanding; it must be organized, interpreted, and integrated.

Charcot excelled precisely at this. He gathered clinical descriptions, autopsy findings, and earlier accounts—most notably Parkinson's—and shaped them into a unified diagnostic framework. The clinical picture he articulated continues to underpin the diagnosis of Parkinson's disease nearly two centuries later, a testament to the durability of his method.

If one explains Parkinson's disease to medical students today, the core symptoms described by Charcot still form the foundation of clinical teaching. The tremor, the rigidity, the slowing of movement, and the progressive postural alterations that develop over time remain the essential elements of the syndrome. This continuity between nineteenth-century observation and modern clinical practice is remarkable.

One of the most striking aspects of Charcot's work concerns his attention to tremor. His analysis of tremor and its differential diagnosis was extraordinarily refined. He carefully described the frequency and characteristics of tremor and distinguished the tremor of Parkinson's disease from other forms. In particular, he separated it from what he called "senile tremor," which likely corresponds to what we now identify as essential tremor. His descriptions demonstrate a remarkable sensitivity to clinical detail.

These insights emerge clearly from works derived from Charcot's lectures, particularly those compiled by his students. Among them, Leopold Ordenstein (1835–1902)'s 1868 thesis stands out for its examination of the differential diagnosis between *paralysis agitans*—the term then used for Parkinson's disease—and multiple sclerosis (*sclérose en plaques*). In these texts, tremor is described as a pattern of continuous, spontaneous oscillations that may intensify under emotional excitation. Charcot repeatedly noted that emotional stimuli could amplify the manifestations of tremor, an observation that remains clinically relevant today.

Charcot also described how, with advancing years of disease, postural deformities and structural changes become more prominent. Patients develop a characteristic forward flexion of the trunk and an increasingly distinctive gait pattern. The clinical picture becomes dominated by postural instability and rigidity. These descriptions are strikingly consistent with modern observations of Parkinson's disease.

Charcot's clinical acuity also manifested in his skill at distinguishing Parkinson's disease from other movement disorders capable of producing tremor or abnormal motor patterns. He described the characteristic facial expression of the Parkinsonian patient and contrasted it with that seen in other conditions, including what we now identify as supranuclear palsy, later described by Richardson, Steele, and Olszewski in 1963 as a form of progressive parkinsonism. His clinical illustrations and atlas plates reveal both the precision of his bedside observation and his uncommon ability to translate complex clinical phenomena into clear visual form.

In these works Charcot also attempted to classify tremors according to their origin. He compared the tremor of Parkinson's disease with cerebellar tremor and other neurological tremors. The analytical clarity of these comparisons is impressive, especially considering the limited physiological knowledge available at the time.

Another fascinating element of Charcot's work is his effort to represent the typical posture of the Parkinsonian patient visually. Remarkably, he even commissioned a sculpture of a patient with Parkinson's disease, intended to illustrate the characteristic posture and facial features of the condition. This representation captured the flexed posture, the incomplete closure of the lips, and the distinctive facial expression associated with the disease. Such artistic and anatomical representation reflects Charcot's deep interest in the visual communication of neurological signs.

At the same time, Charcot and his collaborators were investigating the pathological basis of the disease. Despite their careful autopsy studies, however, they were unable to identify the specific lesion responsible for Parkinson's disease. They examined numerous brains and described various structural changes, but the crucial alteration—the degeneration of neurons in the substantia nigra—remained undiscovered.

Part of the difficulty stemmed from the expectations that shaped nineteenth century pathology. Disease was typically identified through visible, macroscopic lesions, and conditions such as multiple sclerosis offered precisely that: clear structural abnormalities that could be demonstrated in the nervous system. Parkinson's disease, by contrast, involved subtle and localized neuronal degeneration that left no obvious trace with the investigative tools then available. The absence of a demonstrable lesion made it harder for clinicians to anchor the disorder within the prevailing pathological framework, delaying its integration into the anatomical–clinical method that defined Charcot's era.

As a result, Charcot and his colleagues concluded cautiously that the true lesion responsible for the disease had yet to be identified. They acknowledged that although various anatomical alterations could be observed, none provided a consistent explanation for the clinical syndrome.

The link between Parkinsonian symptoms and damage to the substantia nigra was clarified only later, when Paul Oscar Blocq (1860-1896) and Gheorge Marinescu (1863-1938), studying midbrain tuberculomas, observed that lesions involving this region produced clinical features resembling Parkinson's disease. Their findings laid the groundwork for Constantin Tretiakoff (1892-1956)'s subsequent work, which identified degeneration of the substantia nigra as central to the pathophysiology of the disorder.

Charcot's therapeutic explorations reveal a clinician who, despite working within the limits of nineteenth-century medicine, pursued every plausible avenue for symptom relief. His interest extended from pharmacology to mechanical intervention, and although the tools at his disposal were

Charcot tested several preparations derived from plant alkaloids, noting that they could temporarily lessen tremor and rigidity. Their effect was attributed to anticholinergic properties, which would later become a recognized pharmacological mechanism in the management of Parkinsonian symptoms. He emphasized, however, that these improvements were short-lived—often only a few hours—and insisted on the need for further systematic observation before drawing firm conclusions. This caution reflects his broader methodological stance: clinical impressions were valuable, but they required careful corroboration.

Charcot also explored mechanical stimulation as a therapeutic strategy. He designed a vibrating chair and even a vibrating helmet intended to reduce tremor and stiffness, inspired by his observation that certain mechanical stimuli could transiently diminish motor symptoms. The device attempted to reproduce these effects in a controlled therapeutic setting. Although primitive by modern standards, such experiments illustrate an early attempt to modulate motor circuits through external physical input—a concept that resonates, in a distant way, with later developments such as physiotherapy techniques and even deep brain stimulation.

A decisive therapeutic breakthrough would not arrive until the twentieth century. In 1967, George Cotzias (1918-1977) introduced high-dose Levodopa, demonstrating that replenishing dopamine could reverse many of the motor symptoms Charcot had described with such precision. This discovery established the central role of dopamine in Parkinson's disease and transformed clinical practice. What had been a largely symptomatic and palliative field became one in which dramatic, measurable improvement was possible.

Despite the extraordinary advances that followed, Charcot's clinical descriptions remain strikingly accurate, also with regards to their details. For instance, his observations on the influence of emotional states on tremor and posture continue to hold true: stress and emotional excitation can still exacerbate Parkinsonian symptoms, precisely as he noted in his lectures.

Modern research has revealed, however, that Parkinson's disease is far more complex than nineteenth century clinicians could have imagined. It is now understood as a multisystem disorder marked by widespread pathological changes, including the accumulation of Lewy bodies in neurons throughout the nervous system and even in peripheral organs. The disease extends well beyond the motor system that first drew Charcot's attention.

Charcot also speculated about hereditary influences in neurological disease, an idea that later provoked debate among figures such as Sigmund Freud, who questioned whether familial predisposition had been overstated. Contemporary genetics has shown that hereditary factors play a significant role in many neurological disorders—including Parkinson's disease, amyotrophic lateral sclerosis, and Alzheimer's disease—confirming the prescience of Charcot's intuition. Even without access to modern genetic tools, he recognized patterns that would only be scientifically validated many decades later.

For these reasons, Charcot's contribution to the understanding of Parkinson's disease remains foundational. By refining Parkinson's initial observations and shaping them into a rigorous clinical framework, he laid the groundwork for modern neurology and for the systematic study of movement disorders. His legacy endures not only in the accuracy of his descriptions but in the methodological clarity with which he approached the complexities of disease.



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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.

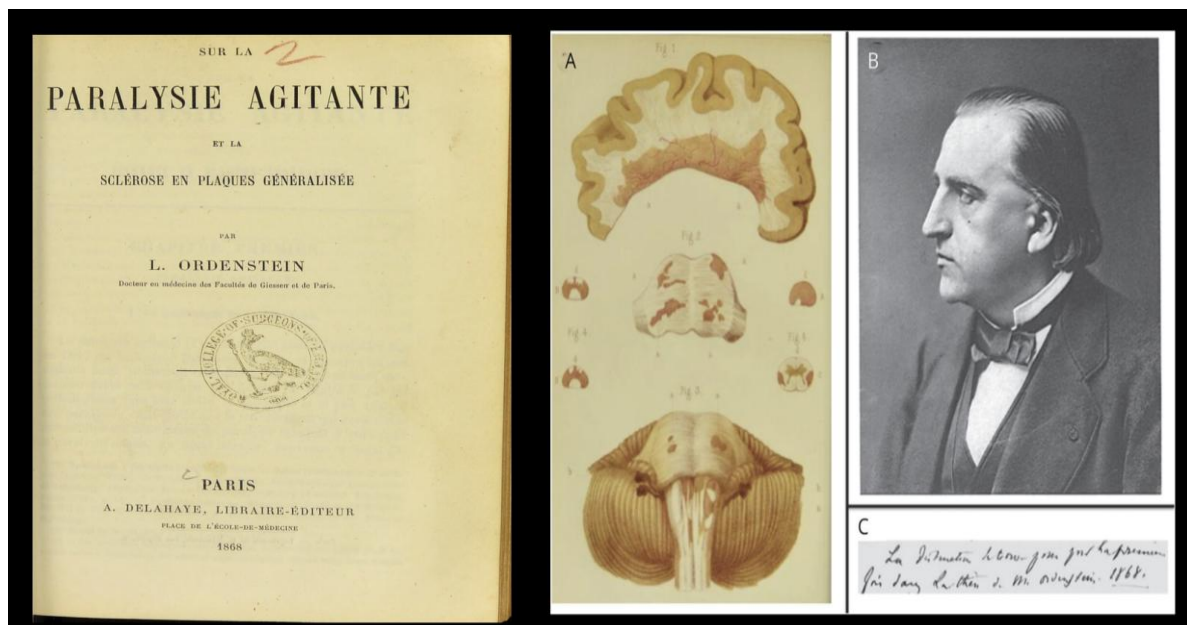


Figure 1. Title page of Leopold Ordenstein's 1868 doctoral thesis *Sur la paralysie agitante et la sclérose en plaques généralisée* (Paris).

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.

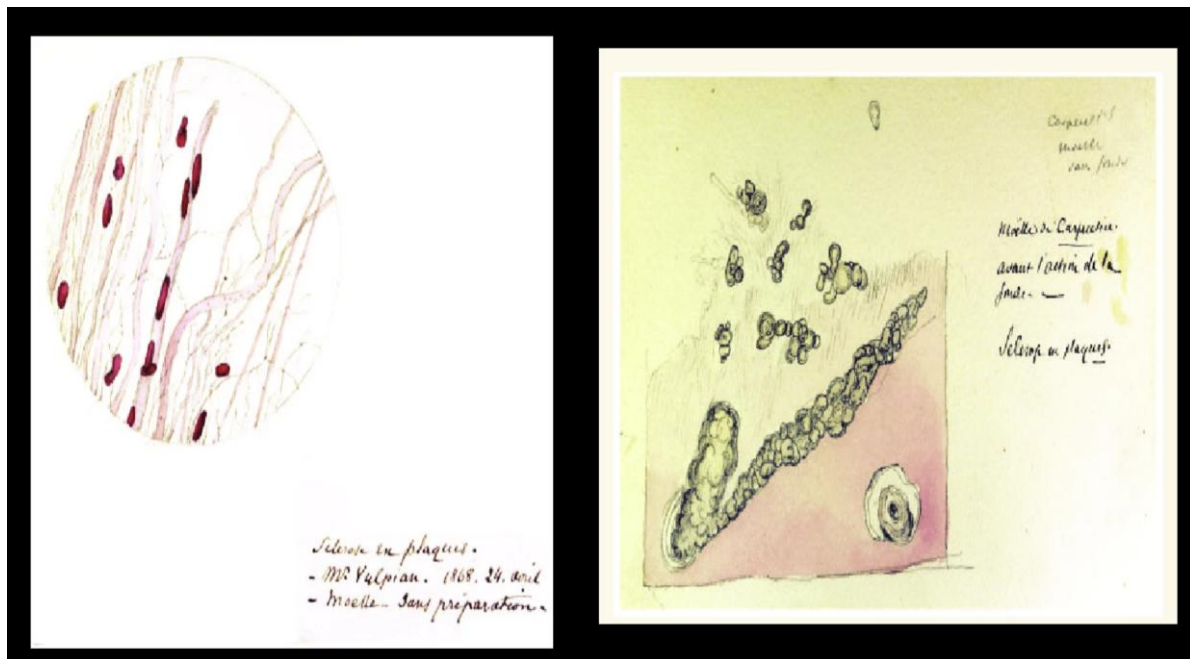


Figure 2. Neuropathological illustration of a sclerotic plaque as described and drawn by Charcot.

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.

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William Rivers' Croonian Lectures of 1906: an early account of blinding in medical research

(History of Neurology)

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Abstract

A critical step along the path of evolution of clinical trial design, the blinding of research subjects to administered medications, was pioneered by William Rivers (1864-1922). Although best known for his work with survivors of “shell-shock” during the First World War, Rivers initially trained as a neurologist. His investigation of the effects on fatigue, both muscular and mental, of various substances, particularly caffeine and alcohol, was reported in his Croonian Lectures delivered at the Royal College of Physicians of London in 1906. Key to these controlled studies was Rivers’ method “to exclude the influence of interest, sensory stimulation, and suggestion” on the results. This article examines the setting, the study, the methodology and the aftermath of Rivers’ study. Rivers’ work is found to anticipate several key factors in controlled trial methodology, including: the need for a prolonged initial washout period; the possible confounding effect of craving; the need for placebos to be fully disguised; and the relevance and value of dramatic effects as strong evidence for an intervention.

Keywords: blinding; clinical trials; fatigue; history of neuroscience; William Rivers.

Introduction

William Halse Rivers (1864-1922) is perhaps best known to posterity for his work with soldiers suffering from “shell-shock” during the First World War, particularly the poet Siegfried Sassoon (1886-1967), even though this clinical work as a psychiatrist accounted for only a brief period of his multi-faceted career. In academic circles, Rivers is known as a founder of anthropology and ethnology, as well as experimental psychology (*Slobodin 1997*). However, initially he gained medical qualifications at St Bartholomew’s Hospital, London, in 1886 and in the early 1890s he worked as a neurologist, being taught by John Hughlings Jackson (1835-1911) at the National Hospital for the Paralysed and Epileptic, Queen Square, London (*Larner 2025a*) and contributing to the neurological literature (*Rivers 1891a*). He was elected to membership of the Neurological Society of London in 1891 and later (1897-1898) served on its Council.

Early in his career, Rivers also made presentations to the Abernethian Society, the medical and philosophical society at St Bartholomew’s Hospital, reading papers on hysteria and neurasthenia. The accounts of these meetings, as published in the *St. Bartholomew’s Hospital Reports*, are very brief (*Rivers 1891b, 1893*) but it would seem highly likely that Rivers was aware of Charcot’s work on these subjects and may have discussed them in this context. Rivers was elected to membership of the Medico-Psychological Association (the forerunner of the United Kingdom Royal College of Psychiatrists) in 1893.

In the neurological context, Rivers was later involved in a classical study of sensory nerve regeneration following the surgical section of a cutaneous nerve in the forearm of his colleague Henry Head (1861-1940) (*Head et al. 1905; Rivers and Head 1908*), work which continues to attract comment and analysis (e.g. *Watt Smith 2014, 125-163; Jacyna 2016, 125-130*). It may therefore be of some interest to historians of neurology, and indeed come as some surprise, to learn that another study by Rivers performed in the first decade of the twentieth century was “one of the first occasions, possibly the very first, on which the ‘double-blind’ procedure was used in an experiment” (*Slobodin 1997, 31*). The claim that Rivers “used double-blind placebo-controlled trials” has been repeated elsewhere (*Guest et al., 2021, p.2*).

The study in question (*Rivers 1908*) was briefly alluded to in Kaptchuk’s historical perspective of blind assessment and placebo controls in medicine (*Kaptchuk 1998, 419; 2011*) and also in a biographical article about Rivers in the Cochrane Library (*Adams 2004*) and online (<https://whrrivers.co.uk>), but none of these publications included discussion of Rivers’ methodology, nor to our knowledge has any other article specifically addressing this issue been published.

The concept of blinding, and specifically of “double-blind”, is now an integral element in clinical trial methodology with ramifications throughout clinical research and practice, including neurology. Hence the aims of the current article are to document Rivers’ rationale and methodology for blinding, and briefly to assess his contribution to clinical trial methodology.

The setting

Rivers had been recruited to Cambridge University in 1893 by Michael Foster (1836-1907), founder of the Cambridge physiology school, in order to lecture on the physiology of the senses and to set up a laboratory of experimental psychology (*O’Connor 1991, 17-19*). In Cambridge, Rivers also became associated with St John’s College, eventually becoming a Fellow (1902);

his rooms in the College were also used for some of his experimental studies to ensure the necessary degree of silence. However, the demands of his teaching and research duties meant that it was “impossible, as a general rule, to carry out any experimental work during term-time” (*Rivers 1908, 16*).

Rivers spent the summer of 1893 in Heidelberg in Germany where he worked with the distinguished psychiatrist Emil Kraepelin (1856-1926), undertaking a study which attempted to measure mental fatigue, later published in Kraepelin’s house journal, *Psychologische Arbeiten* (*Kraepelin and Rivers 1896*). Rivers presented some of these experimental data to the Medico-Psychological Association at their meeting held in Cambridge in February 1896 (*Rivers 1896*). This work appears to have kindled Rivers’ interest in fatigue and was the prelude to further study of the subject undertaken several years later.

The study and its methodology

Rivers’ studies on fatigue were undertaken intermittently between August 1904 (*Rivers 1908, 42*) and, at least, September 1906 (*Rivers 1908, 38*; hence, this internal evidence contradicts the dating of “1906-7” given by *Slobodin 1997, 31*). Many of Rivers’ experiments were performed in conjunction with “Mr. H.N. Webber”, with whom some of the results were later published (*Rivers and Webber 1907, 1908*). This was Harald [*sic*] Norris Webber (1881-1954) who had taken the Natural Sciences Tripos at Cambridge in 1903 and then remained in the town until 1908 (Cambridge only gained city status in 1951) when he commenced his medical studies in London, later practising as an anaesthetist at University College Hospital (*Anon. 1955*).

Funding for “the expenses of the researches” performed by Rivers came, at least in part, from the Croonian Trust of the Royal College of Physicians of London (*Rivers 1908, Preface* [unpaginated]). The experimental findings were initially presented in Rivers’ four Croonian Lectures delivered at the Royal College of Physicians on 12th, 14th, 19th and 21st June 1906 (as announced in *BMJ* 1906;1:1311; no announcement has been found in the *Lancet* or the *Medical Press and Circular*). Hence, Rivers’ experiments continued for at least three months after the delivery of the Croonian Lectures.

The purpose of the work was to examine the time course of both mental fatigue, as per Rivers’ previous studies with Kraepelin, and muscular fatigue, and the influence upon them of certain drugs, principally caffeine and alcohol, but also cocaine, strychnine, and tobacco.

Mental fatigue was assessed by performing blocks of multiplications and typewriting, both the number of lines completed and the number of errors being quantified, with rest periods in between blocks. Mental fatigue was also assessed using a method recently devised by William McDougall (1871-1938); Rivers had been his doctoral advisor at St John’s College. McDougall’s device required the subject to hit a succession of dots printed on a Morse tape which passed before a slit, the rate of movement being just the maximal rate for the subject (*McDougall 1905; Rivers 1908, 12, 13, 125-126*).

Muscular fatigue was studied using the ergograph, a technology originally devised by Angelo Mosso (1846-1910) around 1890 and also used by Kraepelin. In this device the fingers and forearm were inserted into graduated fixtures and one finger, usually the middle, undertook repeated cycles of contraction and relaxation (in time to a metronome) to lift a weight. Movements were recorded on a kymograph. Both the number and height of the contractions could thus be recorded and hence work performed (in kilogrammetres). In Rivers’ studies, both

the weight and the evolving ergogram were hidden from the view of the test subject. This appears to be the first instance of Rivers intentionally “blinding” participants, in this case to their own performance.

The experimental subject was more frequently Webber (“Subject W”) than Rivers (“Subject R”), and in occasional studies the subject was MacDougall (*Rivers 1908, 45-46, 98-99*) using the method he had devised to assess mental fatigue.

Rivers adopted the systematic manner previously used by Kraepelin to keep all experimental conditions exactly alike on different test days, excepting the administration of the drugs being investigated on some days but not on others: “it is essential that all the conditions of life be kept as constant as possible” (*Rivers 1908, 15*), these conditions encompassing sleep, meals, exercise, and any other work performed. Accordingly, research subjects “must cut themselves off from many of the ordinary pursuits of life so long as the experiments last” (*Rivers 1908, 15-16*). In addition, exclusion of extraneous sources of test drugs was required, namely cessation of all tea, coffee, cocoa, alcohol, and tobacco, stipulations which Rivers recognised to be challenging: “So drastic a procedure is not likely to attract workers [i.e. participants] to this subject” (*Rivers 1908, 17*). Fortunately, this was no obstacle for Webber on account of his lifelong abstinence (*Rivers 1908, 84, 131*; also *Anon. 1955*: he “never drank alcohol at all”).

However, certain environmental factors were beyond Rivers’ control. As mentioned, his teaching duties precluded experimental work during term time, so experiments were often carried out during student vacations, when the weather might influence results: the summer of 1906 was very hot, a factor which Rivers acknowledged could impact on mental vigour (*Rivers 1908, 85*) when experiments could last nine to ten hours each day over a period of nine days (*Rivers 1908, 45, 46, 47, 85, 95, 98*).

Rivers was at pains to emphasize his methodology: “in my own work I have been chiefly interested in the influence of certain psychical factors which I believe to have had a great effect on the results of previous workers” (*Rivers 1908, 4*). These factors were the “influence of interest” (presumably meaning attention or engagement), “sensory stimulation” and “suggestion”. Hence for Rivers it was “a feature of method in which lies the chief interest of the new work” which was “designed to eliminate the influence of certain psychical factors” (*Rivers 1908, 18*). He noted the “interest and excitement produced by taking a substance when the discovery of its effect is the motive of the whole experiment”, particularly so when “the subject is himself the experimenter” (*Rivers 1908, 19, 20*). Accordingly, Rivers carried out the research “with the use of control mixtures which have usually been wholly indistinguishable from those containing the active substances” such that the experimental subject was “wholly unaware whether he has taken the substance which is the motive of the experiment or some inactive imitation of it” (*Rivers 1908, 20*).

The extent to which Rivers sought to make his “control mixtures” indistinguishable is of particular note. These were prepared by Walter Ernest Dixon (1871-1931), the Cambridge pharmacologist (*Rivers 1908, 20, 66, 67, 73*; for Dixon, see *Cuthbert 2001*). Specifically, gentian and citric acid were used as a control for the active citrate of caffeine (*Rivers 1908, 21, 43*). Concealing alcohol proved more challenging. Initially Dixon prepared a control solution which contained a mixture of capsicum, cardamoms, and a small amount of chloroform (*Rivers 1908, 66*) but later a modification by means of adding some peppermint was required (*Rivers 1908, 73*).

The specific results of Rivers' drug studies comparing active versus control substances, were largely inconclusive, with different observations being sometimes made in the two principal experimental subjects.

Contemporary assessments: the immediate aftermath

One would be intrigued to know the responses of the Fellows of the Royal College of Physicians who attended Rivers' lectures in June 1906, but to our knowledge none is available.

No contemporaneous publication of the Croonian Lectures has been found in any of the weekly medical journals but two papers documenting some of Rivers' findings later appeared. The first, describing the work on caffeine, appeared in the *Journal of Physiology* (Rivers and Webber 1907; this publication was not included in the Bibliography of Rivers' works in Slobodin 1997, 275-277) and was later acknowledged in passing by Rivers (Rivers 1908, Preface [unpaginated], 29n1). The second, describing the work on alcohol, appeared in the *British Journal of Psychology* (Rivers and Webber 1908; incorrect pagination in Slobodin 1997, 277), the journal which Rivers had co-founded in 1904; again, this publication was acknowledged in passing (Rivers 1908, 69n1, 78n1).

The definitive account of the studies appeared in book form thereafter (Rivers 1908). A perfunctory, anonymous review of this book appeared in *Brain* (1908;31(1):217), the leading neurological journal. Although amounting to a meagre nine lines, the reviewer at least noted that in Rivers' experiments "every precaution was taken to avoid suggestion: control mixtures indistinguishable from those containing the drug under investigation were taken by the subject". Hence the conclusion that "In many ways this work is a considerable advance in the psychological study of the influence of drugs on man".

A longer commentary on Rivers' book appeared in the *British Medical Journal* (Anon. 1908). Again, the reviewer noted Rivers' methodology, quoting his statement to the effect that the "part played by psychical factors" had "been allowed to complicate most [other] work on this subject", and noting that:

Soon after beginning his investigation Dr. Rivers became aware of the unsatisfactory nature of previous researches on the capacity for muscular work in man, and much of his work has been occupied in perfecting exact methods and eliminating disturbing factors. The method he used was to take six series of ergographs a day, at intervals of one hour, the subject not being allowed to see either the weight lifted or the tracing produced. To eliminate physical [should this have read psychical?] factors the subject took control mixtures, so that he did not know the days when he took the drug. This last precaution is obviously most important, but does not seem to have been taken by any previous worker. (Anon. 1908, 1192).

This reviewer concluded with the encomium that "Dr. Rivers is to be congratulated on the exact scientific spirit in which he has carried out these researches, and we hope to see them carried a step farther" (Anon. 1908, 1193). No review of Rivers' book has been identified in the pages of the *Lancet* or the *Medical Press and Circular*.

Kaptchuk (1998, 419-420) noted that Rivers' ideas concerning blinding were introduced to the United States by three different groups of researchers who published between 1912 and 1916 but "with only minimal effect". That little, if any, further note of Rivers' methodology was made by later investigators would be in keeping with the argument that the history of blinding was, prior to Kaptchuk's work, largely ignored.

Rivers himself never returned to the subject of blinding. His studies of fatigue (*Rivers 1908*) and of sensory nerve regeneration (*Rivers and Head 1908*) were his final forays into physiological psychology (*Slobodin 1997, 44*). Despite allusions to Webber continuing the fatigue work (*Rivers 1908, 75, 83, 107, 118*), to our knowledge he did not publish anything further. Indeed, it was later noted of Webber that he "did not make many contributions to medical literature" (*Anon. 1955*) other than co-authoring a textbook on anaesthesia (*Rood and Webber 1930*).

Discussion

The history of blinded studies dates back at least to the eighteenth century (*Kaptchuk, 1998, 2011*): the examination of animal magnetism in the late eighteenth century by Benjamin Franklin and others is often cited as the earliest example. If one includes necessarily blind assessment, i.e. by subjects who were actually blind, earlier descriptions might also be considered (*Larner 2006; 2025b, 116-118*).

In the Conclusion of his Croonian Lectures, Rivers was explicit: "The chief interest of the work which has been recorded in these lectures lies in its bearing on method. [...] One point of method has, I hope, been clearly established – viz., the absolute necessity that experiments with drugs on man should be carried out with adequate control, designed to exclude the influence of interest, sensory stimulation, and suggestion" (*Rivers 1908, 117-118*). However, nowhere did Rivers use the terminology of "blind" or "blinding", nor "concealment", "masking", or "placebo". Hence the characterisation of his work as "one of the first occasions, possibly the very first, on which the 'double-blind' procedure was used in an experiment" (*Slobodin 1997, 31*) is a retrospective judgment, likewise the argument that "Rivers needs to be given credit for blinding of subjects in a controlled study when he lectured on his research on alcohol and fatigue in 1906" (*Bader 2023, 140*). However, Rivers did speak of "disguise" as a means of eliminating the "influence of interest", a factor which he deemed to be of greater importance than either "sensory stimulation or suggestion" in affecting experimental outcomes. The word "bias" appears in his work but infrequently, specifically with respect to advocacy for either temperance or, contrariwise, the virtues of alcohol (*Rivers 1908, 52, 90*) rather than the specific notion of observer bias. Nevertheless, the latter might be implied in his recognition of accessory, psychical factors being allowed to influence previous workers and their results (*Rivers 1908, 80, 82*) which, in the case of alcohol, were "almost certainly due to defects of experimental method" (*Rivers 1908, 100*).

Exercising the benefit of hindsight (indeed, possibly the condescension of posterity), we might disparage Rivers' methods in his work on fatigue. Both mental and muscular fatigue are sensitive to contextual factors such as time of day, prior cognitive or physical activity, and environmental conditions. Rivers attempted to take these factors into consideration, although he did not document them for each individual experiment. Thus, although his studies were clearly "controlled" in the sense that the conditions of life were kept as equal as possible, nonetheless they were methodologically limited according to current standards: few

experimental subjects (two or three); no randomisation; no inferential statistics; no overt hypothesis testing. However, this is to ignore the historical context. In his studies of fatigue, Rivers seems to have inaugurated a new methodology in his work. Certainly, there is no indication of any awareness of the place of such methodology in his extensive review of previous work related to the physiology of vision (*Rivers 1900*). In the Rivers-Head experiment, which occurred contemporaneously with the fatigue studies, Rivers also made efforts to ensure that his subject, Henry Head, was blind to the nature and order of the sensory stimuli applied (*Rivers and Head 1908, 342-355*). This arrangement was commemorated in one of the classic photographs of the experiment, in which Head looks away with eyes closed as Rivers applies a stimulus (*Henson 1961, 537*). The image has often been reproduced (e.g. *Watt Smith 2014, 126; Jacyna 2016, 126*).

Whence came Rivers' epiphany as to the importance of disguise? His written text might suggest that it came from within: "In my first experiment with a drug, I soon became aware of such interest" (*Rivers 1908, 20*). Blinding may thus have emerged almost naturally within the context of research in physiological psychology as Rivers attempted to measure factors, particularly mental fatigue, which were inherently vulnerable to psychological influences such as expectation, interest, and suggestion. This could help explain why Rivers conceived of blinding in this context before it appeared in other areas of biomedical experimentation with more "hard," objectively measurable endpoints. However, contrary to this argument, Rivers' prior knowledge of the works of other investigators, whether acknowledged or not, may have contributed to this awareness, specifically the "precautions" adopted by Schumburg and by Sobierański of using "control-substances" (*Rivers 1908, 18-19*). Wacław Sobierański, working in Marburg in 1895, preceded his assessments of the effects of caffeine and cocaine on muscle strength, as measured with ergography, by saline injections and emphasized the need to control for "autosuggestion" (*Sobierański 1896; see also Kaptchuk 1998, 418*).

Whilst Webber, as "Subject W", was almost certainly blind to the drug, active or control, administered by Rivers in most cases (see below), the latter was likely aware of the sequence in which the substances were given, hence this experiment was unlikely to have been "double-blind". For "Subject R", it is difficult to conceive how Rivers could have been unaware of whether he took active or control substance: he mentions that Dixon supplied him with "two or more bottles, and it has only been at the end of the experiment that I have been made acquainted with the exact nature of their contents" (*Rivers 1908, 20*) but, nevertheless, when "the subject is himself the experimenter" (*Rivers 1908, 20*) this arrangement can only ever be "single-blind". Moreover, instances of unblinding certainly occurred: caffeine sometimes disturbed Rivers' sleep, necessitating either discontinuation of the experiment or change of protocol (*Rivers 1908, 36, 43, 127-129*), and higher doses of alcohol were recognised by Webber necessitating the modification of the control mixture (*Rivers 1908, 71, 73, 84, 131-132*). Hence, Rivers' efforts at blinding were not entirely successful. At best these studies were single- rather than double-blind; herein we disagree with previous characterizations of this work as using the double-blind methodology (*Slobodin 1997, 31; Guest et al., 2021, p.2*).

Rivers' study may be seen to incorporate several key contributions to the development of controlled trial methodology:

- The importance of a very long period of "washout" (our word) before any intervention: "For these reasons it seemed best to give up completely the use of all the stimulating articles of diet in ordinary use for several months before beginning my next research, and much of the work to be described in these lectures was done more than a year after

the use of alcohol and caffeine-containing articles of diet had been given up” (Rivers 1908, 17).

- The importance of considering the confounding effect of a “craving” (thus requiring the long washout period): “Even in those who only take such a substance [alcohol] in moderate amounts, its disuse is probably followed in some degree by the craving which is so pronounced after discontinuance of large amounts, and, slight and hardly noticeable as this craving may be, it may yet be sufficient to produce an obvious effect when the article of which the person has been deprived is administered experimentally. The effect of the substance given experimentally may be the result, not of its normal physiological action, but of the satisfaction of a craving” (Rivers 1908, 17).
- The need for placebos to be fully “disguised” and “wholly indistinguishable”, hence the need to involve a “specialist” (our word; in this case, Dr W.E. Dixon) in the process of disguising active and control substances. Shortcomings of previous attempts at disguise were evident to Rivers: “In experiments on the action of coffee, Schumberg [...] used a control coloured so as to resemble coffee, but there can have been no question here of a control wholly indistinguishable from the coffee” (Rivers and Webber 1907, 33n1).
- The recognition of the relevance and value of dramatic effects as strong evidence for an intervention. Discussing “the most satisfactory method” first adopted by Kraepelin, Rivers notes that “In many cases the drug-days will give an average which deviates from that of the normal days so greatly that there can be no question as to the action of the drug” (Rivers 1908, 15).

In addition, Rivers’ approach appears to adopt a basic cross-over method in the administration of active and control substances, a method little used hitherto (Cooper and Cooper 2026; Larner et al. 2026).

Why has this item of Rivers’ oeuvre been relatively neglected by posterity? Though of interest at the time, the inconclusive results, despite the (relative) novelty of the methodology, probably accounted for the limited uptake of Rivers’ approach. Hence the subsidiary question, what influence did Rivers’ use of blinding in his studies of fatigue have on the field of biomedical investigation, answers itself: in all likelihood, very little. Nevertheless, from our vantage point in history, this may indeed have been one of the first attempts at blinding from a neurological perspective, one episode in the gradual, cumulative development of the concept of blinding. It may be added to extraordinary breadth of Rivers’ many contributions in many disciplines, the application of this one spanning many disciplinary boundaries.

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Little-known aspects of the work of Jean-Martin Charcot

(History of Neurology)

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Abstract

Jean-Martin Charcot, recognized as one of the founding fathers of neurology, began his hospital career as an internist and geriatrician responsible for some 2,500 elderly women at what was originally a nursing home and asylum, the Hospice de la Vieillesse Femmes at La Salpêtrière Hospital. For some twenty years, he thus had the opportunity to introduce pathologies identified in England and Germany to French physicians, such as Graves' disease and Addison's disease. In cardiology, he worked on the pathophysiology of intermittent claudication and pulmonary embolism. He then extended the concept of embolism to infectious pathology. Over many years, his clinical and metabolic research on gout led him to conduct multiple studies on rheumatology, notably chronic forms of rheumatoid arthritis. This summary is only a limited overview of the nearly 100 publications on various subjects covering all medical fields. Charcot's contributions may thus be considered as significant as those he made to neurology.

Keywords Jean-Martin Charcot, Geriatrics, Gout, Pulmonary embolism, Intermittent Claudication

Introduction

Jean-Martin Charcot (1825–1893) is unanimously recognized as one of the founding fathers of neurology (Figure 1). The numerous historical works devoted to him have analyzed in detail his decisive contributions to this emerging specialty. When he returned to the La Salpêtrière hospice on July 1862, to take over the department headed by Eugène Cazalis (1808–1883), whom he succeeded after having been an intern there ten years earlier, he took charge of 2,635 women, the majority of whom were elderly. This explains why his early publications were those of a geriatrician and internist (*Husson, 1862*). To illustrate this more precisely, I propose to review his numerous articles published from the time of his dissertation until 1867, the year in which his work began to focus exclusively on diseases of the nervous system (*Lellouch, 1992*).



Figure 1. A little-known photograph of Charcot from around 1870, from Françon F. Le centenaire de la thèse de Charcot (1853-1953). *Rhumatologie* 1954;6(1):27-31. (Collection OW).

Brief Biographical Note

Jean-Martin Charcot, born in Paris on November 29, 1825, was the eldest son of a saddler and coachbuilder. Of his four other brothers, Eugène, born thirteen months after him, died at the age of 15 days; Pierre would take over the family business; Émile and Jean-Eugène would become soldiers. After passing his baccalaureate on August 31, 1843, he began his medical studies. After passing the externship exam in December 1845, Charcot was appointed provisional intern in 1847, then admitted on December 18, 1848, to the internship program at the Paris Hospitals alongside Alfred Vulpian (1826–1887) and Alexandre Axenfeld (1825–1876). He served successively as an intern under Louis Béhier (1813–1876), Pierre Rayer (1793–1867), Pierre-Adolphe Piorry (1794–1879), and, in his fourth year, under Cazalis at La Salpêtrière: “there he gathered the material for his inaugural thesis, learned to appreciate the inexhaustible resources amassed in that hospital, and resolved from that point on to return there as a physician” (*Joffroy, 1893*). Piorry, a professor of clinical medicine who was already advocating the use of the microscope, offered him the position of chief resident in 1853 and 1854. But it was Rayer who would have a decisive influence on Charcot’s career. Working alongside him, Charcot absorbed the role of a powerful mentor attentive to his students. Before allowing him to take the agrégation exam, Rayer admitted him to the Société de Biologie, which he had helped found and was then presiding over. Charcot became a full member in 1851, “a young man, a colleague of eminent figures” such as Claude Bernard (1813–1878), Charles Brown-Séquard (1817–1894), François Magendie (1783–1855), and Émile Littré (1801–1881). These leading figures discussed advances in clinical science and laboratory research, strongly influenced by the positivist philosophy of Auguste Comte (1798–1857). By belonging to this society, Charcot was able to publish his own work at a very early stage. He remained loyal to it throughout his career, ensuring that he, in turn, introduced most of his residents to it (*Bonduelle et al., 1996*).

His friend Vulpian was appointed head of the second department. At a time when the nosography of chronic pathologies—particularly those affecting the nervous system—was still in its infancy, “we saw the two young professors, traversing together all the wards of this immense asylum, examining all the patients, gathering all the observations, and compiling a colossal dossier that was to be gradually supplemented by postmortem and histological studies, or by the invaluable contributions of laboratory research” (*Joffroy, 1893*). There, they put into practice the anatomo-clinical method that had established the Paris School’s reputation since the turn of the century, perfecting it through the systematic use of the microscope. Another innovation introduced by Charcot was the systematic measurement of the residents’ temperature using a mercury thermometer rather than simply placing a hand on their forehead. His resident in 1868, Désiré-Magloire Bourneville (1840–1909), would make this the subject of his thesis and subsequent publications (*Bourneville, 1870*) (*Bourneville, 1873*).

The thesis, a pioneering nosographic work

Charcot’s thesis was his first nosographic work. The defense took place on March 16, 1853, presided over by Piorry (*Charcot, 1853*). In this monumental work, he distinguished gout from chronic rheumatism (now recognized as rheumatoid arthritis on the one hand and osteoarthritis on the other) (Figure 2).



Figure 2. A drawing by Charcot illustrating his thesis. (BIUsanté, Paris Cité University)

The importance he places on references from English and German literature not only attests to his erudition and mastery of foreign languages but also represents an innovation for this type of personal work. His talents as a draftsman are evident in the plate of hands with deformed fingers illustrating his thesis. Charcot would continue to take an interest in gout throughout his career. For example, in 1860, he provided a detailed description of tophaceous deposits on the earlobes: “tophaceous concretions of the external ear appear to occupy an important place in the clinical history of gout” (*Charcot, 1861 c*). In 1867, he translated into French the treatise on gout by the Englishman Alfred Baring Garrod (1814–1917) (*Garrod, 1867*). Charcot would always keep abreast of advances in the understanding of rheumatic diseases and gout. Thus, in 1863, he reported an observation made by Garrod regarding the high frequency of gout patients who had previously exhibited signs of lead poisoning (*Charcot, 1863*). However, he had not previously noted this association, which was attributed to a toxic effect of lead on the kidneys preventing the normal elimination of uric acid. He encouraged physicians to investigate this association, which was likely not coincidental, in order to clarify the matter. In 1866, as he began teaching courses on diseases of the elderly, Charcot devoted several lectures to gout—its clinical presentation, pathological anatomy, and emerging biology—which were published in *La Gazette des Hôpitaux* in 1866 and 1867.

Early Years at the Society of Biology

As early as 1852, Charcot gave several presentations at the *Société de Biologie* addressing a variety of topics: valvular lesions in endocarditis (Figure 3), hydatid cysts of the pelvis, predisposing factors (eclampsia) for idiocy and imbecility, fetal smallpox, gout, pyelonephritis

due to pyeloureteral obstruction (ureteropelvic junction syndrome), biliary peritonitis, gastric ulcer followed by pyloric stenosis, and rupture of the spleen in a fetus.

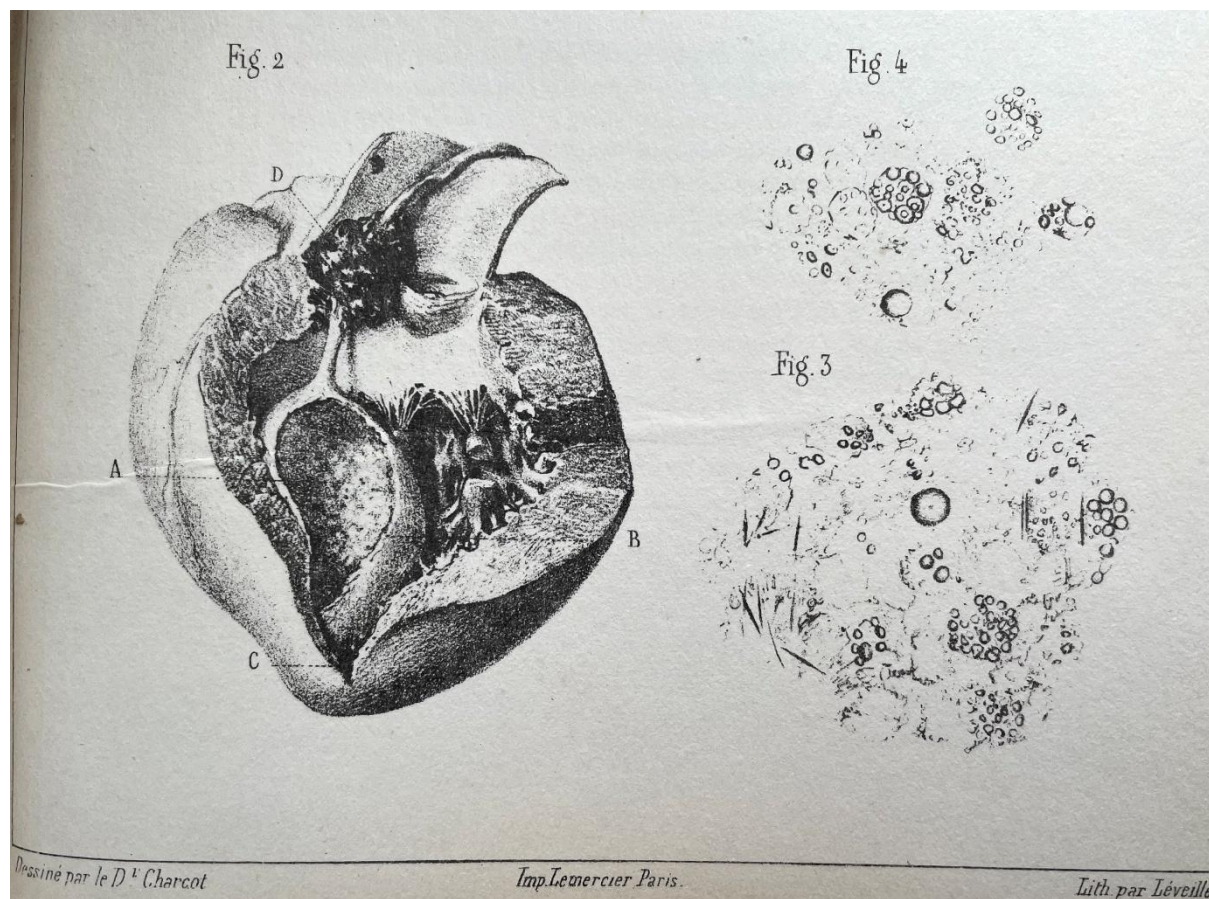


Figure 3. Engraving taken from: Charcot JM. Cas de tumeurs fibrineuses multiples contenant une matière puriforme situées dans l'oreillette droite du cœur. *Comptes Rendus des séances et Mémoires de la Société de Biologie* (année 1851). Paris: Au bureau de la Gazette médicale 1852;3:189-200. (Collection OW).

In May 1856, the year he was admitted to the Central Bureau (hospital physician), Charcot wrote the first French-language treatise devoted to Graves' disease, a condition previously unrecognized in France (*Charcot, 1856*). Inspired by the Irish physician Robert James Graves (1797–1853), the first to describe the clinical picture, Charcot presented French physicians with the cardinal signs—goiter, tachycardia, exophthalmos, and agitation—as he had observed them at La Charité Hospital in young women. He insisted that the heart should not be considered the source of the pathology but noted changes in the structure and dimensions of the thyroid arteries. He hypothesized increased gland activity due to stimulation of the vasomotor nerves, as, upon auscultating the goiter, he observed “a continuous murmur.” For him, the increase in the volume of the acini was the consequence. Death occurred in nearly half of the identified cases! In the same vein, in 1859, Charcot reported on his German readings. He recounted the observation made by August Hirsch (1817–1894) of Königsberg regarding a fatal subarachnoid hemorrhage marking the culmination of a case of Graves' disease, and those of the ophthalmologist Albrecht von Graefe (1828–1870) of Berlin, highlighting the risk of severe

corneal changes secondary to exophthalmos (*Charcot, 1859a*). In concluding this article, Charcot agreed with the proposal put forward by Hirsch to name this disease Basedow's disease (Karl Adolph von Basedow 1799–1854), an eponym still in use today (*Déchy, 2021*).

An interest that would remain unwavering throughout his career, Charcot took an interest in art and medicine as early as 1857, describing with Amédée Dechambre (1812–1886), the journal's editor-in-chief, "some ancient marbles pertaining to anatomical studies" (*Charcot and Dechambre, 1857*).

On September 18, 1857, Charcot published an article in the *Gazette hebdomadaire de Médecine* devoted to melanosis: "The alteration of the blood consists essentially in the presence within this fluid of a more or less considerable number of granules, corpuscles, or pigment cells" (*Charcot, 1857*). First described in Germany by Heinrich Meckel von Hemsbach (1821–1855) in 1847 (*Meckel, 1847*), this blood abnormality was linked to intermittent fevers, specifically malaria. For Charcot, these circulating colored corpuscles "belong to that group of substances that derive their origin from the dissolution, or the regressive metamorphosis undergone by red blood cells, under certain pathological circumstances." Charcot reports on the numerous German and Italian publications related to the discovery of melenemia. He attributes its origin first to the activity of the spleen, and then to that of the liver. While he recognizes renal melanemia associated with proteinuria as the cause of nephritis secondary to bouts of malaria, he rejects this melanemia as the cause of neuropsychiatric disorders (delusions, convulsions, etc.) occurring during malaria. Charcot wondered about the nosological classification of melanemia: was it a symptom or a disease? He was unaware of causes other than fevers.

Together with Vulpian, Charcot presented an observation of Addison's disease to the Société de Biologie in 1857. Macroscopically, the adrenal glands appear normal, but microscopic examination reveals degeneration: "Following the typical symptoms of Addison's disease, the adrenal capsules would be deemed healthy without having been examined under a microscope or treated with appropriate reagents. From a theoretical standpoint, this must be considered null and void." This text reveals the commitment to rigor that drove the two colleagues at La Salpêtrière (*Charcot, 1878*).

On February 26, 1858, Charcot reviewed a series of articles by German authors, notably Rudolf Virchow (1821–1902), to discuss the amaurosis affecting many patients with "albuminuric nephritis" and during the course of Bright's disease, that is, chronic renal failure, as he had observed while serving as Rayer's intern. Whereas previously, macroscopic pathological anatomy had revealed no lesions, the practice of examining the fundus while the patient was alive and microscopic examinations made it possible to identify retinal damage and central retinal artery thrombosis, in particular. The concept of hypertension was still unknown. Charcot thus became a champion of fundus examination, a new diagnostic technique invented by Hermann von Helmholtz (1821–1894) in 1851.

Together with Casimir Davaine (1812–1882), the biologist and bacteriologist who discovered the anthrax bacterium, Charcot presented to the Société de Biologie an observation of multiple hydatid cysts in the liver and pelvis, as he had already done in 1852 (*Charcot and Davaine, 1858*). The patient presented with a severely deformed abdomen due to an enormous mass on the right flank. "This tumor is fluctuant; no hydatid quivering is perceptible." They punctured the cyst, draining three liters, then administered several successive injections of caustic agents. Examination of the fluid revealed echinococci. A fistula developed, continuing to discharge parasites. After the patient's death, the autopsy noted widespread dissemination of the parasitic infection. It should be noted that the discovery of the parasite's life cycle by the Bavarian Karl

Theodor Ernest von Siebold (1804–1885) was still very recent, in 1853, but was evidently known to Charcot and Davaine (*von Siebold, 1853*).

François-Amilcar Aran (1817–1861) devoted his 1853 agrégation thesis to the causes of sudden death, among which he identified pulmonary embolism, though without specifying its pathophysiology. Benjamin Ball (1833–1893) and Charcot demonstrated in 1858 that the clot obstructing the pulmonary artery originated from venous phlebitis in a lower limb (*Charcot and Ball, 1858*). Charcot recognized elevated fibrin levels as a factor promoting clot formation, even though the physiology of hemostasis was still poorly understood. He noted the frequency of these incidents among young women and those who had recently given birth. This pioneering description, inspired by the work of Rudolf Virchow (1821–1902), demonstrates the vast medical knowledge of a 33-year-old Charcot who read English and German authors. Having been a hospital physician for two years, he was filling in for colleagues. It was while filling in for Louis-Alfred Becquerel (1814–1862) that he met Benjamin Ball, then an intern in that department at La Pitié. Ball would defend his thesis on the same subject before Armand Trousseau (1801–1867) four years later, on January 3, 1862. Charcot would recall this fruitful collaboration when he successfully nominated Ball for the Chair of Mental and Brain Diseases in April 1877.

The collaboration between Charcot and Ball continued with the 1860 publication of a work that now holds only historical value, titled: “On the Coincidence of Visceral Gangrene and External Gangrenous Conditions; Gangrenous Erysipelas and Gangrenous Dissecting Pneumonia” (*Ball and Charcot, 1860*). A fifty-seven-year-old woman with heart failure at the anasarca stage, due to mitral stenosis, underwent an ascites tap. An incomplete tap drained eight liters but was complicated by erysipelas at the puncture site, rapidly progressing to gangrenous sphacelus and death. At autopsy, the base of the right lung was occupied by a gangrenous sequestrum, an exceptional finding rarely described previously. The term “*gangrenous dissecting pneumonia*” was introduced by the German Hermann Lebert (1813–1878) in 1845 in the French edition of his treatise on pathological physiology (*Lebert, 1845*). Ball and Charcot mention “septic fluids originating from the primary focus, or even blood clots laden with gangrenous pus and formed initially in the veins passing through the focus,” which they suppose spread the gangrene; that is, they considered septic emboli before the era of microbiology! Were these cases of gas gangrene caused by *Clostridium perfringens*?

Following a presentation to the Society of Biology, Charcot was the first to publish, in 1859—and quite originally, in a veterinary medical journal, the *Recueil de médecine vétérinaire* (Figure 4), and then in *La Gazette médicale de Paris* (*Charcot, 1859d*)—the observation that allowed him to describe claudication of arterial origin: “This report seems to us to be closely related to cases of intermittent lameness due to arterial obliteration, now well known in equine pathology, and to which our colleagues Ms. Goubaux and H. Bouley—to whom we owe important work on this subject—have repeatedly drawn the Society’s attention” (*Charcot, 1859c*). Armand Goubaux (1820–1890), who would later become director of the National Veterinary School of Maisons-Alfort, described “paralysis in horses caused by occlusion of the posterior aorta” in 1846 (*Goubaux, 1846*). Henri Bouley (1814–1885), known as “the Great Bouley,” was the first to draw attention to this form of lameness in horses in 1830 (*Bouley, 1830*). After the clinical description of the exertional lameness experienced by his patient, which appeared nearly three decades after a war injury, Charcot discovered, during the autopsy, the presence of a bullet compressing the primary iliac artery, reproducing in a quasi-experimental manner what veterinarians had observed in horses. Charcot thus elucidated the pathophysiological mechanism of ischemia: “As we can see, physiology can provide us, to a certain extent, with

the key to the main phenomena observed during an episode of claudication.” Knowing that arterial narrowing causes transient or permanent ischemia, he could extend this explanation to the various arterial territories and attribute the narrowing of the arterial lumen to atheroma. Did he have the same thought in 1893 when he himself was suffering from angina attacks?

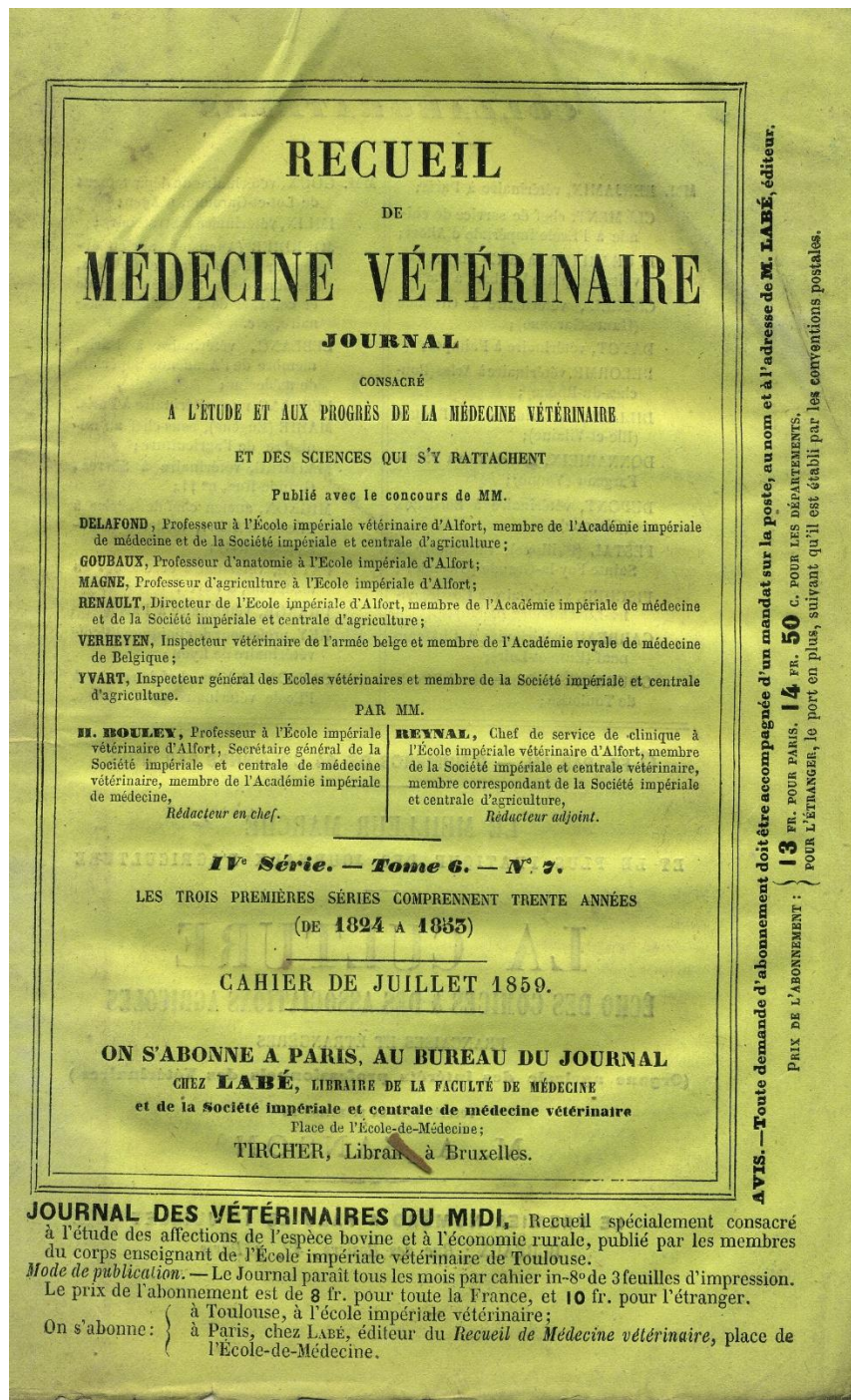


Figure 4. Front page of the journal Recueil de médecine vétérinaire July 1859. (Collection OW).

Charcot, after examining two chemists exposed to “experiments on the fusion and vitrification of certain substances by the action of an electric battery,” on February 14, 1858, described photokerato conjunctivitis, since then known as “arc flash” or snow blindness, accompanied by facial erythema, even though UV radiation would not be discovered until 1893. He does not fail to compare this burn to a sunburn, even though the experimenters had not perceived any excessive heat (*Charcot, 1859b*).

By the time he became vice president of the Society of Biology, 1860 marked his success in the agrégation exam on his second attempt. His thesis “On Chronic Pneumonia” is a compilation of studies, most of them (*Charcot, 1860*) describing a prolonged febrile course of acute lobar pneumonia, leading to a severe deterioration in general health and ultimately death. The autopsy revealed gangrenous changes in the lung, with large non-functional fibrous segments, sometimes cavitary, but not tuberculous. The etiology remained a mystery at that time, as bacteriology was still unknown.

Charcot-Leyden crystals

In 1853, Charcot and Charles Philippe Robin (1821–1885) presented a case of acute leukemia to the Société de Biologie, a condition then largely unknown in France but already described in Germany by Virchow (*Virchow, 1845*) and in England by John Hughes Bennett (1812–1875) (*Bennett, 1845*). The patient, who was pale and had significant splenomegaly, died after throwing himself down the hospital stairs. During the autopsy, blood was examined from the contents of the ventricles. A significant increase in white blood cells and a decrease in red blood cells were observed. Robin added: “In the blood of the right ventricle, mixed with the white blood cells, a large quantity of rhomboid crystals, very regular in shape, and slightly yellowish-red in color. These same crystals are extremely abundant in the spleen tissue, where they form considerable clusters, though visible only under a microscope” (*Charcot and Robin, 1854*). Charcot and Vulpian, in 1860, described these crystals in relation to another case of leukemia: “very elongated octahedrons, of very regular shape and fairly uniform,” which they measured at 6 to 8 μ (*Charcot and Vulpian, 1860*) (figure 5). Friedrich Albert von Zenker (1825–1898) is credited with first describing this type of crystal during his identification of trichinosis (*Zencker von, 1862*). The eponymous Charcot-Leyden crystals, still in use today, pay homage to the description by Charcot and Robin in 1853, adding the name of Ernst Victor von Leyden (1832–1910), who identified them in the sputum of asthmatics in 1872 (*Leyden von, 1872*). These colorless, double-pointed, and often needle-shaped crystals, observed in serous fluids such as bronchial secretions in asthma and in stool in certain cases of intestinal parasitism, consist of an enzyme, lysophospholipase, which is synthesized by eosinophils, blood cells that were not yet identified in Charcot’s time.

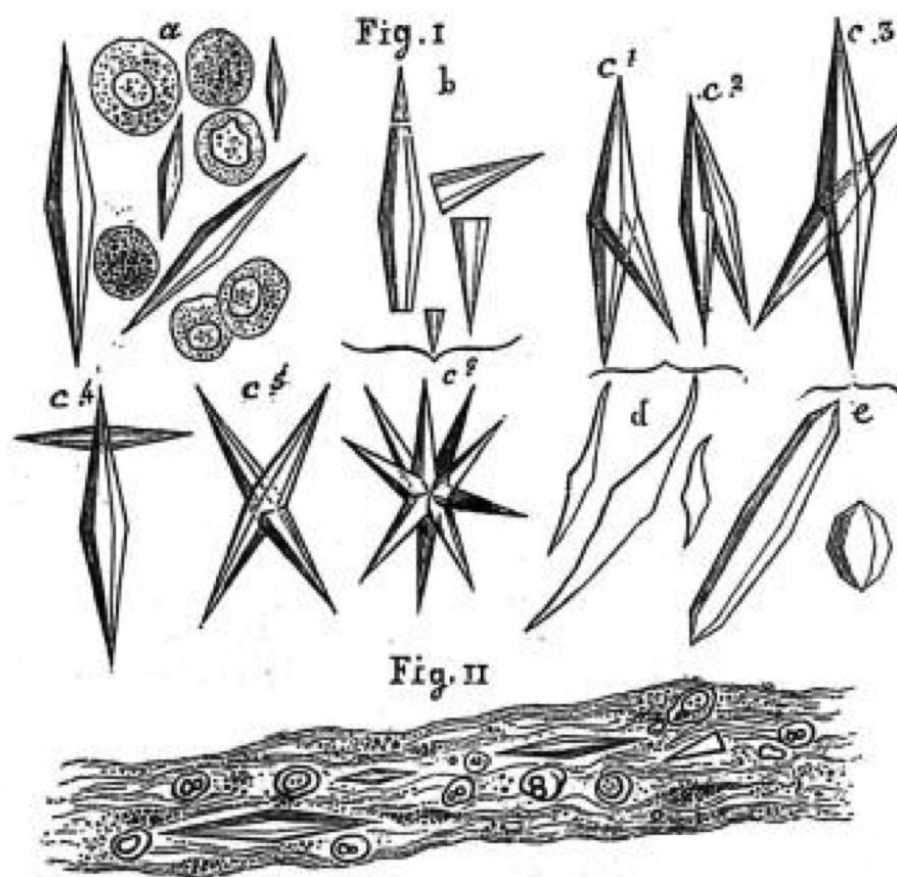


FIG. 4. — Cristaux octaédriques trouvés dans le sang d'un sujet leucémique.
a. Cristaux et globules blancs représentés à l'aide de la chambre claire, avec un grossissement de 450 diamètres.
b. Cristaux rompus : modes de rupture les plus ordinaires.
c¹, c², c³, c⁴, c⁵, c⁶. Cristaux groupés.
d. Cristaux modifiés par l'acide azotique.
e. Cristaux représentés, soit au moment où la chaleur commence à les dissoudre, soit au moment où ils se reforment après leur dissolution.

FIG. 5. — Concrétion fibrineuse expectorée par un sujet non leucémique, et dans laquelle on a trouvé des leucocytes et des cristaux analogues aux précédents.

Figure 5. Charcot-Leyden crystals drawing by Charcot from *Gazette hebdomadaire de médecine et de chirurgie* 1860;7:755-758. (Collection OW).

An insatiable curiosity in all fields

To illustrate Charcot's insatiable curiosity, consider his translation of an article from the English journal *London Medical Times* describing a case of sudden graying in 1861 (*Charcot, 1861a*). Seeking to refute an irrational explanation of a supernatural nature, he traces the history of this issue—a testament to his vast medical knowledge—by compiling clinical cases gathered from European literature. He correctly attributes this phenomenon to stress and distinguishes it from vitiligo, lamenting that “the physiological cause still eludes us.” How could he have conceived of an autoimmune phenomenon triggered by the activation of the hypothalamic-pituitary-

adrenal axis, leading to the disappearance of melanocytes that darken hair follicles and precipitate hair loss, while hair that is already white—lacking melanocytes—remains alone and gives the hair a gray-white appearance (Sikkink et al., 2020).

In 1861, Charcot turned his attention once again to gangrene, and more specifically to the form that complicates diabetes (*Charcot, 1861b*). In his review of the literature, he pays tribute to the original description by Charles-Jacob Marchal de Calvi (*Walusinski, 2023*) in 1852 (*Marchal, 1852*) and 1856 (*Marchal, 1856*). Charcot divides his study into three categories, based on cases he observed and others reported in the literature: diffuse phlegmons, so-called senile gangrene, boils, and anthrax. The concept of microbial infection is obviously still unknown to him. He does not specify the state of arterial circulation or the presence of sensory disturbances, unlike Marchal. His lecture on Tuesday, December 13, 1887, devoted to intermittent claudication in diabetics, attests to the progress made in understanding the pathophysiology of these diabetic complications between 1861 and 1887 (*Charcot, 1887*).

Starting in 1862, the year he became head of the department at La Salpêtrière, neurological topics became more frequent, while those from other medical fields became less common.

In response to a column by Sigismond Jaccoud (1830–1913) reporting on a presentation made to the Royal Society of Medicine and Surgery in London regarding the expected benefits of treatment with potassium bicarbonate to alleviate an acute attack of rheumatoid arthritis (*Jaccoud, 1862*), Charcot discusses his own therapeutic trials with high-dose sodium bicarbonate, conducted at Lariboisière Hospital while he was replacing Claude-Hermann Pidoux (1808–1882)—trials carried out in collaboration with Vulpian at the Hôtel-Dieu (*Charcot, 1862*). They used sodium bicarbonate—known for its anti-inflammatory properties—with real benefits for the patients. Thus, Charcot demonstrated his continued interest in the study of rheumatism, building on his memorable doctoral thesis.

Also in 1862, Charcot recounts the story of a young woman he examined alongside Armand Trousseau (1801–1867). Suffering from a severe form of Graves' disease, and with none of the modest treatments offered having curbed her hyperthyroidism, the onset of pregnancy led to the disappearance of all the alarming symptoms she had been experiencing. This return to near-normalcy persisted four months after childbirth. For Charcot, and supported by other similar cases, this outcome was no mere coincidence. Pregnancy can reduce goiter, exophthalmos, tachycardia, and weight loss, and should be recommended whenever possible! This empirical clinical observation had no pathophysiological explanation at the time. The child appears to have shown no pathological symptoms at birth. Thyroxine (T4) was isolated in 1910 by Edward Calvin Kendall (1886–1972).

Based solely on clinical findings, without yet knowing bacteriology, it was very difficult to distinguish typhoid fever from septicemia or endocarditis. For example, in 1862, Charcot and Vulpian reported a case of ulcerative endocarditis of the tricuspid valve (*Charcot and Vulpian, 1862*). They note the higher frequency of left-sided valve involvement compared to right-sided and detail the tissue destruction caused by the infection, which severs the chordae tendineae and the free edges of the valves. They also describe the varied and multiple localisations of infectious emboli originating in the heart, referred to as a “special morbid poison.” The febrile picture described is of the magnitude of a gravely serious historical case, the likes of which no longer exist.

It is frequently claimed that Charcot had no interest in therapeutics and paid little heed to the suffering of the poor patients who respectfully came to beg his opinion on the origin of their

suffering. Numerous facts contradict these disparaging assertions. His 1864 publication in the *Bulletin général de thérapeutique* provides evidence of this in a medical field unexpected given the image we have of Charcot: sexuality. His article describes the dangers of treatments with Fowler's solution—that is, the use of arsenic, particularly for extensive psoriasis. His introduction reflects his ambivalence regarding the risk of arsenic poisoning: “The unfounded fears that once caused undue apprehension regarding the prolonged use of arsenic preparations in the treatment of certain chronic conditions have now largely dissipated in light of rigorously observed facts, and it even seems that they have given way, in some minds, to an optimism that is undoubtedly not without its dangers” (*Charcot, 1864*). Charcot then recalls the risk of tremors and peripheral neuropathies (*Hall, 2002*), which can lead to paralysis, but adds—a fact that seems to have been overlooked at the time—the onset of impotence, which he euphemistically refers to as anaphrodisia or “inertia of the genital organs.” He does not recommend abandoning this remedy but rather modifying the way it is prescribed, that is, starting with slowly increasing doses and reducing them once the therapeutic goal is achieved.

On April 13, 1865, Charcot informed his colleagues of the nature and progression of an epidemic that had begun in Saint Petersburg (*Charcot, 1865b*). Having ruled out the plague and typhus, Charcot, citing articles published in Germany, settled on the diagnosis of “relapsing fever.” He copied the article published in *Centralblatt für die medicinischen Wissenschaften* by editor-in-chief L. Herrmann on March 25, 1865. Preceded by flu-like symptoms, the acute phase involved fever, prostration, jaundice with hepatosplenomegaly for about ten days, with all symptoms gradually improving over the course of about ten days. Some patients progress to a coma with fatal, uremic, and icteric collapse, while others relapse two or three times over the course of one to two months and then recover. The disease is contagious and was transmitted to many caregivers. Charcot notes, on this occasion, that he had devoted a paragraph to relapsing fever as described by English authors in the medical treatise he completed after the death of its original author, Achilles Requin (1803–1854) (*Requin and Charcot, 1863*). Charcot advises “to gather all documents relating to this singular and formidable condition, so that we are not caught off guard if, by some impossibility, it should reach us in the more or less distant future.”

In 1865, Charcot delivered a presentation to the Medical Society of the Hospitals: “My former mentor and predecessor at the La Salpêtrière Hospital, Dr. Cazalis, used to point out to his students that, in patients who succumb to the disease (cancer), secondary deposits—most often multiple—are very commonly found within the vertebral bodies” (*Charcot, 1865a*). Charcot then refers to what he considers the first case of “painful paraplegia,” that is, vertebral collapse with spinal cord compression. He describes in detail the terrible pain in the spine and limbs, which gradually or suddenly become paralyzed. This was the case for six out of thirty-five women with breast cancer in his department over the past three years. Next, Charcot discusses the cases of four women with uterine cancer who developed arterial thrombosis—in the femoral, humeral, or sylvian arteries—without any atheromatous changes in the arterial walls or evidence that the healthy heart had released emboli. He noted that such thromboses can progress to gangrene in cases of gastric or breast cancer.

In 1866, Charcot presented a study “on rectal temperature in Asian cholera,” conducted during the recent epidemic that had affected Paris. When “the symptoms of coldness and choleraic cyanosis were most pronounced,” temperatures ranged from 37.8°C to 38.5°C. (*Charcot, 1866b*). In a few cases, the temperature exceeded 40°C a few hours before death. He seems to regret that the epidemic ended before he could obtain more data and refine his analysis. While this may seem primitive and of little interest to us today, we must remember that it was innovative and original in 1866.

Conclusion

In 1866, Charcot began his open lectures—that is, lessons given within his department and unrelated to the university curriculum—devoted to diseases of the elderly and recorded by Benjamin Ball. While these lectures were compiled into a book in 1867, the opening of the article published in the *Gazette des Hôpitaux* includes a description of the hospice residents that does not appear in the book: “The large population in our wards (2,500 patients) allows us to examine, from the most diverse perspectives, the main types of a single disease category; but what is even more important, we are able here to follow patients over long periods of their lives, rather than witnessing a mere episode in their history; thus we see the pathological process unfold to its very limits, whereas generally we are familiar only with its initial phase” (Charcot, 1866a). This was the first specialized course in geriatrics in Paris. The only work Charcot recommends to his students dates from 1725, a work by the Englishman John Floyer (1649–1734) (Floyer, 1725). His first lecture is devoted to fever, particularly in cases of “biliary gravel,” a common and fatal condition, pneumonia, etc. All these pathologies are described without reference to microbiology, which had not yet emerged. Many of his lectures are devoted to rheumatism and gout. This book is somewhat like the culmination of Charcot’s geriatric work. After 1868, with the founding of the Archives de physiologie normale et pathologique alongside Vulpian and Charles-Edward Brown, Charcot published exclusively on his research into the nervous system and its disorders.

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Seeing Seizures: From Charcot to Artificial Intelligence in Epilepsy and Functional Disorders

(Neuroperspective)

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Modern epilepsy care is increasingly shaped by algorithms, large datasets, and computational models. Yet its intellectual roots lie in a very different clinical world, the nineteenth-century wards of the Salpêtrière Hospital, where Jean-Martin Charcot (1825–1893) built a discipline founded not on machines, but on observation (*Goetz 1995*).

Charcot's neurology was, above all, a neurology of the eye. In an era without EEG, neuroimaging, or digital recording, the principal instrument of the neurologist was careful attention to clinical detail. Charcot and his pupils documented the phenomenology of neurological disorders through meticulous bedside examination, drawings, and early medical photography. Seizures, paralyses, tremors, and abnormal postures were analyzed as if they were natural phenomena unfolding in real time. From these observations emerged the anatomo-clinical method: the systematic effort to correlate symptoms observed during life with pathological findings discovered after death (*Goetz 1995; Charcot 1881*).

This approach proved particularly influential in the study of epileptic seizures and related paroxysmal disorders, including what we now call functional (dissociative) seizures (*Bourneville and Regnard 1878*).

At the Salpêtrière, Charcot confronted a complex diagnostic landscape in which epilepsy overlapped with what was then called hystero-epilepsy. Rather than dismissing the ambiguity, he attempted to describe it. His lectures carefully distinguished patterns of seizure activity, while his collaborators, including pioneers of medical photography, captured sequential images of attacks that today might be classified as epileptic or functional seizures (*Charcot 1881; Bourneville and Regnard 1878*). In the absence of electrophysiology, semiology became the

primary diagnostic tool, highlighting the critical importance of careful observation in understanding paroxysmal attacks of diverse origins (*Kanner 2020*).

In the twenty-first century, neurology operates within a radically different technological environment. EEG, magnetic resonance imaging (MRI), and genetic testing have transformed the diagnostic landscape in epilepsy (*Berg et al. 2010*). More recently, artificial intelligence (AI) has begun to enter clinical practice: machine-learning systems analyze EEG recordings, detect seizure patterns, and assist in neuroimaging interpretation (*Qamar et al. 2025*). Large computational models can identify subtle correlations within datasets that would be impossible for individual clinicians to recognize, including biomarkers of seizure onset and propagation (*Qamar et al. 2025*).

Yet the contrast between Charcot's neurology and contemporary AI-driven neurology is not merely technological, it is epistemological. Charcot's method was grounded in narrative clinical reasoning. Each patient represented a unique constellation of symptoms requiring careful interpretation within a broader clinical context. AI, by contrast, excels at pattern recognition across massive datasets, often producing results without explicit explanatory frameworks (*Shoeb 2009; Topol 2019*). Where Charcot sought to understand the meaning of symptoms within the lived experience of a patient, AI frequently operates through statistical inference and pattern discovery.

This tension raises an important question for modern epileptology: does technological sophistication risk distancing clinicians from the observational traditions that originally defined the discipline? Algorithms can detect patterns, but they do not watch patients in the same way Charcot and his students did in the amphitheater of the Salpêtrière. The neurologist of the nineteenth century learned from prolonged clinical observation, sometimes from a single patient studied over years. In contrast, contemporary systems may derive insights from thousands of recordings but remain blind to the subtleties of human expression, behaviour, and context that often guide nuanced clinical diagnosis (*Bourneville and Regnard 1878; Kanner 2020*).

At the same time, the relationship between Charcot's legacy and modern artificial intelligence is not purely oppositional. In some respects, AI can be seen as an extension of the same intellectual project Charcot began: the search for reproducible patterns within complex neurological phenomena. The difference lies in scale. Charcot's patterns emerged from the disciplined eye of the clinician; today they may emerge from computational models trained on vast quantities of data (*Qamar et al. 2025; Topol 2019*). Yet the essence remains the same: understanding the unfolding of seizures and paroxysmal events in all their clinical richness.

The challenge for contemporary epileptology is therefore not to choose between human observation and AI, but to integrate them. Charcot's approach reminds us that clinical meaning cannot be entirely reduced to data. The subtle phenomenology of seizures — the gestures, postures, emotional expressions, and contextual triggers that he documented so carefully — still requires attentive clinical interpretation (*Kanner 2020*).

In this sense, the age of AI may ultimately reaffirm rather than replace the principles that guided Charcot's work. Technology can augment diagnosis, but it cannot fully substitute the clinician's capacity to observe, interpret, and understand the patient as a whole, whether the crisis is epileptic or functional (*Bourneville and Regnard 1878; Berg et al. 2010*).

More than a century after his death, Charcot's lesson remains strikingly relevant: epileptology begins with seeing. Even in an era increasingly mediated by algorithms, the careful observation



of seizures, epileptic or functional, remains the foundation upon which all neurological knowledge must rest.

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