Shaking up the Salpêtrière

Jean-Martin Charcot and mercury-induced tremor

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ABSTRACT

Objective: To analyze Jean-Martin Charcot's studies of mercury-induced tremor.

Methods: This study examines Charcot's original notes on mercury intoxication from the Bibliothèque Charcot, Paris, and his show-and-tell patient presentations that were hand-transcribed by his students and later published.

Results: Using his standard method of presenting multiple patients with a similar disorder side by side, Charcot assembled a series of patients with mercurial intoxication from the clinics of Paris. He emphasized the rest and action components of mercury-induced tremor and stressed the value of using graphical tremor recordings rather than relying only on visual observation. He drew attention to the importance of air ventilation to avoid intoxication and of removal from intoxicating environments. He distinguished the characteristics of mercury-induced tremor from tremor associated with Parkinson disease, multiple sclerosis, and general paresis. Based on the similar intention tremor in multiple sclerosis and mercury intoxication, human pathology studies in multiple sclerosis, and animal experiments with mercury, he suggested that axonal demyelination underlay this form of tremor in both conditions, the former restricted to the CNS and the second to peripheral nerves.

Conclusions: These cases illuminate Charcot's diagnostic strategy and his reliance on the clinico-anatomic method to correlate pathology with clinical signs. Whereas much of Charcot's work emphasized hereditary etiologies of neurologic disease, these examples allow an understanding of his views on environmental factors in neurologic disorders as well as treatment strategies.

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GLOSSARY

MS = multiple sclerosis; **PD** = Parkinson disease.

Jean-Martin Charcot (1825–1893) was the most celebrated clinical neurologist of the 19th century.¹ His teaching courses, both the formal Friday lectures that focused on 1 disorder or topic and his Tuesday lectures that were clinical show-and-tell exercises with many contrasting cases shown side by side, were pivotal educational venues for training peers and students.²⁻⁵ These latter presentations were especially important for establishing the evolving nosology or classification system of clinical neurology that has largely remained unaltered into the 21st century.

One of the clinical topics of particular interest to Charcot was tremor. His seminal clinical studies of rest and action tremor separated Parkinson disease (PD) and multiple sclerosis (MS), 2 entities that had been clinically confused. Using a variety of clinical techniques and recording devices, he established that PD had predominant rest tremor, whereas MS was characterized by the absence of rest tremor and had the contrasting hallmark of a severe tremor during attempted activity.⁵

In the midst of these well-publicized and seminal studies, Charcot also identified a number of other tremor conditions that were important at the time. Whereas Charcot considered most primary neurologic conditions to have a hereditary foundation, he studied some environmentally induced neurologic disorders, with mercury-induced tremor being a particular example of a disorder clearly founded in toxic exposure. Although mercurial intoxication is not a frequently encountered cause of tremor in the modern environment, the extensive decorative metal industry of fin de siècle Paris and the inadequate ventilation that still characterized many factories and work shops led him to encounter several cases.⁶

This study is based on Charcot's original Tuesday lessons on mercurial tremor that were hand-transcribed by his students and later printed first in hand-script lithograph format and then as edited printed volumes.

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The lithograph and typeset versions are not identical, and Charcot's editing of the hand-transcriptions sometimes included modifications in the final printed versions. Whereas the hand-transcriptions likely capture the ambience and spontaneity of the teaching forum better than the printed texts, the latter edition is often clearer, because recording errors are corrected and vague allusions are explained in more detail. As such, both sources are needed for a full evaluation of teaching tenor and content. The study also is anchored in original source documents at the Bibliothèque Charcot in Paris, where Charcot's notes and professional files are housed.⁷

Mercury was mixed with gold for coating luxury objects, and the heating of the metal amalgams to create the detail work for fine craftsmanship placed workers at risk for intoxication with mercurial fumes. Likewise, leather tanning and felting involved the use of mercury dinitrate and was known to be an occupational risk for mercury intoxication. Mercury was also a medicinal substance used for treating wounds as well as syphilis. On May 22, 1888, Charcot presented 3 cases of mercurial intoxication-induced tremor to his audience.³ All were middle-aged men: 2 were employed in the process of painting or dipping gold over lower-grade metals, and 1 was a leather worker. Side by side, they allowed Charcot to reveal the salient and distinctive features of this form of environmentally induced tremor. Charcot also listed mirror dipping and thermometer production among occupations of particular risk for mercury intoxication. Although tremor was the specific focus of his presentation, Charcot's notes from the Bibliothèque Charcot note an appreciation of other neurologic and medical signs of mercury exposure.⁷

The 3 cases covered different severities of tremor and different durations of mercury exposure, 1 with many hospitalizations for recurrent shaking and walking disability. The patient interviews indicate that Charcot and his patients were well-informed on the causative relationship between poor ventilation or inadequate precautions within the workplace and tremor. Charcot also appreciated that the chronicity of metal working was not the determinant risk factor, but rather the work in specific environments not meeting the public hygiene standards.

In conversations during these past days, our patient has informed us that for long periods, in fact more than 29 years, he worked in certain workplaces that took careful note of hygienic rules, especially at Barbedienne Company, without ever having been afflicted with the slightest tremor. Whereas, it required only a few months in other poorly ventilated workplaces for him to develop the tremor that we see today.^{3(p486)}

The character of mercurial tremor was distinct from the archetypes of PD and MS. With mercury intoxication, a fine, rest tremor that was faster than seen with PD could occur when the patient was emotionally stressed, but otherwise was absent or very minimal; clearly, there was no continual rest tremor as typical of PD. However, when the patient moved, he or she developed a marked tremor with characteristics similar to MS, becoming more accentuated as the patient tried to reach an endpoint. This point of increasing accentuation caused spilling and severe handwriting problems that were not seen with the action tremor associated with exophthalmic goiter, a point that Charcot stressed in his comparative session of January 22, 1889.⁴ Naturally, with the fine work required by craftsmen working with precious metals, this type of crescendoing action tremor prohibited working. The hands were the most affected, but some patients had head, lip, and tongue tremor with the same characteristics of being present at rest with emotional stress and clear exacerbation with movement. The speech could be severely compromised because of the tremor, and Charcot admitted that he in fact erred in the past by missing the diagnosis of mercurial intoxication because the speech resembled that seen in general paresis:

With this patient, and I declare it publicly, when he first presented to us, our impression was a diffuse meningo-encephalitis, based primarily on his speech problems. In truth, our impression almost immediately took an about-face when we learned that he was a goldsmith.^{3(p487)}

Whereas the action tremors of mercury intoxication and MS were highly similar, the scanning, dysarthric speech typical of MS was different from the tremorous and stuttering quality of mercury intoxication.

To demonstrate the characteristics of tremors, Charcot relied on visual observation, clinical maneuvers, and recording devices. He was emphatic that special techniques could amplify tremor, and pointed out to his students that tremor could be accentuated if a glass is picked up from a tray held in front of the patient rather than allowing him or her to pick up the glass from a secure table. Charcot also relied on tremor recordings with a variety of early registration tools:

You already know that one cannot judge the rapidity of the rhythmic oscillations that constitute a tremor with only the information gleaned from your eye. To shed light on this topic, you also need to use the graphical method, and we doctors know well that the data provided by such measurement techniques are of considerable clinical importance.^{3(p483-4)}

Special recording devices allowed the documentation of the fine rest tremor induced with emotional stress with sudden exacerbation during

Figure 1 Tremor recording of mercury tremor

Tremor recording presented on January 22, 1889, demonstrating the hallmarks of mercury-induced tremor: a minimal rest tremor that can be increased under emotional stress that suddenly accentuates at the moment that action is initiated (A) and further augments with attempted activity.^{4(p279)}

activity (figure 1). Based on such recordings, Charcot incorporated schematic drawings into his presentation on May 22, 1888, to show the prototype of PD and MS and then to demonstrate the contrasting pattern of mercury-induced tremor (figure 2).

The teaching focus was primarily on hand tremor, but Charcot acknowledged that the legs were also involved, and an unsteady gait with risk for falling was an important part of mercurial in-

toxication. In exceptional cases, leg tremor could incapacitate a patient to the point of becoming bedridden at least transiently. Intrinsic to the gait difficulty was demonstrable weakness of the legs, and this finding perplexed Charcot. In this context, Charcot made a rare reference to the value of animal experimentation. Charcot explained to his students that most tremors indicated pure CNS disease, but in this case, he suggested that mercury must be affecting peripheral nerves. To support this view, he turned to studies in the laboratory of his old colleague, Alfred Vulpian (1826–1887), performed by Dr. Maurice Letulle (1853–1929), where experimental animals were chronically intoxicated with mercury.⁸ Charcot lauded the careful techniques of his laboratory colleagues in this case, emphasizing that they discovered that mercury intoxication on a chronic and unremitting basis damaged peripheral nerves through demyelination. This coupling of weakness and tremor was also characteristic of MS, although Charcot knew that the hallmark of this condition was CNS demyelination. The clinical similarities of the 2 forms of intention tremor and their anatomic bases in demyelination, but in different areas of the neuraxis, fostered Charcot's evolving understanding of motor circuitry and formed important examples of the fruits of his clinico-anatomic methods. Although Charcot did not invest extensively in discussions of pathophysiology in most of his teaching, he considered the parallels between the combination of tremor in the context of weakness and demyelination without axonal destruction in both MS and mercury intoxication. In both instances:

It is this denuding of the preserved axonal cylinder, still able to transmit at least to some extent the willed intent, that underlies these oscillations, leading to compromised intentional movements.^{3(p494–5)}

Whereas Charcot's major neurologic contributions involved autopsy studies that complemented clinical material, in the case of mercury intoxication

Figure 2 Teaching schema used by Charcot to separate mercury tremor from the tremors seen in Parkinson disease (PD) and multiple sclerosis (MS)

Based on tremor recordings, Charcot developed graphic displays of tremor in archetypal disorders for teaching and showed this figure to his audience on May 22, 1888. 1–2 represents rest, 2–3 represents action. (A) Depicts the typical rest tremor of PD that resolves with activity; (B) depicts the crescendo action tremor without rest tremor of MS; (C) represents the pattern of mercury-intoxication tremor and shows the intermittent rapid and low amplitude tremor that is particularly brought on by emotional stress during rest and the marked action tremor that increases as the subject attempts to complete an action.^{3(p489–490)}

in humans, he had not studied human material. With a certain intellectual lament, he stated:

We have no human autopsy material. I believe this reality relates most likely to the fact that, in terms of survival [*quoad vitam*], mercury-induced tremor is a benign condition in the sense that it leads only quite indirectly to a fatal outcome.^{3(p499)}

This reference to a benign condition was anchored in the observations that the natural induction of mercury-induced tremor occurred after approximately 2 months of exposure and largely abated in terms of serious clinical consequences after only 6 weeks of removal from the toxic source. Full resolution did not regularly occur, and a small, but largely inconsequential, tremor persisted. In the cases Charcot presented, the workers had experienced multiple bouts of mercury tremor consequent to episodic exposure.

An interesting conversation on placebo intervention occurs in this presentation on mercurial tremors. Clearly understanding that good ventilation and nourishment were the only treatments needed for rapid abatement of the tremor, Charcot tells his audience that he has also prescribed 3 to 4 daily teaspoons of sodium chloride solution. Only the medical audience understands the placebo product, because Charcot uses terminology far outside the reach of the humble patients.

Specifically, he uses the term “expectation déguisée” [masked nonintervention]^{3(p491)} and follows in Latin: “Populus non vult decipi [People do not want to be fooled].”^{3(p491)} (The hand-transcribed notes of this lesson differ from the later printed version that had undergone copyediting and correction. In the handwritten version, the citation is the traditional *Populus vult decipi* [People like to be fooled], but this phrase was corrected in the printed version to insert the negative. Charcot is clear in his meaning, adding: “This [salt] solution is aimed exclusively to mask the fact of non-intervention, something patients strongly dislike.”)

The other forms of tremor that Charcot studied included tremors seen with hysteria, Friedreich ataxia, alcoholism, and in association with exophthalmic goiter.^{3,4} The patterns of these tremors were less articulated in detail than mercurial tremor, and fewer observations are available on his views on long-term outcome. Charcot also studied the toxic effects of silver and lead, but these were not specifically re-

lated to tremor and occupy the focus of other lectures.⁷

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DISCLOSURE

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REFERENCES

1. Goetz CG, Bonduelle M, Gelfand T. Charcot: Constructing Neurology. New York: Oxford University Press; 1995.
2. Charcot J-M. Œuvres Complètes (9 volumes). Paris: Bureaux du Progrès Médical; 1877–1890.
3. Charcot J-M. Leçons du mardi à la Salpêtrière (tome 1, 1887–1888): lesson of May 22 1888 (pp. 483–512). Paris: Bureaux du Progrès Médical; 1888 (lithograph version of hand-transcribed notes and typeset printed versions published with the same publication year).
4. Charcot J-M. Leçons du mardi à la Salpêtrière (tome 2, 1888–1889): lesson of January 22, 1889 (pp. 277–292). Paris: Bureaux du Progrès Médical; 1889.
5. Charcot J-M. Leçons sur les maladies du système nerveux (vol 1): de la paralysie agitante (pp. 155–188); de la sclérose en plaques disséminées—anatomie pathologique (pp. 189–220); de la sclérose en plaques disséminées—symptomatologie (pp. 221–248). Paris: Bureaux du Progrès Médical; 1873. [In English: Charcot J-M. Lectures on the diseases of the nervous system (transl G. Sigerson). On paralysis agitans (pp. 129–156); Disseminated sclerosis—pathological anatomy (pp. 157–181); Disseminated sclerosis—its symptomatology (pp. 182–202). London: New Sydenham Society; 1877.]
6. Desrosières A. Official statistics and medicine in nineteenth century France. *Soc Hist Med* 1991;4:515–537.
7. Letulle M. Recherches cliniques et expérimentales sur les paralysies mercurielles. *Arch Physiologie Normale Pathologique* 1887;9:301–338, 438–468.
8. Charcot JM. Mercurialisme MA VIII. 12.6 Bibliothèque Charcot; Paris, France.