

# Louis Pasteur's first stroke: a capsular warning syndrome *avant la lettre*

J. J. Zarranz Imirizaldu

Emeritus chair. Department of Neuroscience. Universidad del País Vasco.

## ABSTRACT

**Introduction.** In his own right, Louis Pasteur is recognised as one of humankind's greatest benefactors for his contributions to chemistry and especially for his research into the nature and prevention of infectious diseases. Laudably, he conducted much of his work after overcoming the severe sequelae of a stroke at the early age of 46 years.

**Material and methods.** The life and work of Louis Pasteur have been described in several biographies, and are summarised here. To attempt to reconstruct the nature of his stroke, we essentially rely on details from the accounts of his grandson and son-in-law.

**Results.** Pasteur developed complete left hemiplegia with no symptoms or signs of cortical or brainstem involvement, suggesting a capsular lesion.

**Discussion.** The most specific detail of the clinical picture is that hemiplegia was established after a succession of 20 to 30 transient ischaemic attacks within less than 24 hours, known today as capsular warning syndrome, which was disconcerting for the physicians treating him. The pathological basis of the syndrome and the treatment options are discussed.

## KEYWORDS

Stroke, Pasteur, stroke warning syndrome, capsular warning syndrome, lacunar state, small vessel disease, lacune

*Louis Pasteur n'a été ni médecin ni chirurgien, mais nul n'a fait pour la médecine et la chirurgie autant que lui.*

*Parmi les hommes à qui la Science et l'Humanité doit beaucoup, Pasteur est resté souverain.* (Henri Mondor)<sup>1</sup>

*No one man has it ever been given to accomplish work of such great importance for the well-being of humanity.*  
(Sir William Osler)<sup>2</sup>

## Introduction

As noted in the preceding quotes from Dr Osler (one of the greatest clinicians and thinkers in the history of medicine) and the distinguished Dr Mondor (surgeon, politician, and member of several academies), Louis

Pasteur (Figure 1) is among mankind's great benefactors due to the vast number of problems he helped to solve with his tireless research.<sup>1-7</sup> His work is even more laudable in the light of his courage in conducting a significant amount of research after presenting a stroke at the young age of 46 years, which left him with left-sided hemiplegia. While he presented considerable motor sequelae, his mental faculties and indomitable will were preserved, and he was able to continue his extraordinary work.

Few articles have analysed the nature of Pasteur's cerebrovascular disease. Dr Norris<sup>8</sup> accepted the opinion of Vallery-Radot,<sup>9</sup> who was not a physician, that Pasteur

had presented a haemorrhage, which he attributed to an arteriovenous or venous malformation. In turn, Rumbach et al.<sup>10</sup> concluded that the most probable diagnosis was a cavernoma.

The main objective of this study is to analyse the clinical details of Louis Pasteur's first stroke, particularly its unusual form of onset, with numerous symptom fluctuations over a period of hours, raising suspicion that he presented a subcortical infarct preceded by a capsular (or stroke) warning syndrome.<sup>11-24</sup> Therefore, this would constitute an *avant la lettre* description of this syndrome, long before it was recognised under that name in the neurological literature.<sup>11</sup> The subsequent relapses are also suggestive of and compatible with small-vessel infarcts, and led to a deterioration of Pasteur's condition until he ultimately reached a state of near-mutism and motor disability.

### Material and methods

The summary of Pasteur's life and work is based on some biographical texts, among other sources.<sup>1-7</sup> Little information on his disease is included in these and other works that are not cited. Practically the only author providing sufficient detail to reconstruct the clinical history of Pasteur's cerebrovascular disease, particularly the first stroke, is his son-in-law.<sup>2,3</sup> His grandson's contribution is less relevant, with the exception of his description of the sequelae and progression of the first stroke.<sup>4</sup> Pasteur's *Correspondance*, compiled and annotated by Pasteur Vallery-Radot, contains other details of human interest and on Pasteur's stroke.<sup>9</sup>

### Results

Summary of the biography of Louis Pasteur

Table 1 presents a timeline of Pasteur's life. He was born in Dole in 1822, to a modest family; from his father, a tanner, he inherited a devotion to Napoleon I, in whose ranks his father had fought. In 1827, the family moved to Arbois. After his primary studies, he earned a Bachelor of Letters degree in 1840 and a Bachelor of Science in Mathematics in 1842. He was admitted to the Lycée Saint-Louis in Paris, where he discovered his passion for chemistry in the lessons of Jean-Baptiste Dumas, Pasteur's main mentor throughout his life, whom he always reverentially addressed as "*mon cher maître*." He entered the École Normale Supérieure in 1843, earning the degree of *licencié ès sciences* in 1845, becoming an



**Figure 1.** Photograph of Louis Pasteur by Eugène Pirou, published in *Galerie Contemporaine*. While it is officially dated ca. 1880, the facial expression is that of a young man. By 1880, Pasteur's appearance would be closer to that observed in the portrait from 1885, in Figure 4. The normal posture of his left hand suggests that the image was taken before his stroke, or that the pose fortunately concealed his sequelae.

assistant professor in 1846 and earning his doctorate in 1847 with two theses, one in chemistry and the other in physics.

In 1848, he presented his first communication to the Académie des Sciences; a total of 213 contributions addressing a wide range of subjects are recorded up to 1886 (available at: [https://www.academie-sciences.fr/archivage\\_site/activite/archive/dossiers/fonds\\_pdf/Fond\\_Pasteur.pdf](https://www.academie-sciences.fr/archivage_site/activite/archive/dossiers/fonds_pdf/Fond_Pasteur.pdf)).

In 1848, Pasteur's mother died several hours after a stroke. In 1849, he was appointed professor of chemistry by the University of Strasbourg. For several years, he worked on crystallography and molecular asymmetry. In 1853, he was awarded the honour *Chevalier de la*

**Table 1.** Timeline of Louis Pasteur's life.

1822. Born in Dole	1865. Death of his father and daughter Camille
1827. Pasteur family moved to Arbois (tanner's workshop)	1866. Begins studying silkworm diseases. Death of his daughter Cécile
1840. Bachelor of Letters	1868. Stroke causes left-sided hemiplegia. <i>Commandeur de la Légion d'Honneur</i>
1842. Bachelor of Sciences in mathematics	1869. Resumes working life in February
1843. École Normale Supérieure	1870. Franco-Prussian war. His son is wounded. Bombardment of Paris
1845. Degree of <i>licencié ès sciences</i>	1873. Member of the Académie Nationale de Médecine. Brazilian Imperial Order of the Rose
1846. Assistant professorship	1877. Studies infectious diseases in animals and the first vaccines
1847. Doctorate	1881. Vaccine against anthrax
1848. First communication to the Académie des Sciences. Pasteur's mother dies.	1882. Académie Française
1849. Professor of Chemistry in Strasbourg. Marriage to Marie Laurent	1885. Administers first rabies vaccine in human patients
1853. <i>Chevalier de la Légion d'Honneur</i>	1887. Two minor strokes, significant speech impairment
1854. Professor and dean of the Faculty of Science in Lille	1888. Inauguration of the Institut Pasteur
1855. Begins studying fermentation and anaerobic life	1889. Dedication at the inauguration of the monument to Jean-Baptiste Dumas
1857. Administrator and director of studies at the École Normale Supérieure in Paris	1892. Retirement ceremony at the Sorbonne
1860. Presence of germs in the air. Refutes "spontaneous generation"	1894. Loss of consciousness ("attack of uraemia")
1862. Procedure for industrial production of vinegar. Member of the Académie des Sciences	1895. Dies at Villeneuve-L'Étang. State funeral at Notre-Dame cathedral
1863. Begins studying the preservation of wine. <i>Officier de la Légion d'Honneur</i>	

*Légion d'Honneur*. In 1854, he was appointed professor and dean at the Faculty of Science in Lille. In 1855, he began studying fermentation and anaerobic life. In 1857, he returned to Paris and was appointed administrator and director of studies at the École Normale Supérieure. From 1860, microscopy research enabled him to discover the presence of germs in the air and he began to refute the theory of "spontaneous generation." In 1862, he finalised a procedure for the industrial production of vinegar, and was admitted as a member of the Académie des Sciences. In 1863 he began his studies on wine. French wine producers, who had recently been allowed to access the British market, faced severe problems, with their wine all too often becoming "vinegarised." It was Napoleon III, apparently also driven by sailors' mutinies due to the same problem, who requested that Pasteur search for a solution. He adapted the old family home in Arbois and installed a laboratory (which is preserved today) for his experiments with wine. He discovered that heating the wine solved the problem of undesired fermentation, as

with other products (beer, milk, etc), giving rise to the pasteurisation method of food preservation.

In 1865, his father and his daughter Camille died; his daughter Cécile died in 1866. From 1866, he dedicated his efforts to the diseases affecting silkworms (known as *pébrine* and *flacherie*) and demonstrated their infectious nature and how only susceptible species were affected. By selecting specimens that were resistant, he was able to solve the problem; this was the first time that genetic predisposition to an infectious disease was demonstrated. In 1863, he was named *Officier* and in 1868 *Commandeur de la Légion d'Honneur*. In 1873, he was elected to the Académie Nationale de Médecine and was awarded the Brazilian Imperial Order of the Rose. In 1882, he became a member of the Académie Française. In 1874, he received a letter from Lister thanking him for his research into germs involved in putrefaction, which led to the development of his own antiseptic techniques, revolutionising surgery.



**Figure 2.** Immortal painting of the solemn ceremony held to honour Pasteur on his 70th birthday at the Sorbonne's great theatre, attended by members of all the scientific institutions, ministers, diplomats, etc. Pasteur is shown leaning on M. Carnot, President of the Republic, and we can imagine that he would be dragging his spastic left leg. Charcot is the fourth of the academics in red gowns, at the left of the picture.

From 1877, Pasteur began to study infectious diseases. In 1878, after observing the terrible death tolls linked to infections in surgical patients and due to puerperal fever among women delivering children, and identifying streptococcus as the causal agent, he distributed a memorandum to surgeons in which he unassumingly explains “what he would do if he held such an important position”: sterilising materials and the water used for handwashing with heat, and flaming instrumentation; in other words, the basis of asepsis.

He developed the principle of vaccination with attenuated microorganisms, first against fowl cholera, then against anthrax and swine erysipelas. By 1885, much progress had been made in the inoculation of animals against rabies, but no tests had been conducted in humans. That year, he was brought the Alsatian child Joseph Meister, who had been bitten by a rabid dog. The inoculation was effective, and was subsequently administered successfully to other patients. In January 1886, in a letter

to his granddaughter Camille,<sup>9</sup> Pasteur mentioned that he had inoculated 108 people; by May, in a letter to Horsley,<sup>23</sup> this figure had increased to 1124. These first human anti-rabies vaccines represent the great push that gave rise to the Institut Pasteur, which was inaugurated in 1888, with a clinical/therapeutic focus; it not only had a clinic for treating patients with potential cases of rabies, but also produced serums and vaccines for use worldwide. In 1892, a solemn ceremony was held for Pasteur's retirement at the Sorbonne University, and was immortalised in a famous painting (Figure 2). He died on 28 September 1895 at Villeneuve-L'Étang, and a state funeral was held at Notre-Dame Cathedral.

In 1849, he married Marie Laurent, daughter of the rector of the university of Strasbourg, who dedicated her life to facilitating his work and creating a warm family atmosphere (Figure 3). However, the couple had the misfortune of losing three daughters, of their five children. Pasteur's wife Marie drafted much of his



**Figure 3.** Pasteur in old age, surrounded by his wife, children, and grandchildren. We may appreciate the contracture of his paretic left hand. Behind him, his daughter Marie-Louise and son-in-law René Vallery-Radot, who wrote his biography; beside him, his grandson Louis-Pasteur Valley-Radot, who compiled his complete works.

work after his stroke, although he was still able to use his right hand. His son-in-law, René Vallery-Radot, was also a significant collaborator in drafting his articles and correspondence; later, he wrote two biographies on Pasteur<sup>3</sup> and published selected drawings and pastel paintings. His grandson, Louis Pasteur Vallery-Radot (who shortened his name to Pasteur Vallery-Radot) was a highly prestigious physician, professor of medicine, academic, and politician. He compiled Pasteur's complete works in seven volumes, as well as four volumes of correspondence<sup>9</sup> and a selection of his best pages, images, and an abbreviated biography.<sup>4</sup>

#### Louis Pasteur's first stroke and sequelae

The first months of 1868 were filled with frenetic activity for Pasteur, who was immersed in the experiments that

led to the pasteurisation of wine, and made numerous visits to various sites. In September, he wrote to his friend and confidant Chappuis<sup>3</sup> that he was very pleased with the results. In October, now in Paris, his work was overwhelming: lectures at the Sorbonne, organisation of his laboratory, polemics, experiments with silkworm diseases, etc: "this accumulation of mental work brought about extreme cerebral tension."<sup>1,a</sup>

According to Vallery-Radot,<sup>3</sup> on the morning of 19 October he noticed a strange tingling sensation on his left side. After this, he presented an alarming attack of shuddering and tremor that forced him to rest in bed after lunch. Despite this, he insisted on travelling to the Academy at half-past two because he was highly interested in the session being held. On the pretext that she needed to go shopping, his wife accompanied him to the foyer of the Academy. There, she met Balard, instructing him not to leave Pasteur alone and to accompany him home. Pasteur read the article that Salimbeni had sent him and evaluated his results on the cause of silkworm diseases.

<sup>4</sup>Translator's note: direct quotes in this and the following section are taken from Devonshire's English translation of the Vallery-Radot's biography of Pasteur. Vallery-Radot R. *The life of Pasteur*. Devonshire RL, translator. New York: Doubleday, Page & Company; 1915.

He sat through the entire session and returned home with Balard. After a light supper he went to bed at nine o'clock. He soon noticed the same paraesthesia he had felt at midday. He was unable to speak for several minutes but managed to call for help. His wife contacted his close friend Dr Godélier, a military surgeon and professor at the Val-de-Grâce school. Pasteur himself, who recovered as quickly as he became paralysed (*"tour à tour paralysé et deparalysé"*),<sup>3</sup> explained his symptoms during intervals in the "dark struggle that threatened his life." He may have presented 20 to 30 transient attacks in the following hours, before being left permanently hemiplegic.<sup>3</sup>

René Vallery-Radot believed that a haemorrhage had left Pasteur paralysed on the left side of the body, in line with Dr Godélier's diagnosis.<sup>9</sup> On the morning of the following day, Pasteur was visited by Dr Noël Guéneau de Mussy,<sup>25</sup> who attempted to cheer him with an "I heard you were unwell and thought I would come to see you"; Pasteur responded with the smile of a patient without illusions. Godélier and Guéneau decided to call for Dr Gabriel Andral,<sup>26</sup> a well-regarded clinician and professor, considered the father of haematology, who arrived in the afternoon and prescribed 16 leeches behind the ears, removing a considerable amount of blood. Today's neurologists may be surprised that nobody sent for any of the famous Parisian figures in the study of neurological diseases, such as Charcot or Vulpian. In 1868, both men were still in their forties and it would be years before they reached the highest point of their careers, after the foundations were laid for what we now know as neurology, yet to be conceived at that time.

That afternoon, Dr Godélier noted "speech clearer, some movement of the paralysed limbs, intelligence perfect." At around 10 o'clock at night, Pasteur complained about his paralysed arm: "it is like lead"; "if it could only be cut off." By two in the morning, Mme. Pasteur was losing hope. The patient entered a state with "intense cold, anxious agitation, features depressed, eyes languid"; this was followed by a period of sleep that appeared to foretell his death. But by dawn, he awoke with his "mental faculties still totally intact."

On Wednesday, 21 October, at half-past twelve, Godélier wrote that "the cerebral lesion, whatever it may be, is not worse, there is an evident pause." Two hours later he remarked on Pasteur's "active mind" and the surprising assertion that he "would willingly talk science."

Over the following days, many collaborators and friends took turns helping Mme. Pasteur to assist her husband with eating, caring for him, and lifting his spirits regarding the future. Trying to keep Pasteur calm, they required silence around him and that all visitors, who were many in number and came from all branches of the sciences, crowded in his study, a room with padded doors at the other end of the corridor on the same floor of the house.

A private letter from his cousin Mme. Cribier<sup>3</sup> includes essential details of the events of the following days. The Emperor and his wife sent a servant to gather news each morning, which Dr Godélier sent in a sealed envelope. Everybody concerned was hopeful that he would recover, given his young age and "absolutely untouched" mind. However, the progression of his disease was disconcerting to the entire Faculty.

His stroke is accompanied by symptoms which are now occupying the attention of the whole Academy of Medicine. Paralysis always comes abruptly, whilst for M. Pasteur, it came on in little successive fits, 20 or 30 perhaps, and was only complete at the end of 24 hours, which completely disconcerted the doctors who watched him, and delayed their having recourse to an active treatment. It seems that this fact is observed for the first time, and is puzzling the whole Faculty.

It was repeated numerous times that Pasteur's mind remained clear, although he obviously feared that he may die. The clearest and most direct account is that of one of his closest friends, M. Gernez,<sup>3</sup> who almost never left his bedside throughout that terrible week. He wrote that he would try to distract Pasteur from his thoughts, but eventually gave up and allowed him to dictate the ideas that came to his mind, finding,

[...] to my surprise, that they had his accustomed clearness and conciseness, I wrote what he dictated without altering a word, and the next day I brought to his illustrious colleague Dumas—who hardly credited his senses—the memorandum which appeared in the report of the Académie on October 26, 1868, a week after the stroke which nearly killed him!

The text described a very ingenious procedure for early testing to identify silkworm eggs liable to be spoiled by disease. The members of the Academy received the note with great joy, celebrating that Pasteur was on the way to recovery.



**Figure 4.** This famous portrait, painted by Albert Edelfelt in 1885, took pride of place in the dining room of the Pasteur household. It was painted many years after Pasteur's stroke, and shows his paralysed left hand. The painter skilfully placed Pasteur's left hand in a position that enabled him to hold a sheet of paper between his thumb and other fingers, concealing his disability.

However, the ambience around Pasteur was much more pessimistic, they thought he was finished, and the work to build his new laboratory, which Pasteur observed disconsolately from his window, was interrupted. It fell to the Emperor himself to order that work be resumed in order to help lift the patient's spirits and the hopes of his recovery.

On 27 November, Pasteur's wife sent another letter to the Empress to inform her that, fearing that his life was in the balance, her husband had requested that she tell the Emperor, via M. Dumas, that he would die "regretting that he had not done enough to honour his reign." Pasteur did not leave his bed until 30 November, moving to an armchair. He was conscious of the direness

of his situation at the young age of 46 years. But, knowing that complaining would sadden his wife and family, he never lamented his situation: his only worry was burdening them and the other devoted friends who cared for him. General Favé would read to him from a book entitled *Self-help*, a collection of biographies and stories illustrating the power of courage and intelligence to overcome adversity.<sup>3</sup> Pasteur was a believer in material and moral progress. He greatly admired the words of Pascal that "man is produced but for Infinity" and "he finds constant instruction in progress." He also enjoyed Bossuet's description of human nature: "the idea of an infinite wisdom, of an absolute power, of an infallible rectitude, in one word, the idea of perfection."

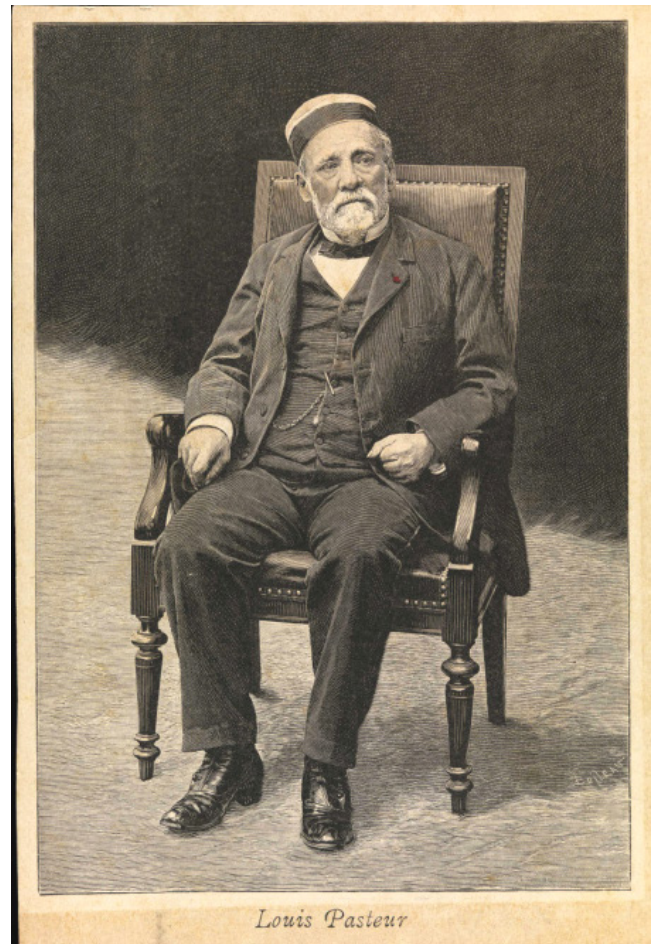
In December, Godélier's notes record a significant improvement, with a good general status, excellent morale, recovery of some motor activity in the left limbs, future plans, many visitors, dictation of letters (the first, dated 9 December, included extensive scientific instructions), etc. By late December, he was able to take a few steps unassisted.

On 23 December, he was able to walk by "pushing a chair and arduously dragging his leg." One letter from Pasteur<sup>9</sup> describes how he was recovering "with excessive slowness." In February, he had a fall, which left him in pain and slowed his recovery. He received electrotherapy with a Ruhmkorff apparatus that he was kindly sent by Dr Godélier, although Pasteur was sceptical of its efficacy, even suspecting it had a deleterious effect on spontaneous finger movement. In a letter to his teacher Dumas, he described his day-to-day life.<sup>9</sup> In the morning, he received visits from his collaborators and organised the day's work. He took breakfast in bed and had the newspaper read to him or dictated a letter. He got up at midday, and if the weather was fine, he would spend an hour or two in the garden. If he was feeling well he would dictate a page or half a page of a small book he was preparing, summarising his observations. In the afternoon, before dinner with his family, he would again receive his collaborators, who would report on their work. By half-past seven he was exhausted, ready to sleep for 12 hours, but would wake at midnight, only sleeping for one or two more hours in the early morning. He was hopeful for his recovery as he felt that these few hours of sleep were sufficient, and because he maintained his appetite. On 18 January 1869, three months after his stroke, he travelled for the first time, visiting silkworm farms.

1870 was a particularly difficult year. His son had enlisted in the army and was wounded during the Franco-Prussian War. Pasteur desolately witnessed the Prussian siege of Paris, whose population, already on the edge of capitulation due to starvation, was savagely bombarded, with thousands of casualties. Like Bourneville, who also suffered that bombardment,<sup>27</sup> he never forgave the Germans for that gratuitous, merciless assault on defenceless civilians. He describes his feelings in a letter to Raulin<sup>9</sup>: “Every one of my future works will bear on its title page the words: hatred to Prussia. Revenge! Revenge!” Pasteur returned the title of Doctor of Medicine he had been awarded by the University of Bonn to the head of the faculty of medicine at the institution, as he found it “odious” and “offensive” to see his name beside that of *Rex Guilelmus*, who was massacring his homeland. The German academic responded contemptuously with four lines that ended by expressing “all his disdain” and returning his “defamation.”<sup>9</sup> Even then, Pasteur responded with another letter<sup>9</sup> charged with the suffering of war and his conviction that the person who had ordered the bombardment of Paris would be forever tainted.

#### Progression and sequelae

In 1872, he wrote to Thiers, the president of the new Republic, to request that he be allowed to retire from teaching but continue as director of the laboratory.<sup>9</sup> He included certificates from Godélier and Andral testifying that excessive work had probably contributed to his stroke. Pasteur gradually returned to his research activity despite his permanent, severe motor sequelae. In a letter to M. Dumas, he described them as follows<sup>9</sup>: “My leg is better, but my hand leaves much, much, to be desired. It is, in other words, of no use at all.” Pasteur’s grandson summarised the sequelae very well<sup>4</sup>: “His left side remained paralysed. The wrist was bent and contracted. The fingers were motionless in a closed fist [Figures 3, 4, and 5]. The leg was stiff, hindering walking [Figure 2].” Despite this and everything else, Pasteur made his greatest contributions in the following years: the pasteurisation of beer and wine, as well as the identification and prevention of numerous infectious diseases. He progressively gained international recognition, and had great success at the Third International Medical Congress in London in 1881 (where he met Charcot, who considered Pasteur’s presentation one of the greatest advances in the history of science).



**Figure 5.** This photograph, apparently taken the same day as that shown in Figure 3, shows Pasteur in his latter years, and clearly depicts the characteristic posture of a limb affected by pyramidal spasticity, with semi-flexion of the left arm and the fingers flexed into a fist.

In the following years, the race to find a vaccine against rabies was exhausting for Pasteur. After his success with animals, but not yet having tested his technique with humans, he was brought Joseph Meister, a child from Alsace, who had been bitten by a rabid dog. Pasteur sought advice, including from Vulpian, who was highly influential in the Academy and who, like others, considered it justified to test the inoculation in the boy. Meister did not develop the disease, and eventually became a porter at the Institut Pasteur, until he took his own life in 1940 when the Germans reached Paris.



Pasteur's work on rabies was exhausting and became a source of great anxiety. He was involved in the follow-up of the treated patients, case by case, and maintained correspondence with many of them, and particularly with young Joseph Meister. In late 1886, he developed symptoms of a heart disorder, which is not described in detail in his biographies. His trusted physicians, Villemin and Grancher, convinced him to spend the rest of the winter resting in the south of France. Raphaël Bischoffsheim, a powerful banker, invited him to his magnificent villa in the Mediterranean paradise of Bordighera (Italy), and Pasteur and his family (wife, daughter, son-in-law, and two grandchildren) moved there in late November. The pleasant climate and tranquillity were good for him, and he was soon able to go for walks. However, this peace was short-lived, and he soon heard rumours of strong criticism against his rabies vaccine and against himself. One of the vaccinated patients had died and he had been accused of murder! Vulpian was his great defender against these attacks, which ironically came mostly from within France. As though this were not enough, on 23 February the region of Bordighera was struck by a violent earthquake, and Pasteur expedited his return to Arbois, where he rested for several weeks before travelling back to Paris.

In July, he had the great satisfaction of learning that the British ad hoc commission on rabies vaccination (whose secretary was Victor Horsley) fully corroborated the efficacy and safety of his vaccine, considering it as important a development as the inoculation against smallpox had been. Pasteur lamented that Vulpian had been unable to receive such happy news, as he had recently died. Charcot enthusiastically praised Pasteur and his rabies vaccine. Pasteur was elected as permanent secretary of the Académie des Sciences, substituting Vulpian.

#### Relapses and final years

On the morning of 23 October 1887, as he was writing a letter in his bedroom, Pasteur tried to speak to his wife but was unable to.<sup>3</sup> He recovered his speech in the afternoon, and nobody noticed anything amiss when he attended the École Normale Supérieure two days later. However, the following Saturday, he presented a similar episode, from which he did not recover; after this, his speech was troubled and weak.

He resigned as secretary of the Academy after these new strokes, although throughout 1888 he continued following up patients and overseeing building work at the Institut Pasteur, which was inaugurated with a solemn ceremony in November. His health continued to deteriorate, and moving became ever more difficult; despite this, he insisted on visiting Alais in October 1889 for the erection of a statue of his esteemed teacher Dumas, to whom he dedicated a few words.

In May 1892, Denmark, Sweden, and Norway took the initiative to create committees to celebrate the 70th anniversary of Pasteur's birth. The Académie des Sciences supported a popular petition to honour him and commissioned a splendid medal. The ceremony in his honour took place on 27 December, at the Sorbonne's great theatre, which was filled to the rafters with his disciples and representatives of all the scientific institutions, ministers, members of parliament, ambassadors, etc. Pasteur entered arm-in-arm with M. Carnot, President of the Republic, an image that has been immortalised in a famous painting (Figure 2). He received numerous gifts and mementos. His voice was too weak, so his son read his speech. In the following days, he received letters of support and gratitude from all corners of the world.

On 1 November 1894, while preparing to visit his grandchildren, as he did every day at midday, he lost consciousness in what his biographer Vallery-Radot<sup>3</sup> described as an "attack of uraemia." However, it seems unlikely that a metabolic disorder should present such sudden onset; in fact, Pasteur Vallery-Radot<sup>9</sup>, a distinguished physician, also questions this supposition and suggests that it may have been another stroke, as Pasteur probably had "arterial sclerosis, myocarditis, and nephrosclerosis." He remained in bed, barely conscious, for four hours. He recovered somewhat in the afternoon and was able to speak, asking not to be left alone. For days, all his family and collaborators took turns caring for him. In late December, he improved to the extent that on 1 January he received his great friend Alexandre Dumas. This improvement continued, and he received visits from former students at the École Normale Supérieure. He also visited the laboratory, where his devoted disciple Roux had kept all the material that Pasteur had used in his early experiments.

On 13 June 1895, he visited Villeneuve-L'Étang, where a hundred horses (some donated by prominent

individuals) were being used to produce diphtheria antitoxin. His physical health continued to deteriorate, and he did not return to Paris, unable to leave his bed. No sudden exacerbations suggestive of further strokes were reported. On 27 June he refused to drink a glass of milk. He reclined his head, closed his eyes, and died 24 hours later, surrounded by his disciples and family.

### Comments

The most striking feature of the story of Louis Pasteur's stroke is the young age of onset (46 years), known among neurologists as young stroke. Strokes at such an unusual age typically have rare aetiologies, other than atherosclerosis, hypertensive arteriolosclerosis, or cardioembolism (particularly due to atrial fibrillation), the most frequent causes of stroke in older patients. However, no detail of Pasteur's history prior to the stroke, or in the 20 years until his second stroke, suggests either a rare aetiology such as vasculitis or clotting disorders, or a more common one, such as early atherosclerosis or emboligenic heart disease. With any of these causes, in the absence of preventive treatment, we may expect him to have presented more and earlier relapses, or signs of peripheral ischaemia, heart failure, or arrhythmia.

The only relevant detail noted by his biographers is the great stress he experienced in the weeks and months prior to his stroke, due to problems related to his work. It is reasonable to assume that this stress would have caused high blood pressure, either permanently or with intermittent episodic increases. However, blood pressure monitors had not yet been introduced in clinical practice. He may have had a familial predisposition to arterial hypertension, as his father, mother, and sister also presented strokes.<sup>3,10</sup> The two types of stroke most closely associated with arterial hypertension are haemorrhagic stroke (either intraparenchymal or subarachnoid) and lacunar infarcts secondary to hypertensive arteriolosclerosis. However, few data are available to support a retrospective diagnosis of either subtype in Pasteur's case; the only available evidence is the clinical picture, both in terms of onset and the possible localisation of the lesion.

Regarding localisation, I have no doubt that the lesion massively affected the corticospinal tract, causing severe hemiplegia. Sensory symptoms were limited to paraesthesia in the left hemibody during the first two transient attacks. Given the complete hemiplegia at

onset, we may expect that if the cause was an infarct in the cortical territory of the right middle cerebral artery secondary to large vessel occlusion, it would have been accompanied by intense, permanent sensory disorders, hemianopsia or visual inattention, anosognosia, or alterations in the body schema. Pasteur seems not to have presented any of these signs. According to his son-in-law,<sup>3</sup> Pasteur complained on the night of the stroke that his arm was "like lead," suggesting that he was aware of the deficit; this rules out hemiasomatognosia and anosognosia, which we may expect to observe in a patient with massive frontoparietal infarction of the right middle cerebral artery. Therefore, all the available evidence suggests a subcortical capsular or brainstem lesion, selectively disrupting the corticospinal tract. This subcortical lesion topography is also supported by Pasteur's grandson's description of the residual hemiplegia.<sup>4</sup> It was very proportionate, with similar intensity in the arm and the leg, and accompanied by the typical signs of intense spasticity, such as dragging the leg, the flexed posture of the forearm, and the forced closure of the fingers, with the hand left completely impotent (Figures 3, 4, and 5). Analysing the case in further detail, a capsular lesion is clearly much more likely than a brainstem lesion, not only due to the relative frequencies of each, but also because Pasteur did not present even mild signs of brainstem involvement, such as diplopia or ophthalmoparesis, peripheral facial nerve palsy, etc.

Assuming that the lesion was localised in the internal capsule, it may have been either a haemorrhage (as suggested by Pasteur's biographers<sup>1-3</sup> and some modern authors<sup>8,10</sup>) or an infarct in the territory of the perforating branches of the middle cerebral artery. The severity of hemiplegia, both in the acute phase and as a sequela, suggests that the lesion was relatively extensive. However, for a large haemorrhage, there were few clinical signs of such a severe situation. None of the classical signs of intracerebral haemorrhage, such as intense headache, vomiting, or lasting alterations in the level of consciousness are described. He only displayed alarm signs for a few hours, between two o'clock in the morning and dawn on the night after his stroke; these may simply have been explained by the patient's exhaustion, as his deep sleep that night would have been restorative and he awoke in the morning with his "mental faculties totally intact." This progression is more compatible with an infarct than capsulolenticular haemorrhage.

But the most important detail supporting the ischaemic nature of the lesion is its form of onset, with a series of 20-30 transient attacks over a period of hours, prior to the permanent hemiplegia. This form of presentation is nearly never observed in patients with haemorrhagic stroke, although both Norris<sup>8</sup> and Rumbach et al.<sup>10</sup> note that mild symptoms may occur prior to definitive hemiplegia in the context of venous malformations. A cluster of transient ischaemic attacks is also atypical in atherosclerotic and cardioembolic stroke. While these patients may present history of transient ischaemic attack, they are fewer in number and do not occur in such a short time span, often with intervals of days; they also tend not to be stereotyped (ie, they are not always purely sensory or motor). According to first-hand accounts, this clinical progression disconcerted the entire Faculty. The received wisdom at the time was that onset of paralysis was sudden and complete, rather than a succession of oscillating or intermittent smaller strokes. We know today that this natural history is almost always associated with lacunar infarcts, most frequently in the capsular region, known as capsular warning syndrome. The syndrome was first described in these terms by Donnan et al.,<sup>12</sup> although it had been recognised shortly before by Crespo et al.<sup>11</sup> Similar cases were subsequently described in patients with brainstem infarct (pontine warning syndrome)<sup>16</sup>; as a result, other authors opted for a broader term, stroke warning syndrome.<sup>18,24</sup>

The discussion of the type of stroke and its pathological basis in the case of Pasteur is highly speculative, given the lack of data. The type of stroke that most commonly displays this intermittent or stuttering form of onset, with stereotyped repetitions over a period of hours, is lacunar stroke due to probable lipohyalinosis of a perforating artery.<sup>23</sup> However, the clinical manifestation of these small infarcts due to arteriolar occlusion is not generally as severe or as long-lasting as in Pasteur's case, which resulted in intense, spastic hemiplegia. This more severe manifestation suggests a more extensive capsulolenticular infarct. For this type of stroke, occlusion of a relatively large perforating branch of the middle cerebral artery due to microatheroma seems a more likely aetiology than thrombosis of an individual arteriole. This syndrome has also been described in patients with dissection of the middle cerebral artery, occluding the perforating branches at their origin.<sup>19</sup> Extensive capsulolenticular stroke is often observed in cardioembolism of the middle cerebral artery; however,

these patients present sudden onset rather than a cluster of transient ischaemic attacks.

Since the description of capsular warning syndrome, the best possible treatment is applied during the oscillating hemiplegia phase with a view to preventing the definitive stroke. A preventive treatment would have been of great interest to Pasteur, both in light of his own circumstances, of course, and because of the principle that guided all his research, captured as follows in one of his many famous phrases: "when meditating over a disease, I never think of finding a remedy for it, but, instead, a means of preventing it." However, attempts to prevent stroke in patients with stroke warning syndrome, through the use of anticoagulants, thrombolytics, and antiplatelet drugs, have not achieved convincing results, probably due to the variation in pathogenesis.<sup>15,17,23,24</sup> Another proposed explanation for the failure of preventive treatments is that, in some cases, treatment may be ineffective because the stroke is already established from the time of symptom onset, with symptoms subsequently oscillating due to the functional properties of the ischaemic tissue or activation of motor circuits, rather than as a result of intermittent ischaemia.<sup>20</sup>

Few data are available on the subsequent progression of Pasteur's disease. He is known to have presented two further minor strokes in October 1887, making him lose the ability to speak, although he subsequently recovered it. It is plausible that these strokes may also have been small subcortical infarcts of the perforating arteries, or small vessel disease, due to unconfirmed arterial hypertension. Both Norris<sup>8</sup> and Rumbach et al.<sup>10</sup> acknowledge that Pasteur's progression suggests encephalopathy due to subcortical ischaemic lesions, and propose that he presented two separate processes: first a haemorrhagic stroke due to a venous malformation, and subsequently multiple lacunar infarcts. However, according to Occam's razor, we should attempt to find a single explanation for everything.

We may deduce that until late 1892 he presented neither aphasia nor dementia, as he dictated his speech for the ceremony honouring his 70th birthday, which was read out by his son. The episode diagnosed as an "attack of uraemia" in 1894, in which he lost consciousness for several hours, is difficult to interpret. This may have been a seizure or hypertensive crisis, or, to the contrary, syncope due to hypotension with prolonged cerebral anoxia; however, we lack data to confirm either

hypothesis. His biographers do not describe any focal signs suggesting another stroke, although he may have presented ischaemia in the distal territory of the basilar trunk.

His motor function deteriorated between 1892 and 1895, but his mental status seems not to have severely declined, as until the final months of his life, he continued to receive visitors with whom he interacted and to whom dictated letters. Norris<sup>8</sup> believed the opposite and concluded, submitting no argument, that at the age of 71 (in 1893), Pasteur had dementia or aphasia, and spent his days immobile in his garden; this is not consistent with the accounts of those close to Pasteur. Norris<sup>8</sup> dismisses the descriptions of Pasteur's family, which contradict his view, as "adulatory and flowery descriptions [...] couched in protective and euphemistic terms by laymen" who lack reliability. According to those close to Pasteur, it was Pasteur himself who in 1895 decided to visit Villeneuve-L'Étang, where he died. Some authors attribute the immediate cause of death to a further stroke, although information from members of Pasteur's family do not support this.

In conclusion, Louis Pasteur presented a stroke at the age of 46 years, followed by complete left-sided hemiplegia, which he overcame with laudable courage. He subsequently completed some of the most important scientific work in human history. Analysis of the available clinical data suggests that his stroke may have been a capsulolenticular infarct, with the characteristic initial progression in the form of a cluster of multiple transient ischaemic attacks over a period of several hours, described in the literature more than a century later as capsular warning syndrome.

### Conflicts of interest

The authors have no conflicts of interest to declare. This study has received no public or private funding.

### References

1. Mondor H. Pasteur. Paris: Corr ea; 1945.
2. Vallery-Radot R. The life of Pasteur. London: Constable & Co.; 1911.
3. Vall ry Radot R. La vie de Pasteur. Paris: Hachette; 1900. Available from: <https://gallica.bnf.fr/ark:/12148/bpt6k2033085/f70.item#> [accessed: 4 Nov 2020].
4. Vallery-Radot L-P. Louis Pasteur: a great life in brief. New York: Knopf; 1958. Available from: <https://archive.org/details/loispasteur0000unse/page/n5/mode/2up> [accessed: 30 Oct 2020].
5. Besson A. Louis Pasteur: un aventurier de la science. Paris: Rocher; 2013.
6. Portraits de M decins [Internet]. [s.l.]: Jean-Yves Gourdol; [s.d.]. Louis Pasteur: 1822-1895; 18 Oct 2017 [accessed: 30 Oct 2020]. Available from: <https://www.medarus.org/Medecins/MedecinsTextes/pasteurl.html>
7. Mart nez Baez M. Pasteur: vida y obra. Mexico City: Fondo de Cultura Econ mica; 2017. Available from: <https://books.google.es/books?id=FCITDwAAQBAJ&printsec=copyright&hl=es#v=onepage&q&f=false> [accessed: 31 Oct 2020].
8. Norris JW. Pasteur's stroke. *Neurology*. 1992;42:933-4.
9. Vallery-Radot P. Correspondance de Pasteur: 1840-1895. Paris: Flammarion; 1951. Available from: <https://gallica.bnf.fr/ark:/12148/bpt6k6353665n.texteImage> [accessed: 1 Nov 2020].
10. Rumbach L, Tatu L, Mercet P. La maladie neurologique de Pasteur. *Rev Neurol (Paris)*. 1996;152:630-3.
11. Crespo M, Melo TP, Oliveira V, Ferro JM. Clustering transient ischemic attacks. *Cerebrovasc Dis*. 1993;3:213-20.
12. Donnan GA, O'Malley HM, Quang L, Hurley S, Bladin PF. The capsular warning syndrome: pathogenesis and clinical features. *Neurology*. 1993;43:957-62.
13. Frey JL. Capsular warning syndrome. *Neurology*. 1994;44:195-6.
14. Staaf G, Geijer B, Lindgren A, Norrving B. Diffusion weighted MRI findings in patients with capsular warning syndrome. *Cerebrovasc Dis*. 2004;17:1-8.
15. He L, Xu R, Wang J, Zhang L, Zhans L, Zhou F, Dong W. Capsular warning syndrome: clinical analysis and treatment. *BMC Neurology*. 2019;19:285.
16. Saposnik G, Noel de Tilly L, Caplan LR. Pontine warning syndrome. *Arch Neurol*. 2008;65:1375-7.
17. Vivanco-Hidalgo RM, Rodriguez-Campello A, Ois A, Cucurella G, Pont-Sunyer C, Gomis M, et al. Thrombolysis in capsular warning syndrome. *Cerebrovasc Dis*. 2008;25:508-10.
18. Tassi R, Cerase A, Acampa M, D'Andrea P, Guideri F, Giudice G, et al. Stroke warning syndrome: 18 new cases. *J Neurol Sci*. 2013;331:168-71.
19. Chen ZC, Sun JZ, Shi ZH, Lou M. Capsular warning syndrome caused by spontaneous middle cerebral artery dissection. *CNS Neurosci Therap*. 2012;18:702-4.
20. Springer MV, Labovitz DL. The capsular warning syndrome reconsidered. *Cerebrovasc Dis*. 2013;36:152.
21. Li W, Wu Y, Li X-S, Liu C-C, Huang SH, Liang CR, Wang H, et al. Intravenous tirofiban therapy for patients with capsular warning syndrome. *Stroke Vasc Neurol*. 2019;4:22-9.

22. Kim JG, Choi H, Sohn SY, Kim DH, Lee SJ. Transient ischemic attacks preceding acute lacunar infarction. *Eur Neurol.* 2016;76:278-83.
23. Hawkes MA, Braksick SS, Zhang W, Wijdicks EFM, Rabinstein AA. Can we stop the stuttering in stroke? Interventions in 40 patients with acute lacunes. *J Neurol Sci.* 2019;401:1-4.
24. Sen A, Birns J, Bhalla A. Stroke warning syndromes. *Br J Hosp Med (Lond).* 2020;81:1-5.
25. Wikipedia, the free encyclopedia [Internet]. [s.l.]: Wikimedia Foundation; [s.d.]. Noël Guéneau de Mussy [accessed: 28 Oct 2020]. Available from: [https://en.wikipedia.org/wiki/No%C3%A9l\\_Gu%C3%A9neau\\_de\\_Mussy](https://en.wikipedia.org/wiki/No%C3%A9l_Gu%C3%A9neau_de_Mussy)
26. Historia de la medicina [Internet]. [s.l.]: José L. Fresquet; ©2015. Gabriel Andral (1797-1876) [accessed: 28 Oct 2020]. Available from: <https://www.historiadelamedicina.org/andral.html>
27. Zarranz JJ. Bourneville: un neurólogo en acción. *Neurosci Hist.* 2015;3:107-15.