

LLUÍS SAYÉ I SEMPÈRE

BURNAND-SAYÉ

SYNDROME

The eponym

Burnand-Sayé syndrome. Miliary tuberculosis^{1,2}, also known as chronic miliary tuberculosis³ or Sayé-Burnand syndrome.



Lluís Sayé i Sempere
(1888-1975)

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Lluís Sayé i Sempere was born in Barcelona on 19 February 1888. His life was dedicated almost exclusively to tuberculosis. Perhaps this was because two of his brothers died from the disease and a third also contracted it, but recovered after a stay at the sanatorium in Davos, Switzerland⁴ –the sanatorium that inspired Thomas Mann’s novel *The Magic Mountain*.

Sayé i Sempere studied medicine in Barcelona, graduating with highest honours in 1911. While still a student, he showed his interest in tuberculosis by presenting a paper, *Las opsoninas en la tuberculosis pulmonar* (Opsonis in pulmonary tuberculosis), at the International Tuberculosis Congress in Barcelona in 1910 together with Joan Baptista Darder. The following year, together with Jacint Reventós, Sayé performed the first pneumothorax to treat tuberculosis in Spain at *Hospital Clínic de Barcelona*. It bears reminding that this procedure invented by Forlanini was quickly consecrated as an important therapeutic option that would only be abandoned 40 years later with the generalised use of antituberculous drugs.

After graduating, Sayé began practicing as an intern physician in the Department of General Pathology chaired by Professor Eusebio Oliver Aznar. With Joan Baptista Darder, who was well versed in the tuberculin test, and Jacint Reventós, they convinced Oliver to authorise the setting up of a dispensary, and they began to attend tuberculosis patients there⁵. Shortly afterwards, the *Hospital Clínic’s* renown from therapeutic pneumothoraces enabled an entire ward to be devoted to patients with tuberculosis, thanks to a donation from Joaquim Sans, and Sayé became its director⁶. The experience he gained there allowed him to complete his doctorate in Madrid in 1912, with the thesis *Tratamiento de la tuberculosis pulmonar por el neumotórax artificial* (Treatment of pulmonary tuberculosis by artificial pneumothorax)⁷. In 1913, he earned the title of Associate Professor of Pathology and General Pathology at the

Universidad de Valladolid. However, he would soon leave this position to continue his work in Barcelona, where he remained associate professor of physiology under Pi i Sunyer's chair. In 1914, he received a grant from Spanish government to improve his knowledge about tuberculosis in Professor Brauer's department at Eppendorf Hospital in Hamburg. However, his internship was interrupted by the outbreak of World War I. As early as 1919, Sayé founded *Archivos Españoles de Tisiología*, the first journal in Spain specialising in tuberculosis⁸.

Although he was very young, Sayé was well known and his work in the field of tuberculosis was arousing great interest. His capacity for hard work and organisation were evident when the *Institut d'Estudis Catalans* created the *Centre d'Estudis Sanitaris* in 1918 to compile data that could be employed to solve health problems in Catalonia⁵. At this time, a working group on tuberculosis was created, headed by Sayé, in which Tomàs Seix played an important role. The data that Seix obtained enabled them to issue the report *Mortalitat tuberculosa a Catalunya i especialment a Barcelona* (Tuberculosis mortality in Catalonia and especially in Barcelona), which recommended founding the *Servei d'Assistència Social dels Tuberculosos de Catalunya*. This initiative would flourish with the creation of a dispensary under Sayé's direction and Seix's organisation that began operating in Poble Sec, a working-class neighbourhood in Barcelona on 23 April 1921⁴. Despite the shabby appearance of its exterior (they even called it the "*barraca*" or shanty), it became a highly important centre for clinical care and scientific dissemination. In fact, the first vaccinations with Calmette-Guérin (BCG) vaccine in Barcelona began there in 1924. This dispensary worked at a slower pace during Primo de Rivera's dictatorship, but the restoration of the *Generalitat de Catalunya* (Government of Catalonia) during the Second Republic enabled a new center to be built on Goya and Torres Amat streets. Known as the *Dispensari Antituberculós*, it was the work of the architects Josep L. Sert, Joan B. Subirana, and Josep Torres. It opened in January 1937 while Sayé was already outside Catalonia, in exile⁶.

The period from his graduation until his exile was an extraordinarily prolific one for Sayé professionally. When the *Universitat Autònoma de Barcelona* was planned, he was appointed associate professor of tuberculosis studies at the Faculty of Medicine⁷. Shortly afterwards, Sayé asked the university board to create the Anti-Tuberculosis University Program. His request was granted on 18 October 1933. At first, all entry-level students and those in the first three years of medical school were examined clinically and radiologically; the following year, these examinations were extended to cover all medical students as well as those in the first three courses of the other schools⁸.

Sayé attained one of the highest pinnacles of Catalan medicine in this period. In addition to his roles as director of the Department of Tuberculosis at the *Hospital Clínic de Barcelona*, the *Servei d'Assistència Social dels Tuberculosos de Catalunya*, the Department of Tuberculosis at the *Quinta de Salut l'Aliança*, the Anti-Tuberculosis University Program, and his university duties, he took on significant work in private practice. Furthermore, he travelled frequently, going to Madrid and Paris monthly to attend scientific sessions, and to Portugal to supervise sanatoriums³. Such frenetic activity meant Sayé became one of the best-known and most prestigious Catalan physicians abroad. Evidence of this is that he was one of the first to publish a scientific paper outside of Spain. He attended meetings of the *Institut Pasteur* in Paris and was renowned in many countries, especially in Latin America. In 1927, the government of Argentina invited him to give a series of conferences at the *Universidad de Córdoba*. After this, he went to New York, funded by the Rockefeller Foundation, to study American anti-tuberculosis work. This scientific reputation was recognised with multiple distinctions: France named him *Officier d'Académie* (1928) and *Chevalier de la Légion d'Honneur* (1930), and Denmark name him a Knight of the Order of Dannebrog (1926)⁵.

He was also very active in the academic sphere. Together with Conrad Xalabarder and Jacint Reventós, he promoted the *Associació de*

Tisiologia, founded in 1930, and became its first president; in 1959, this society would become the *Associació de Patologia Respiratòria* under the presidency of Jacint Reventós⁸. In 1930, Sayé was appointed a member of the *Reial Acadèmia de Medicina de Barcelona*, with an acceptance speech titled *Les fases inicials de la tuberculosi pulmonar a l'adolescent i a l'adult* (The initial phases of pulmonary tuberculosis in adolescents and adults). Sayé's brilliant professional life in Barcelona was cut short by the outbreak of the Spanish Civil War.

In September 1936, Sayé fled Barcelona after being threatened by a patient's husband in the context of the revolutionary atmosphere in the city⁹. Sayé went into exile in Paris, where he lived for a year, working at the *Institut Pasteur*. Accepting an invitation from its director, he wrote the book *La tuberculose pulmonaire chez les sujets apparemment sains* (Pulmonary tuberculosis in apparently healthy subjects). However,

Attendees of the course of vaccination against tuberculosis, focused on the Calmette-Guerin (BCG) vaccine held in Barcelona (1927). In the front row, Guerin (wearing glasses and a dark suit), Calmette (also wearing a dark suit) and Sayé (wearing glasses and a white coat)



Abelardo Sanz, from Uruguay, and Lorenzo Armani, from Argentina, persuaded him to travel to South America⁸. There, Sayé accomplished great things. He organised the fight against tuberculosis in Uruguay; created an examination service for collectives; practiced in the central Montevideo dispensary; gave conferences and courses; acted as consultant to the governments of Cuba, Peru, Brazil, and Chile; and was a consultant at the *Hospital Central* in Buenos Aires⁸. His work was recognised with many honours, such as receiving the medal of the O'Higgins Order in Chile (1951), being appointed knight commander of the National Order of Merit of Carlos Juan Finlay in Cuba (1951), and being named *Doctor honoris causa* from the *Universidad Nacional de San Marcos* in Lima, Peru (1938)⁵. He was also named an honorary member of nearly all the tuberculosis societies in Central and South America as well as of the American College of Chest Physicians in the United States (1950). In Argentina, he would be acclaimed for many years, with the *Liga Argentina contra la Tuberculosis* paying homage to him as late as 1993. Neither was he forgotten in Europe. The *Institut Pasteur* in Paris awarded him its silver medal for his work on anti-tuberculosis vaccination (1951).

In 1951 Sayé returned to Barcelona, but nothing was as he had left it fifteen years before. Compared with his earlier privileged situation, he received a cool welcome. He had lost his influence in the new society. All his posts had disappeared or had been occupied by others for years. It is likely that his personality also contributed to his isolation. As Cornudella noted⁵, Sayé acted as if everything he said was right because he was the authority. His cutting asseverations stemmed from his great erudition, which discouraged the young from speaking up in meetings. Oriol Anguera³ wrote:

“Sayé was marked, more than by his paltry war experience, by those 16 years of exile. Because on his return, he found things different than he had left them, and he did not find the right communicative approach to understand what was happening. Sayé never took

'others' into account. He published without acknowledging his collaborators. He asked you to do things without explaining why he wanted you to do them, and he never told you whether he had used them or why he had not used them... The master Sayé had returned, but now had no power to command, no disciples, no students, no collaborators; he had nothing but hellish emptiness."

Cornudella agreed⁸: "Lluís Sayé was erudite, dogmatic, with an extensive scientific trajectory in Europe and Latin America... His cutting ironic tone was a reproach to young people, losing him friends. The hangover from that mindset greatly influenced the cold reception he received on his return from exile."

On his return, the only public activity he was permitted was BCG vaccination of newborns in the *Casa de la Maternitat* and dedication to the Anti-Tuberculosis University Program, which he undertook for free⁸. But in 1954, the arrival of a new professor of general pathology, Arturo Fernández Cruz, changed the situation. He ordered that his department take charge of examining students for tuberculosis, although he allowed Sayé to keep "camping out" (in Cornudella's words)⁵, vaccinating the nurses in the Anti-Tuberculosis Program⁷.

Even so, he was still respected in many Catalan scientific circles. So, seven years after his return, he published *Tratamiento y profilaxis de la tuberculosis pulmonar* (Treatment and prophylaxis of pulmonary tuberculosis, 1958). Then in 1963, the *Societat Catalana de Biologia* asked him to give the inaugural speech of the academic year, which he titled *L'obra antituberculosa internacional* (International anti-tuberculosis work). The same year, Pedro i Pons, who held him in great esteem, commissioned five tuberculosis lectures from him for his department, which were published in the journal *Medicina Clínica* the following year. That year he was also elected vice-president of the *Reial Acadèmia de*

Medicina de Barcelona and shortly afterward, the *Acadèmia de Ciències Mèdiques* awarded him an honorary diploma.

The final years of his life were unhappy. Used to working unceasingly, he took his retirement with bad grace. Moreover, he was told in the worst possible way: a porter delivered the official notice the day before he turned 70. Shortly afterward, he was asked to vacate the premises of the Anti-Tuberculosis Program where he still worked. Domingo⁹ describes how this occurred:

“When nothing was left to him other than the University Anti-Tuberculosis Service, which he had founded on the first floor of the Faculty of Medicine, one day he had to hear from his nurse –*his* because he paid her wage– the following words: ‘On behalf of the dean of the Faculty of Medicine, I have been instructed to ask you to gather everything that belongs to you and hand me the key, because they intend to install other services here.’”

When he reached home, Sayé said to his wife: “My life is over.” Oriol i Anguera considered that Sayé’s demise began at that moment³, though he would live for 17 more years. As a consequence of cerebral arteriosclerosis diagnosed by Belarmino Rodríguez Arias in 1964, Sayé entered a state of disorientation complicated by dementia that would lead to a purely vegetative life. He was admitted to Francesc Vilardell’s department at the *Hospital de la Santa Creu i Sant Pau* where he died on 27 June 1975. His wife Mirka cared for him until the end, but she also fell seriously ill and died six weeks later⁴.

Immersed in a state of total disconnection from reality, Sayé once again received institutional recognition. On 6 November 1972, the *Comisión Permanente del Patronato Nacional de Enfermedades del Tórax* in Madrid, at the proposal of its general secretary, Carlos Zurita, unanimously agreed to name *Dispensari Central Antituberculós de Barcelona* after

him⁹. Today, the building, inaugurated in 1937, houses the *Centre de Prevenció i Control de la Tuberculosi Dr Lluís Sayé*, the *Dispensari Central de Malalties del Tòrax*, and the *Centre d'Assistència Primària Lluís Sayé*.

Sayé's contribution to the fight against tuberculosis

Sayé's wide-ranging written work comprised hundreds of studies and fifteen books, including *Profilaxis de la tuberculosis* (Tuberculosis prophylaxis, 1924), *Quimioteràpia de la tuberculosis* (Tuberculosis chemotherapy, 1927), *Pneumolyse intrapleurale* (Intrapleural pneumolysis, 1932), *Crisoteràpia de la tuberculosis* (Tuberculosis chrysotherapy, 1933), *Les noves orientacions de la lluita antituberculosa i la seva aplicació a Catalunya* (New perspectives in the fight against tuberculosis and their application in Catalonia) as *Monografies Mèdiques* 68-69 (1933), *La tuberculose pulmonaire chez les sujets apparemment sains et la vaccination antituberculeuse* (Pulmonary tuberculosis in apparently healthy subjects, 1938), *Doctrina y práctica de la profilaxis de la tuberculosis* (Doctrine and practice of tuberculosis prophylaxis, 1940), and a two-volume treatise entitled *La tuberculosis tráqueo-bronco-pulmonar* (Tracheobronchial-pulmonary tuberculosis, 1950), in collaboration with Diego Hernández Luna and Álvaro Benze, which is considered his most important contribution. After his return to Catalonia, he published *Tratamiento y profilaxis de la tuberculosis pulmonar* (Treatment and prophylaxis of pulmonary tuberculosis, 1958).

Among Sayé's many contributions, without a doubt the most important was the fight against tuberculosis, for which he is unanimously recognised as initiating in Spain¹⁰. As mentioned above, Sayé introduced BCG vaccination in November 1924, shortly after it was started in France, with the collaboration of Pere Domingo (who prepared the vaccines in the *Laboratori Municipal*), Tomás Seix, and Manuel Miralbell¹¹. Increasingly positive results with the BCG vaccine

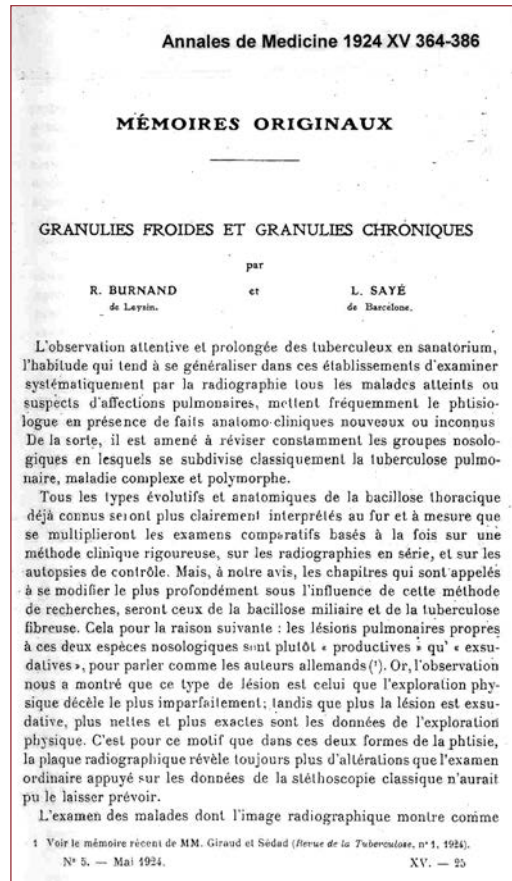
led to the Republican government recommending its use in 1931. By 1933, all babies were being vaccinated¹⁰. Sayé's work was interrupted by the Spanish Civil War. One consequence of this was the lack of a vaccination plan in Spain until the International BCG Congress in 1948. When Sayé returned, the treatment of tuberculosis had changed considerably. The appearance of chemotherapy meant the disease could be cured; it had become a disease in regression and was no longer an epidemic to target. Sayé was one of the men who helped conquer this scourge that had been causing death and suffering for centuries. He would not live to see the disease become a threat yet again in the late twentieth century.

Burnand-Sayé syndrome

In the work we consider the best biographical study on Sayé⁴, Josep Cornudella describes the path to discovery of the syndrome that would come to be called "Burnand-Sayé syndrome", reflected in the article published in *Annales de Médecine* in 1924:

"An example of these concerns was the episode-problem of haematogenous tuberculosis, which was embroiled with hysteria in the 1930s. Sayé threw himself into it with his characteristic impetuosity. He even discovered a clinical form, 'chronic miliary tuberculosis', linked to that pathogeny, that *Anales de la Tisiología* would dub Sayé-Bournand. A slowly evolving form of pulmonary bacillosis with little symptomatology that, because it originated in the bloodstream, could not be treated by collapsotherapy but was treatable by aurotherapy, which was in fashion at that time. The subject gave rise to heated discussions among the *crème de la crème* of European phthisiologists: Brauening, Pagel, Raedeker, Simón and, naturally, Sayé. He even gave courses dedicated exclusively to haematogenous tuberculosis"⁴.

First page of the article
Granulies froides et granulies chroniques, published in 1924
by R. Burnand and L. Sayé
which gave rise to the eponym
“Burnand-Sayé syndrome”



René Burnand, a French physician (Versailles, 1882 - Lausanne, 1960), and Lluís Sayé published a study in 1924, in which they reported 26 observations of “chronic miliary tuberculosis”¹². These forms of chronic miliary tuberculosis, nearly always afebrile, lasted for months and years. At times, they ended in tubercular meningitis; at others, in rapid lung involvement. It was not infrequent for them to heal spontaneously and completely. For Burnand and Sayé, the slow propagation of these forms

occurred through an exclusively lymphangitic channel, through the pulmonary interstitial-lymphatic system.

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