Constantin Levaditi: a pioneer in Immunology and Virology

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Summary: The eminent doctor Constantin Levaditi represents one of the most important researchers in the field of medicine in the 20th century. Although he was engaged in many areas of the rapidly growing field of immunology, his name is associated mainly with research in poliomyelitis. His laboratory research contributed decisively to the clarification of the epidemiology of this dreadful disease that claimed thousands of victims. Moreover, his experimental work constituted the basis for the development of the vaccine against poliomyelitis, initially in 1955 by Jonas Salk (1914–95) using inactivated virus, and then in 1960 by Albert Sabin (1906–93) who used live attenuated virus.

Levaditi's family background

Constantin Levaditi was born on 19 July 1874 in Galatz in Romania, on the coast of the Black Sea. His father, Spyridon Livaditis of Greek descent from Macedonia, was 30 years old and working as a customs officer. His mother, Ioanna Ştefănescu, then aged 18 years, was the daughter of peasants from Focşani. One ancestor came from Livadia, a town 150 km north of Athens. The family name originates from the name of this town (*Livaditis* means *one who comes from Livadia*).[1,2] The researcher Pierre Lépine (1901–87) reported that Spyridon Livaditis was a member of the *Filiki Eteria* (Society of Friends), established to organize the Greek Revolution against the Turks under the leadership of Prince Alexander Ypsilantis (1792–1828).[3] However, after he had graduated from the Medical School, Constantin altered his surname from Livaditis to Levaditi, which is the alternative spelling of the town (*Livadia* is also *Levadia*).[1]

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Constantin Levaditi's life

Constantin Levaditi had a difficult childhood (Figure 1) due to financial problems in the family. In September 1880, he went to the Cuza Vodă primary school in Galatz, and at the same time started work at the store of his uncle Ştefan Ştefănescu, whose Greek wife was Athina Mavrodini.

After the untimely death of his parents in 1883, Constantin's aunt Efrosini, a member of his father's family, took custody and he continued his basic education in Bucharest, showing an inclination towards music and the theatre. On his own initiative, he recommenced the study of the Greek language, a few months before graduation from secondary school in 1892. Meanwhile he had the opportunity to become familiar with a medical environment, as his aunt was working in the Brâncovenesc Hospital in Bucharest, and he was obliged to spend several hours in the wards, the laboratories and the mortuary.[1,3]

In 1892, he entered the Medical School of Bucharest, whence he graduated six years later. His tutor, Professor Victor Babeş (1854–1926), was the first to notice his inclination towards laboratory research. At the age of 23 Levaditi participated as a scientific partner in a research project entitled *Forma actinomicotică a bacilului tuberculozei* (the actinomycotic form of the bacillus causing tuberculosis). This paper was received enthusiastically at the Academy of Sciences in Paris. The praise that followed the publication of this research prompted Levaditi to continue his studies abroad.[3]

Supported by Victor Babeş, Constantin Istrati and Petrini-Galatz, the young Levaditi won a scholarship from the Brâncovenesc Hospital to

Figure 1 Levaditi as a child, with his parents

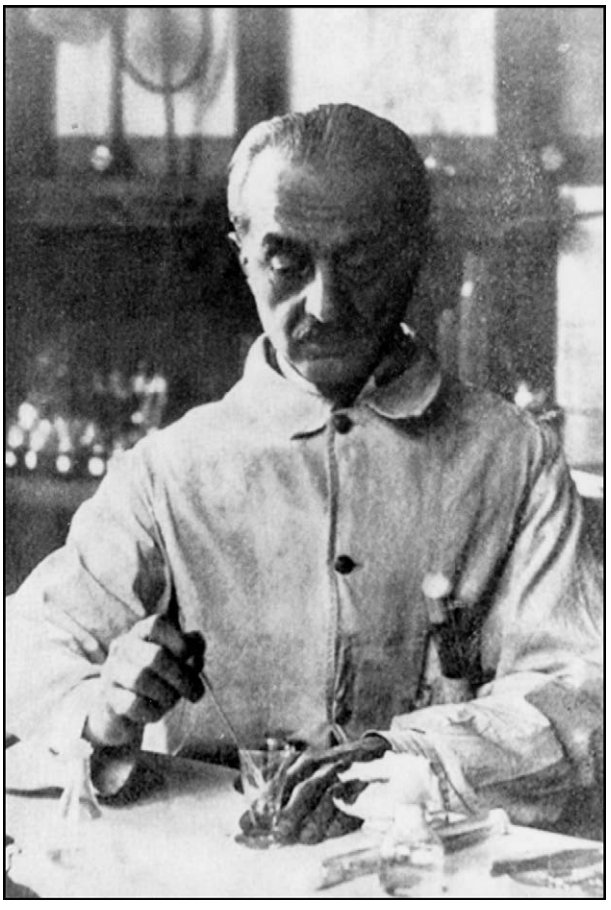

Figure 2 Levaditi in his laboratory at the Pasteur Institute

prepare his doctoral thesis in France. In the autumn of 1898, he departed for Paris with three letters of reference from Babeş that mentioned his talent for laboratory research. In the French capital, Levaditi worked for a short time at the Hôtel-Dieu Hospital as assistant in the laboratory of the academician Charles Bouchard (1837–1915). During the first year of his residence in Paris he was an author in 16 publications that led to renewal of his scholarship. Levaditi continued his postgraduate studies in 1900 and 1901 in Germany with Paul Ehrlich (1854–1915) who was considered the father of modern chemotherapy. Levaditi gained precious knowledge of this new specialty, and eventually his hesitant ideas about medicine crystallized into a clear vision – dedication to medical research. Many years later, Levaditi wrote 'I owe everything to Victor Babeş, Albert Charrin, Elie Metchnikoff and Emile Roux' – it is strange he forgot to include Paul Ehrlich.[1–3]

In the spring of 1901 Levaditi, following the advice of the physician John Kantakouzinos (1863–1934), had the great opportunity to work in the Elie Metchnikoff Laboratory at the Pasteur Institute. In 1902, he completed his doctoral thesis entitled *Contribution a l' étude des Mastzellen et de la Mastzellen-Leycocytose* (Contribution to the study of the mast cells and the mast cells-leucocytes), which was considered a pioneering contribution to haematology. Two years later, in 1904, Emile Roux (1853–1933) recognized Levaditi's abilities and enthusiasm and appointed him director of an independent laboratory at the Pasteur Institute (Figure 2).[2,3]

His enterprising research in immunology led to nomination as Professor in 1924. The American Professor Simon Flexner (1863–1946) proposed him as director of the Rockefeller Institute in New York, but Levaditi refused politely. Meanwhile Levaditi taught at many Universities all over the world including London, Madrid, Barcelona, New York and Philadelphia.

For his multifaceted work, Levaditi was awarded two prizes (the Bréant Prize and the Montyon Prize) by the French Academy of Sciences. He was also a member of 30 Academies and a corresponding member of the Romanian Academy. In 1948, he was appointed a member of the French Academy (Figures 3 and 4). The pioneer researcher retained his position at the Pasteur Institute until 1940, when he retired, but nevertheless he continued to serve medicine as the director of the Alfred Fournier Institute, which was established in 1932.[3]

Levaditi returned to Romania only twice, in 1903 when he married Helen, the younger daughter of Doctor C Istrati, and in 1920 as a guest lecturer at the University of Cluj. During his career in France,

Figure 3 Levaditi wearing his uniform as a French Army Officer

Figure 4 A prestigious medal for Levaditi for his scientific work

he attempted to acquire a position at Romanian Universities several times, but due to various intrigues, his dream of returning to the place of his birth was not realized.[1–3]

Levaditi died in Paris in 1953 at the age of 79.

Scientific work

Levaditi's scientific work was far ranging. He dealt with many branches of immunology and at the same time worked more extensively in the field of virology than any other contemporary Frenchman. He studied the epidemiology of poliomyelitis, suggested a treatment strategy against syphilis and investigated encephalitis lethargica, the pathogenic mechanism of recurrent fever and the aetiologic factors causing multiforme erythema.

The research and treatment of syphilis

Constantin Levaditi dedicated an important part of his research to the study of syphilis, a scourge of the 20th century. From 1907, when he began to investigate venereal disease systematically, he emphasized the importance of studying this widespread problem. Elie Metchnikoff (1845–1916) and Emile Roux, Levaditi's spiritual fathers, had worked extensively on *Treponema pallidum*, which had been discovered by Fritz Schaudinn (1871–1906) and Erich Hoffmann (1868–1959). Then Levaditi studied the invasive capability of this bacterium into the target-organs and at the same time described the technique of staining *T. pallidum* (the Levaditi–Manouelian method). He and Auguste-Charles Marie (1864–1935) traced *T. pallidum* in the brainstem of patients suffering from neurosyphilis, a discovery that confirmed the infiltrating capacity of the organism and opened up new horizons for experimental study in animals. The two pioneer researchers also made the very significant observation that not only the antigens of *T. pallidum*, but also extracts of normal tissues from patients who had been infected by syphilis, gave a positive complement fixation reaction. This observation, in combination with the perfection of the serum detection method (the Wasserman Test), contributed to the discovery of autoantibodies and the phenomenon of autoimmunity.[3]

Levaditi worked in the field of venereal diseases for almost half a century, promoting – among others – the treatment of syphilis with bismuth.[4] He discovered much about chemotherapeutic agents while working with Ehrlich. When in 1916 Benjamin Sauton published, as an abridgement of Metchnikoff's work, his observation regarding syphilis. After a series of experiments Levaditi proved that the *in vitro* inactive bismuth salts could be transformed into active components *in vivo* by an enzymatic reaction in the liver. By studying Dimitri Ivanovich Mendeleyev's (1834–1907) periodical table of the elements, Levaditi demonstrated the connection between this classification and the therapeutic action of these elements. As a consequence, he added to the already known metals of mercury and arsenic a new therapeutic agent against syphilis – bismuth.[3,4]

Levaditi was preoccupied with many other antibiotic agents. He introduced penicillin as a drug against quaternary syphilis by exploiting Mahoney's discovery that penicillin could act against syphilis.[3,4] Levaditi also studied many other antibiotics including streptomycin and chloramphenicol and he published several papers in

well-known medical journals. His last research, concerning terramycin, was published only a few days before his death.[5]

The war against poliomyelitis

Levaditi was almost the first and, for a long time, the only person in France to study viruses systematically. As such, he occupied the position in virology in France that Thomas Rivers (1888–1962) was to hold later in the US. Moreover, he dealt with ultraviruses (filterable viruses) that were small enough in particle size to pass through a filter of a given pore size.[6]

Nevertheless, Levaditi's most significant contributions to mankind are his experiments in poliomyelitis and his catalytic assistance to the clarification of epidemiological factors causing this lethal disease. He cooperated with the Austrian Karl Landsteiner (1868–1943) who was awarded the Nobel Prize in 1930 and who was considered a very important modern immunologist, known for the discovery of the ABO and Rhesus blood groups. Their main areas of cooperation were in the study of scarlet fever and especially of poliomyelitis.[7] Karl Landsteiner and E Popper described the nature of the aetiologic agent of poliomyelitis in 1908. Levaditi's eagerness and enthusiasm led to fruitful collaboration with Landsteiner in some of the latter's investigations. This collaboration produced 12 articles concerning poliomyelitis, published between 1909 and 1911. The two researchers managed to induce poliomyelitis experimentally in monkeys. Meanwhile they isolated the virus in tissue culture other than in the central nervous system (tonsils, salivary glands, pharynx, mesenteric lymph nodes, etc.) that was extremely important for the unravelling of the obscure epidemiology of the disease.[8,9]

In 1910, while experimenting with the serum of patients recovering from poliomyelitis, A Netter and Levaditi detected antibodies that could eliminate the virus.[10] This observation was a landmark in the fight against poliomyelitis. However, its clinical importance was neglected for many years. Levaditi and Landsteiner tried to provoke active immunization in monkeys by inoculating a partially inactivated virus (the virus was boiled at 56°C for 30–60 min).[8] Unfortunately, the attempt was abandoned because some of the inoculated monkeys in the experiment were infected by poliovirus and it was assumed therefore that the technique was not safe. Nevertheless, even after delay, these attempts constituted the basis for the production of a vaccine with live attenuated poliovirus.

Levaditi with Carl Kling, another important researcher in the field of poliomyelitis, in 1913, confirmed the presence of the virus in the intestinal tract. In that year, Levaditi described the technique of incubation of the poliovirus in nerve cells preserved in human blood plasma. Sixteen years later, in 1929, after a series of experiments in the monkey *Macaca cynomolgus*, Levaditi, Kling and Lépine demonstrated that monkeys could be infected by the oral route that caused spread of the disease.[8,11] Unfortunately, this theory was doubted because scientists believed the disease was transmitted via the secretions of the nasal mucosa.

Other research studies

Levaditi's experimental interests were not confined to syphilis and poliomyelitis. In 1920, in cooperation with P Harvier and later with Stefan Nicolau (1896–1967), he studied the viral disorder lethargic encephalitis, the disease linked with the name of the Austro-Greek researcher and physician Constantin von Economo (1876–1931). In 1923, Levaditi progressed further and composed a neurovaccine from an extract of brain culture from a rabbit. Six years later, while studying neurotropic viruses, he described epidemic amaurosis, which is linked with the Schilder–Foix disease.[3] Finally, in 1934, he announced the results of his research concerning the experimental induction of lymphogranulomatosis in animals.

Levaditi was a prolific author. In 1914, he published with Rudolph Kraus (1868–1932), an immunologist known for the discovery of the precipitin reaction, the work *Handbuch der Immunitätsforschung und experimentelle Therapie*, still considered an essential standard work in its field. Five years before this, the two researchers had published a monumental study entitled *Handbuch der Technik und Methodik der Immunitätsforschung*.[7]

Levaditi's scientific contributions

Levaditi's scientific work has been characterized as 'bridging the gap between nineteenth century pathology and twentieth century immunology'. Levaditi exercised an influence on both specialties. According to the historian John Paul, 'there was scarcely a microbiological laboratory in Europe that did not boast of at least one worker who had been trained in Paris by Levaditi.'[8]

Levaditi spent almost his entire career at the Pasteur Institute. Though his was the only career beside Landsteiner's to span the age of Pasteur and modern times, he was not well recognized in the history of poliovirus research. Moreover, unlike Landsteiner Levaditi never relinquished his interest in poliovirus research after the discovery of the aetiologic agent of poliomyelitis by Landsteiner and Popper in 1908. He was the first in France to study viruses systematically.[3] Levaditi's name has not been mentioned much in the history of medicine perhaps on account of his modesty. Those who met him described him as an enthusiastic,

indefatigable researcher, fully aware of his saving work for mankind, and he always kept a low profile.

In the words of his colleague John Paul, 'it was a pity that he did not live two more years to witness the conquest of poliomyelitis achieved through the science of which he had so long been a champion, namely immunology'. Nevertheless 'he lived to see his work with Kling and Lépine vindicated, and that was no small triumph.'[8]

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