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Centenary of the death of Elie Metchnikoff: A visionary and an outstanding team leader

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Abstract

Elie Metchnikoff passed away on July 15th, 1916. He is considered to be the father of phagocytes, cellular innate immunity, probiotics, and gerontology. In all of these fields, he was a visionary. To achieve such a notability and produce so many masterpieces, Metchnikoff used more than 30 animal species to support his findings, and his pasteurian laboratory published more than 200 papers in the Annales de l'Institut Pasteur. As a wonderful team leader and a great mentor, during his 28 years at Institut Pasteur, he welcomed and supervised more than 100 young trainees.Trained as an embryologist, he contributed to the birth of immunology and to the understanding of physiology and pathology. Indeed, Metchnikoff and his team investigated inflammation in guinea pigs, rats, frogs; studied infectious diseases in monkeys, caimans, geese; investigated aging in parrots, dogs, humans; proposed hypotheses to understand age-associated senility using rabbits and humans; developed germ free tadpoles, flies, chicks; studied the gut flora in bats, horses, birds, humans; and popularized the use of probiotics as a tool to delay the deleterious effects of toxic compounds derived from putrefactive gut bacteria. He was also a philosopher and penned essays on human disharmony and on pessimism and optimism.

Keywords: Phagocytes; Macrophages; Gerontology; Microbiota; Aging; Probiotic

1. The centenary of Elie Metchnikoff's death

Hundreds of articles and numerous books have already been published on Elie Metchnikoff, and historians have attempted to critically examine his research in terms of its genesis, conceptual foundations, and scientific impact [1–4]. Thus, while we will include here information previously published about his life, career, and contributions [5–13], we will offer new perspectives on his numerous investigations through the publications of collaborators who were working in his laboratory. For the centenary of the death of this giant, "Microbes and Infection", which is the descendent of the Annales de l'Institut Pasteur, wished to pay tribute to this great scientist. This is all the more remarkable because Metchnikoff was a member of the editorial board of the Annales de l'Institut Pasteur from 1890 to his death in 1916, and Metchnikoff and his numerous lieutenants, the members of his laboratory, published more than 200 papers in the Annales de l'Institut Pasteur. Amazingly, around one hundred trainees and colleagues from all around the world published in the Annales de l'Institut Pasteur acknowledging the work as "from the laboratory of E. Metchnikoff". This was a different period in research, when trainees did not fight to be the 3rd or 4th co-author, when the head of the laboratory did not consider putting his name as senior author, when scientists were not concerned with impact factor and instead published their most important discoveries in their most friendly journal. In all of these reports, the large number of animal species Metchnikoff and his lieutenants used is striking. Like most of their colleagues, by the end of nineteenth century, they rarely used

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mice. Instead, they worked with species such as dogs, pigeons, rabbits, donkeys, pigs, guinea pigs, bighorn sheep, or even foxes. This was indeed fortunate, because Bernard Gaspard (1788−1871), François Magendie (1783−1855), Stéphane Tarnier (1828−1897), Saturnin Arloing (1846−1911), Victor Feltz (1835−1893), Léon Coze (1819−1896), Carl J. Salomonsen (1847−1924), and Nikolai F. Gamaleia (1859−1949), who contributed to the demonstration of the relationship among putrefaction, bacteria, microbial products, sepsis and death, would have failed to do so if they had been working with mice, which are highly resistant to bacterial products and sepsis [14]. When M. Cahanesco from Romania studied the bacterial vaginal flora in Metchnikoff's lab, he noticed that *Staphyloccous aureus* could kill rabbits and guinea pigs upon intreaperitoneal injection but giant *diplodococcus* did not harm mice [15]. In 1888, Metchnikoff sent a letter to Duclaux about a controversial issue he had with George Nuttall (1862−1937): "*Finally, regarding the choice of the animals to use for the experiment, you [Duclaux] believe that Mr. Nuttall was wrong to choose mice to test the strength of the anthrax virus, but you have not noticed, I believe that he seeks to demonstrate the inaccuracy of my results on the lost of virulence in rabbits by experiments made with mice.*"

Elie Metchnikoff was 71 when he was transferred from the hospital of Institut Pasteur to Louis Pasteur's apartment after his health seriously deteriorated due to heart disease. He told Pasteur, "*See how my life is bound with Institut Pasteur. I have worked here for years; I am nursed here during my illness; in order to complete the connection, I ought to be incinerated in the great oven where our dead animals are burnt, and my ashes could be kept in an urn in one of the cupboards in the library*" [16]. Emile Roux, the director of Institut Pasteur thought it was a gruesome joke, but Olga, his wife, confirmed the last will of her husband. On July 15th 1916, at 5:30 pm, Metchnikoff took his last breath after 28 years at Institut Pasteur where he had been deputy-director since 1904 (Fig. 1). He, the pacifist, was dying the day after the celebration of the Bastille day, when French soldiers were marching in Paris before going back to the war front. Obituaries were published in numerous famous scientific journals such as The Chemical News and Journal of Physical Science, The British Medical Journal, The Lancet, La Presse Médicale, the Annales de l'Institut Pasteur, and also in the lay press as in the front page of "Le Figaro", and also in the United States or in Russia. His popularity remained strong as illustrated by a whole page in the New York Times (April 30th, 1922) after his biography written, by his wife, was translated into English. Part of his popularity was due to his investigation of the use of probiotics to limit the effects of aging. On January 1910, Charles J. Brandreth after having visited him, wrote a spectacular article in the London Magazine about "The man who prolongs life" [17]. Brandreth wrote, "*It is interesting to note how Metchnikoff was able to demonstrate the effect on the system of the putrefactive microbes. From the dejections of aged and decrepit persons he extracted the putrefactive microbes, and prepared an "intensified" culture which, he proceeded to inject into the system of a number of young gorillas and baboons. The result was remarkable and conclusive, for within a very short space of time the animals began to show all the signs of decrepitude and old age, and died from pre-mature senility*". Brandreth made an accurate description of the scientist. "*His head was covered with a wild, unkempt mass of hair, which, with a quick, impatient movement of his long, thin hands, he kept brushing back from his broad forehead. A pair of large, round spectacles bridged a very prominent nasal organ, and through the glasses there sparkled two of the brightest, keenest eyes I have ever seen. His features twitched with much inward excitement, and from his chin there fell a long, straggling beard plentifully streaked with grey.*" No doubt that Brandreth fell in love, "*Ilias Metchnikoff is certainly "possessed," but not with an evil demon. The spirit that transfigures him, that makes itself felt in his clear brain, his bright eye, and his harmonious and illuminating speech, is the noble genius of science applied to the cause of the human race.*" To support his enthusiasm, he quoted Max von Gruber (1853−1927), an Austrian bacteriologist who discovered specific agglutination: "*Metchnikoff would seem to have been specially created for the sole purpose of making fruitful scientific discoveries, but he is far more than a prominent scientist; he is a great and good man, one of the loveliest incarnations of those enthusiastic beings so frequently to be found amongst his own race -Slavs. Metchnikoff is an embellishment to mankind.*"]. Constantin Levaditi, who worked with Metchnikoff, further defined the character: *"Convinced pacifist, for him, life had only one goal: scientific research. My master lived in a world apart, made of art and philosophy, for which the discovery of novelties was dominant . Musician, he was at the bottom of his soul. He also loved painting … Outstanding character, scientist of genius, scholar, a tireless researcher, philosopher also and above all Slavic to the end of his soul."* Emile Roux was a colleague, a close friend and an admirer of Metchnikoff, as well. For his jubilee, Roux stated: "*The institute owes you much, you brought the prestige of your reputation, and your work and that of your students have greatly contributed to its glory*". [18].

Another description was given by Alexandre Besredka (1870−1940) in his book published in 1921 entitled "The story of an idea - The works of Elie Metchnikoff". Alexandre Besredka was from Odessa and made a great career at Institut Pasteur after he joined Metchnikoff's laboratory.[1] Having

[1] Interestingly Metchnikoff asked Besredka to undertake medical studies before joining the lab. This demonstrates that Metchnikoff, like Pasteur, supported the complementarity of the two professional tracts of research and medicine, despite the fact that they themselves were not physicians. They fully supported Charles Richet (1850−1935), Nobel prize winner in 1913 for his discovery of anaphylaxis, when he stated in 1888 during his inaugural lecture at the Paris Medical School: "*To oppose the physician to the physiologist and the scientist to the clinician, means that one has understood neither physiology nor medicine.*" Of note, Besredka is considered as the father of desensitization to prevent anaphylatoxic reaction, but he also did key experiments in the field of immunity to bacteria when he obtained the very first anti-endotoxin antibodies in the world [19] Rietschel ET, Cavaillon JM. Richard Pfeiffer and Alexandre Besredka: creators of the concept of endotoxin and anti-endotoxin. Microbes Infect 2003; 5:1407−14.

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