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Authors
Cavaillon, Jean-Marc
Levin, Jack

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Revisiting Metchnikoff's work in light of the COVID-19 pandemic

Jean-Marc Cavaillon[1] and Jack Levin[2]

Abstract

Revisiting Metchnikoff's work in light of the COVID-19 pandemic illustrates how much this amazing scientist was a polymath, and one could speculate how much he would have been fascinated and most interested in following the course of the pandemic. Since he coined the word "gerontology", he would have been intrigued by the high mortality among the elderly, and by the concepts of immunosenescence and inflammaging that characterize the SARS-CoV-2 infection. While Metchnikoff's work is mainly associated with the discovery of the phagocytes and the birth of cellular innate immunity, he regularly invited his closest collaborators to investigate humoral immunity, and it was in his laboratory that Jules Bordet made his major discovery of the complement system. While Metchnikoff and his team investigated many infectious diseases, he also contributed to studies linked to vaccination, such as those on typhoid fever performed in chimpanzees, illustrating that non-human primates can provide animal models which are potentially helpful for understanding the pathophysiology of the COVID-19 virus. In the present review, we illustrate how much his own work and the investigations of his trainees were pertinent to this new disease.

Keywords

Ageing, COVID-19, infection, inflammation, pandemic, phagocytes, vaccines, viral sepsis

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Through their pioneering investigations of immunological mechanisms and infectious diseases, Metchnikoff and colleagues established the groundwork for many of the studies currently being performed on COVID-19.

Scientific publications and international cooperation

COVID-19 has generated a profusion of scientific articles (more than 92,900 in 2020) with an unprecedented free access provided by the publishers. Very few can claim to have read more than a small percent of those. In 1888, Metchnikoff joined Louis Pasteur's new institute. Alexandre Besredka who became the head of the laboratory of his mentor after his death, said of Metchnikoff: "He was for us his collaborators, a living bibliography". It is important to emphasize that within the Pasteurian team, he was the only one to master Russian, German, French and English, which enabled him to read the scientific articles published at that time in the language of their authors. His love for reading is illustrated by a famous portrait by the Russian painter Ossip Perelmanov, known as Ossy de Perelma (1876–1949) (Figure 1). Metchnikoff appears sitting at a desk in front of a mountain of books, newspapers and papers, and leafing through articles, while a photo depicted him in front of his bookcase.

COVID-19 has undoubtedly been a formidable incentive for international cooperation and thinking, and similarly Metchnikoff welcomed into his laboratory no less than one hundred collaborators from Europe and even Japan, with whom he published more than two hundred articles. With our colleagues at the European Shock Society and the European Group on Immunology of Sepsis we have published reviews on what appears to be a new disease caused by the emergence of a newly recognized virus. Thirteen nationalities are represented in these papers.[1,2]

Infectious diseases

COVID-19[2] is a newly described zoonosis, characterized by a severe acute respiratory syndrome and caused by coronavirus 2 (SARS-CoV-2), which resembles bat

[1]National Research Agency, ANR, Paris, France
[2]Departments of Laboratory Medicine and Medicine, University of California School of Medicine, San Francisco, CA, USA

Corresponding author:
Jean-Marc Cavaillon, National Research Agency, ANR, Paris, France.
Email: Jean-marc.cavaillon@pasteur.fr

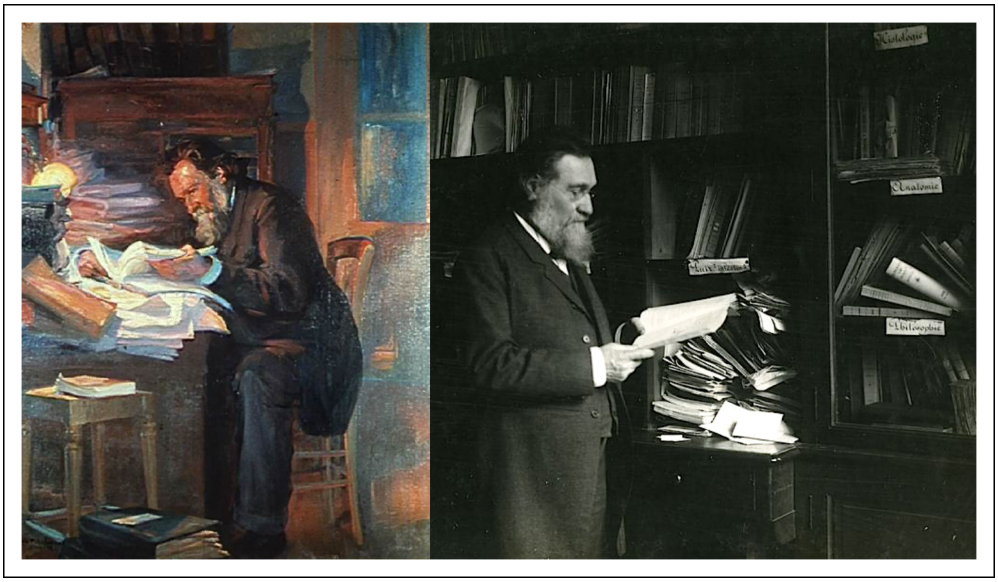

Figure 1. Left : Elie Metchnikoff by Ossy de Perelma (1907). Right: A picture of Elie Metchnikoff in the library of Institut Pasteur.

coronaviruses[3]. Of note, an estimated 3,200 coronaviruses exist in bats[4]. The disease was first reported in Wuhan, China in December 2019, but it was already circulating in Italy on September 2019[5] and in France on November 2019[6].

Greatly distressed by the serious infectious diseases of his wives, Metchnikoff twice attempted to kill himself. The first time was in Madeira, after the death of Ludmilla Federovna because of tuberculosis, by swallowing a large dose of morphine. The second time was after his second wife, Olga Belokopytova, developed typhoid fever, but both survived (1880). He injected himself with the blood of a patient with relapsing fever (which is caused by *Borrelia* bacteria) and became severely ill, demonstrating incidentally that the disease was transmissible. In 1892, studying the specificity of the *Vibrio cholerae,* he consumed a culture of vibrios. He did not contract cholera, and therefore he repeated the experiment on one of his workers: the result was the same. He then accepted the offer of a second volunteer, Jean-Baptiste Jupille, who as a child had received the second rabies vaccine of Pasteur and as an adult was working as a watchman at Institut Pasteur. The young man fell ill and nearly died!

Epidemiology, lung Infection, alveolar macrophages, and sepsis

Epidemiological studies have been playing a major role in the survey and understanding of the COVID-19 pandemic[7,8]. The most severe forms of COVID-19 are associated with a pulmonary tropism of the infection and a major alteration of lung functions[9,10]. The major features associated with lung dysfunction are a pulmonary vascular endothelitis, thrombosis, and angiogenesis. Macrophages derived from infiltrating inflammatory monocytes contribute to the local inflammatory reaction[11]. Pertinently, alveolar macrophages are an integral part of the pathogenesis of COVID-19[12]. In the most severe cases, an acute respiratory distress syndrome (ARDS) is observed and macrophage activation with the local release of inflammatory cytokines contributes to the lung injury, with subsequent tissue damage and respiratory failure.

Very early in his career (1888), Metchnikoff was interested by the deadliest lung infection at the end of the XIXth century, namely, tuberculosis[13,14]. With an estimated frequency of 16% in Europe, tuberculosis was a major infectious threat. Of interest, in 1911, Metchnikoff, accompanied by his Pasteurian colleagues Alexandre Salimbeni (1867-1942), Etienne Burnet (1873-1960) and Tamotsu Yamanouchi (1880-1944), undertook an epidemiological investigation of the occurrence of tuberculosis among the Kalmyk native people living in Russia on the Western shore of the Caspian Sea[15]. Of note, with his colleague Nicolaï Tchistovitch (1860-1926) from Saint Petersburg, he reported that the lung dust cells known at that time as "Staubzellen" were in fact the alveolar macrophages displaying a phagocytic capacity (Figure 2).

COVID-19 is considered to be a viral sepsis[16]. Sepsis is defined as organ failure following a dys-regulated host response to infection. Severe COVID-19 patients experience many features known to occur in patients with bacterial sepsis (lymphopenia, thrombocytopenia, coagulopathy, hypotension, organ failure, and altered immune status).

Septicemia, is a word coined in 1837 by a Parisian physician, Pierre Piorry (1794-1879), from the Greek word sepsis, meaning putrefaction, and aima, meaning blood.

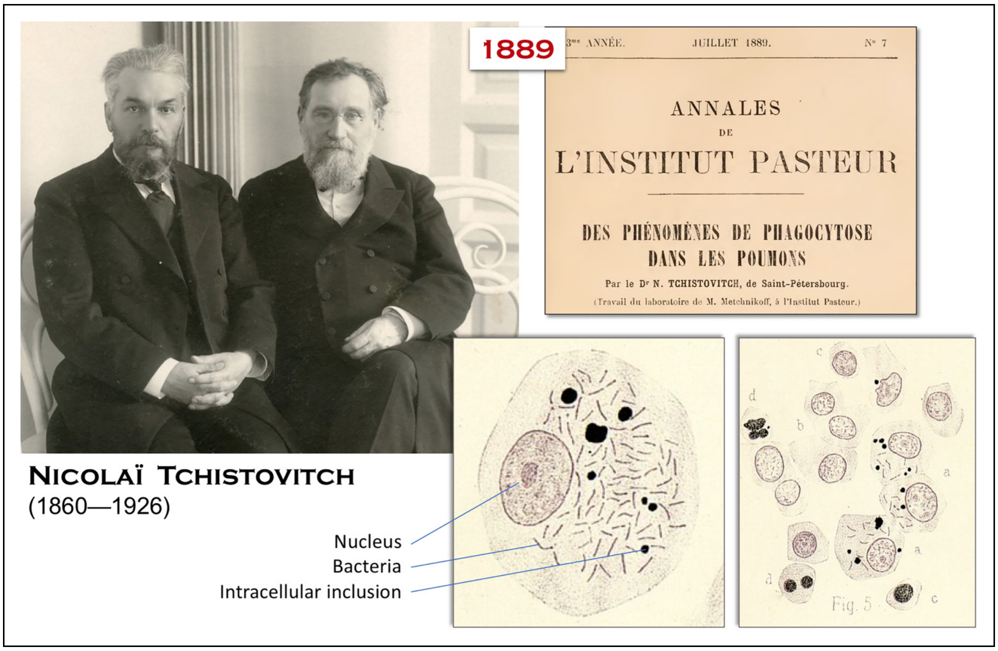

Figure 2. Elie Metchnikoff and Nicolaï Tchistovitch who discovered the alveolar macrophages.

In 1847, Ignaz Semmelweis (1818-1865) attempted to remove the odor of putrefaction from the hands of the medical students who were practicing autopsies of cadavers before joining the materninty clinic to help the women to deliver. By requesting them to wash their hands and nails with calcium hypochlorite he reduced the mortality in his Vienna hospital from 16% to 0.85%. Despite this amazing success, his contract was not renewed and he had to leave Vienna[17]. In 1879, Louis Pasteur studied puerperal fever, confirming the works of Victor Feltz (1835-1893), and of Léon Coze (1819-1896) published ten years earlier[18]. In 1896, one of Metchnikoff's collaborators, Félix Mesnil (1868-1938) published a work on "vibrio" sepsis (Figure 3).

Neutrophils and netosis

Strong evidence has been accumulated since the beginning of the COVID-19 pandemic that neutrophils play an important role in the pathophysiology, particularly in those with severe disease[19]. Particularly, netosis (NET) has been observed in the lungs of patients developing ARDS and contributes to immunothrombosis[20]. NETs released by SARS-CoV-2-activated neutrophils promote lung epithelial cell death *in vitro*[21]. Targeting NETs using recombinant human DNase may have significant therapeutic implications in COVID-19 disease[22].

In Metchnikoff's time, neutrophils were called microphages, and Metchnikoff not only reported their phagocytic properties (as illustrated by colorful hand-drawings in his book on Immunity in infectious diseases published in 1901, figure 4), but also their capacity to be engulfed by macrophages, i.e., efferocytosis, a phenomenon also described by Sir Marc Armand Ruffer (1859-1917), one of his former trainees[23]. In Metchnikoff's laboratory, a Romanian scientist, Constantin Levaditi (1874-1953) noted that "*altered in their vitality, deteriorated, destroyed, neutrophils still contribute to anti-bacterial immunity*" (Figure 4). The process is nowadays known as "netosis". It consists of a particular death of neutrophils, which then release all their intracellular material outside the cell.

Compartmentalization

The severity of COVID-19 is exacerbated in obese patients in whom a contribution of macrophages, in an activated state in adipose tissue, is suspected[24]. Many scientists have mentioned that a cytokine storm was characteristic of COVID-19, but within the peripheral blood, it is more of a small drizzle[25-27]. In contrast, in the most severe patients, this storm operates in their lungs where cytokines contribute to tissue damage and mortality[28]. In addition, we know that COVID-19 can be associated with brain infection. The resident central nervous system cells such as astrocytes and microglia also express ACE-2, the SARS-Cov-2 receptor, thus highlighting the vulnerability of the nervous system to this virus. Indeed, SARS-CoV-2 may be an underestimated opportunistic pathogen of the brain[29,30]. Furthermore, olfactory and taste dysfunctions are common in COVID-19. In the hamster, SARS-CoV-2 induces loss of ciliation in the olfactory epithelium and a viral load can be found within the brain[31]. Most interestingly, it has been suggested that gut microbiota likely

Figure 3. Elie Metchnikoff and part of his team, including Felix Mesnil (circa 1905).

Figure 4. Some drawings of microphages (neutrophils) made by Elie Metchnikoff; Constantin Levaditi, the first to observe the phenomenon of netosis.

Figure 5. Left: Works of Elie Metchnikoff on nerve cells during rabies and the discovery of neuronophages (microglial cells) in aged parrots. Center: A caricature of Elie Metchnikoff's work on microbiota. Right: A paper from Elie Metchnikoff's laboratory analyzing the gut flora of human babies.

influence COVID-19 virulence, while from its side, SARS-CoV-2 may affect the intestinal microbiome, promoting dysbiosis and other deleterious consequences[32]. Furthermore, endotoxemia, which can derive from gut microflora, has been suggested to contribute to the severity of COVID-19 outcomes[33]. Indeed, COVID-19 is associated in more than 17% of cases with gastrointestinal manifestations including anorexia, diarrhea, nausea, vomiting, abdominal pain and discomfort[34].

Metchnikoff was fully aware of the roles of various organs of the body in the fight against microbial invasion[35,36]. And no doubt he would have subscribed to the concept of "compartmentalization". The word was first used by Brandtzaeg to describe an inflammatory response to a compartmentalized bacterial presence within the blood stream[37]. The concept was then extended to illustrate that different or even opposing processes can occur in different tissues during a systemic inflammatory disease such as sepsis[38,39]. Metchnikoff discovered microglial cells in the brain, which he named "neuronophages", and investigated the damage to nerve cells during rabies infection (Figure 5)[40]. Furthermore, Metchnikoff and his team carried out numerous studies on the digestive tract, particularly on microbiota (Figure 5)[41,42].

Inflammation

The yin yang of the host's response to infection combines beneficial and harmful effects. This ambivalence, this dichotomy, these two sides of Janus were nicely illustrated when it was shown that treatment with IFN-α was beneficial when initiated early in COVID-19 patients, but on the contrary, deleterious when administered late[43]. Of course, a highly destructive inflammation is present in the lungs of the most severe patients as a reflection of inflammasome activation[44] and a synergy between inflammatory cytokines such as TNF-α and IFN-γ[45], a phenomenon already described 30 years ago in the case of endotoxin-induced shock[46].

Metchnikoff's lessons on inflammation were famous and were translated into English in 1893, one year after their first publication in French (Figure 6). Metchnikoff was fully aware that there is beneficial physiological inflammation as well as a pathological one[47].

Ageing

Current data show that the most severe cases of COVID-19 and the highest mortality rate occur in the elderly. Immunosenescence, a word that appeared in the early 1980's, would not have been disclaimed by Metchnikoff. It reflects that older people have an altered adaptive immune response during which they produce more inflammatory cytokines, a process known as "inflammaging"[48], another word Metchnikoff would have loved, while he had himself coined the word "gerontology".

Metchnikoff performed many studies on ageing, particularly on parrots, which are birds that can live more than ninety years[49]. These studies led to the discovery of "neuronophages", the macrophages Metchnikoff identified in the brain which he concluded were responsible for the neurodegeneration associated with ageing (Figure 6). This was an idea that was confirmed a century later[50].

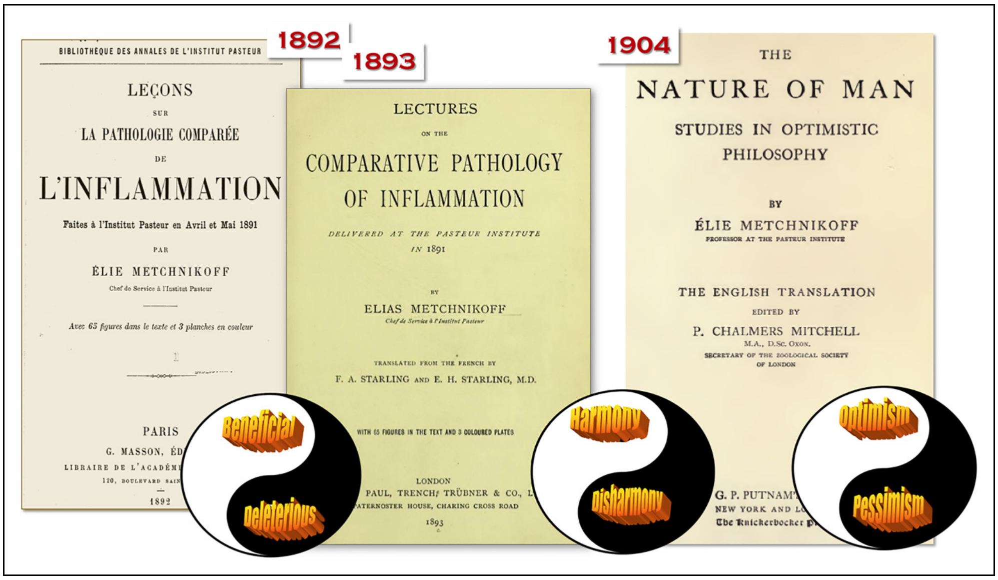

Figure 6. Left: Lectures of Elie Metchnikoff on inflammation; Right: Book by Elie Metchnikoff in which he coined the word "gerontology". The yin yang aspects of inflammation of the human body (i.e., potentially beneficial vs. pathological), and of mood as addressed by Elie Metchnikoff.

Complement System

Not surprisingly, since COVID-19 is an inflammatory disorder, the complement system has been shown to contribute to the pathophysiology of the SARS-CoV-2 induced disorder[51,52], reminiscent of what was demonstrated earlier in sepsis[53]. Quite often, data which have been reported during investigations of COVID-19 were just rediscoveries of what has been known for more than twenty years in the case of bacterial sepsis or endotoxemia, and often published in prestigious journals, without citing the early reports. The terminal sC5b-9 complement complex has been associated with respiratory failure and the activation of the C5a anaphylatoxin axis has been observed in COVID-19 patients[52,54].

In April 1894, Jules Bordet (1870-1961), a Belgian medical doctor joined Metchnikoff's laboratory where he made the key discoveries that resulted in a better understanding of the complement system[55] (Figure 7).

Coagulation

Abnormal coagulation is a hallmark of COVID-19. A generalized thrombosis with microangiopathy has been observed in the lungs of the most severe cases[10], and the combination of high plasma levels of D-dimers with low lung compliance is associated with the poorest outcome[56]. An endotheliopathy has also been shown to importantly contribute to the coagulopathy which is commonly present in COVID-19 patients[57].

In Metchnikoff's laboratory, Jules Bordet and his brother-in-law, Octave Gengou (1875-1957), performed investigations of the coagulation process. They compared the capacity of blood from birds, rabbits and guinea-pigs to coagulate in glass tubes, and showed the interference of paraffin on the coagulation process. Furthermore, they investigated how antisera raised against heterologous sera (e.g., anti-rabbit anti-serum obtained in guinea pigs) could interfere with the coagulation process of rabbit blood[58].

Vaccination

COVID-19 has been the stimulus for unprecedented research in the field of vaccination, and led to the remarkably successful development of new vaccines within an amazingly short period of time[59]. In Russia, the COVID-19 vaccine "Sputnik V" has been prepared by the Gamaleïa Institute. Nikolaï Gamaleïa (1859-1849) had been a long-term collaborator of Metchnikoff while he was heading the Bacteriology Institute of Odessa. Gamaleïa coined the name "*Vibrio metschnikovii*" to pay tribute to his mentor. Both Metchnikoff and Gamaleïa had been attending the inaugural ceremony of the Institut Pasteur on November 14th, 1888[60], since Gamaleïa was expected to join the institute. A quite fascinating picture of Metchnikoff was taken while posing very similarly to Louis Pasteur in the famous painting made by the Finnish artist Albert Edelfelt in 1885 (Figure 8). Pertinently, Pasteur is well known to have proposed four different vaccines (fowl cholera, anthrax, swine erysipelas, and rabies).

In addition to the completely correct statement that Metchnikoff is the father of innate cellular immunity, it should be noted that he also encouraged his collaborators to

Figure 7. Main works of Jules Bordet in Elie Metchnikoff's laboratory on the discovery of the complement system.

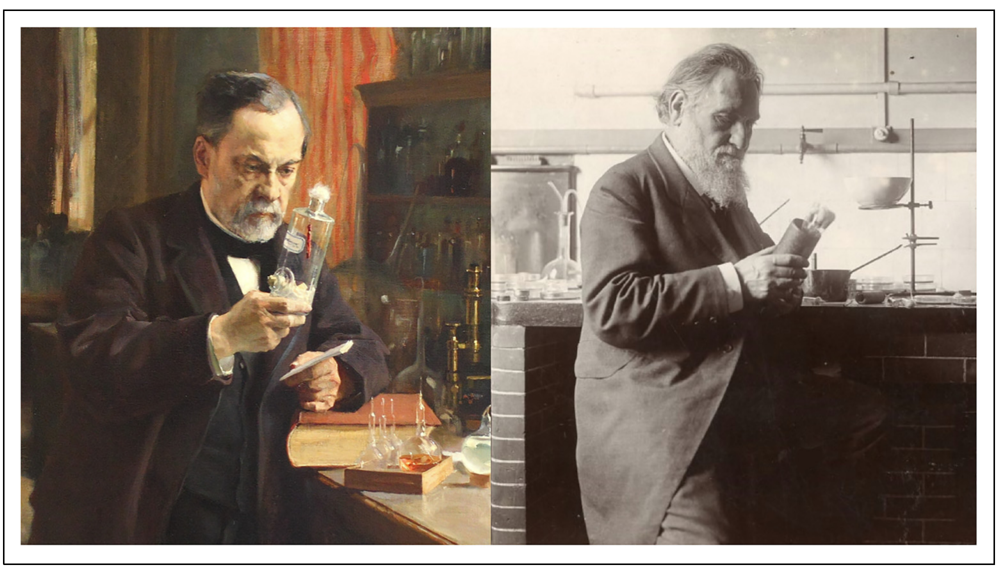

Figure 8. Left: Louis Pasteur by Albert Edelfelt (1885). Right: A picture of Elie Metchnikoff with a similar pose (circa 1908).

investigate adaptive humoral immunity. For example, his colleagues, the Belgian Jules Bordet (1870-1961), the Russian Vassiliy Issaevitch Issaeff (1854-1911), and the Italian Giuseppe Sanarelli (1864-1940) investigated in his laboratory the efficacy of vaccines against *Streptococcus pyogenes*, *Streptoccocus pneumoniae,* and *Vibrio cholera* and produced protective immune sera. *Metchnikoff* with Émile Roux (1853-1933) and Alessandro Taurelli Salimbeni (1867-1942) developed an approach to immunize against the cholera toxin, and with Alexandre Besredka (1870-1940) he vaccinated chimpanzees against typhoid fever (Figure 9). The most notable event occurred after Metchnikoff welcomed into his laboratory Waldemar Haffkine (1860-1930) from Russia. After developing specific vaccines against cholera and plague, Haffkine conducted successful vaccination campaigns to fight corresponding epidemics in India[61].

Animal Models

Studies of COVID-19 have been possible thanks to the establishment of different animal models[62]. In this regard, COVID-19 is a zoonosis derived from bats[63], and pertinently, Metchnikoff also published works based on this animal species. He worked on more than thirty animal species, aware that only some of them were appropriate to investigate and mimic human infectious diseases (Figure 10).

From 1903 to 1906, in collaboration with Émile Roux, his colleague, friend, and at that time director of Institut

Figure 9. Some examples of studies carried out in Elie Metchnikoff's laboratory on vaccines.

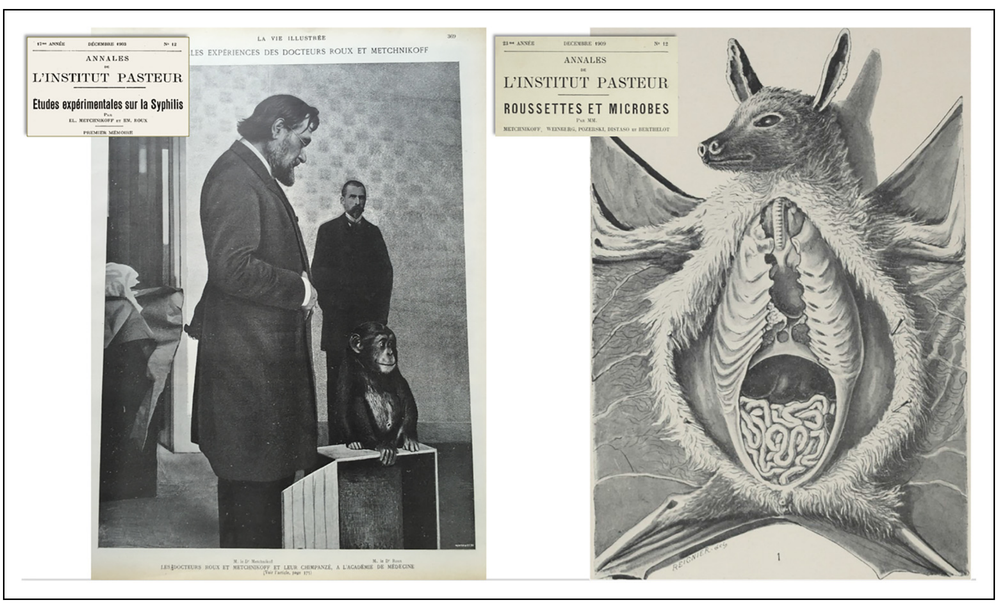

Figure 10. Elie Metchnikoff used numerous animal models, such as chimpanzees for his investigations on syphilis (left) or bats in his studies on gut microbiota (right).

Pasteur, using non-human primates as an animal model, he performed major investigations on syphilis that resulted in the recommendation to use calomel (mercury chloride) as a drug to specifically treat this infection[64,65]. Of note, calomel was already proposed in the XIXth century as a miracle drug to treat numerous diseases.

Psychological consequences

COVID-19 and the associated lockdowns have been associated with many psychological disorders not only in the general public[66,67] but also among healthcare workers[68].

After two attempts to commit suicide, Metchnikoff, as a young adult, was particularly sensitive to emotional events. The psychological behavior of humans had been a topic dear to Metchnikoff who wrote two books on the nature of man, with the optimistic philosophical view he had developed by the end of his life[69] (Figure 6).

Concluding remarks

Let us be as optimistic as Metchnikoff and hope that the pandemic will be soon controlled. Thanks to their cleverness, humans have been able to develop effective vaccines as potentially lethal weapons against the virus. The extensive sharing of data resulted in the remarkably rapid production of multiple anti-COVID-19 vaccines and evaluation of other therapeutic agents, confirming Metchnikoff's wisdom in recognizing the importance of collaborative efforts. Nevertheless, the COVID-19 pandemic has revealed that the self-satisfied humans of the 21st century had failed to consider that pandemics were still at their door and they were therefore poorly prepared. COVID-19 illustrates the complex interplay between the host immune cells and pathogen, as evidenced in studies performed by Elie Metchnikoff whose legacy remains immortal[70].

Photo credit: Institut Pasteur / Musée Pasteur.

ORCID iD

Jean-Marc Cavaillon https://orcid.org/0000-0001-7721-2106

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