

Contribution of physiologists to the identification of the humoral component of immunity in the 19th century

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ABSTRACT

The history of antimicrobial humoral immunity usually focuses on the works of the German school at the end of the 19th century, born in the tradition of chemistry and disinfection. Starting from an old quarrel of priority about serotherapy between Emil von Behring (1854–1917) and the French physiologists Charles Richet (1850–1935) and Jules Héricourt (1850–1938), we first confirm that the latter stated the principle of serotherapy in 1888 and put it into practice before the seminal Behring's article in 1890, observing several adverse effects of this new immunotherapy. We also find that researchers who can be considered heirs of the French school of Physiology founded by Claude Bernard (1813–1878) also investigated the field of humoral immunity in the 1870–1880s. Maurice Raynaud (1834–1881), Auguste Chauveau (1827–1917), and eventually Charles Richet applied the experimental method of Claude Bernard to the young field of microbiology, illustrating a movement called by Jacques Léonard “physiologization of the pasteurism.” However, the contribution of physiologists in this field started before Louis Pasteur, leading to the conclusion that physiologists and chemists synergistically contributed to the birth of bacteriology and immunology.

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Introduction

Several historians have shown that the concept of humoral immunity was born at the very end of the 19th century within the German School, around George Nuttall (1862–1937), Emil von Behring (1854–1917) and Paul Ehrlich (1854–1915).^{1,2,3} The invention of serotherapy in 1890 by Behring and his associate Shibasaburo Kitasato (1852–1931)^{4,5} therefore appears to originate from this movement. However, as recently shown by Jonathan Simon, this discovery needs instead to be placed in the tradition of disinfection: as his colleagues at the Koch's Institute, who were especially interested in disinfectants and had a chemical view of immunity, Behring conceived serotherapy in terms of disinfection.⁶ Rewarded in 1901 with the first Nobel Prize for Medicine, Behring is of course widely recognized as “the pioneer” of serotherapy,^{7,8,9,10} according to the words pronounced by Professor K.A.H. Mörner, Rector of the Royal Caroline Institute, during the Nobel Prize ceremony.¹¹

Another historian, Stewart Wolf, in his Charles Richet's biography published in 1993, relates an old quarrel of anteriority about the discovery of serotherapy. This quarrel opposed Behring to the French physiologist Charles Richet (1850–1935), both of them claiming to be the first inventor of serotherapy. Charles Richet indeed described “*hématothérapie*” with his associate Jules Héricourt (1850–1938) as early as 1888.¹² Their contribution to the discovery of serotherapy has never been studied in detail, neither has the context in which this took place. Whereas almost nothing has been published concerning Jules Héricourt,

Charles Richet is well known because of his discovery of anaphylaxis, awarded a Nobel Prize in 1913, and because of his many other contributions, notably in the field of neurosciences.^{12,13} Charles Richet was the heir of Claude Bernard (1813–1878) and of the French School of Physiology, so could have performed his research with a totally different mindset than that of Behring. Richet and possibly Héricourt can be seen as actors of what the French historian of medicine Jacques Léonard called, using a neologism, a movement of “physiologization of pasteurism,”^{14,15} when physiologists moved into the field of bacteriology in the 1880s, which led to the birth of Immunology. When describing this movement, Léonard both referred to cellular and humoral immunity. However, the fame of Elie Metchnikoff's (1845–1916) discoveries about phagocytosis¹ somehow masked the humoral side of the “physiologization of pasteurism” movement, which remains to be described.

To address this question, we first analyze whether physiologists, after Claude Bernard, investigated the concept of immunity and its physiologic substratum. We then explore the works of Richet and Héricourt, whether they depart from that of the other physiologists, and whether they are truly – or not – the first enunciation of the serotherapy principle. We also analyze the later contribution to serotherapy of Richet and Héricourt, *i.e.*, anti-cancer serotherapy, which has already been explored with the perspective of more general attempts to fight cancer,^{16,17} and has also been evoked by several authors^{12,13,18,19,20} but still needs to be analyzed in the context of serotherapy and immunity.

Input of physiologists in the field of immunity

Maurice Raynaud (1834–1881), who described Raynaud's disease (recurrent vasospasm of the fingers and toes occurring in response to cold exposure) and discussed the neuronal regulation of the vascular tonus in reference to the works of Claude Bernard and that of Etienne-Jules Marey (1830–1904), was probably also the first physiologist to investigate the concept of immunity. In the late 1870s, he questioned the mechanisms of induction of immunity during the process of Jennerian vaccination. According to him, only one of the 3 general systems, *i.e.*, blood circulation, lymphatic circulation or nervous system, could convert the local and transient vaccinia pustule into the long-lasting and general phenomenon called immunity. After having analyzed each of these systems, he concluded that the vaccinia virus was converted inside the lymph nodes into an “elaborated lymph,” which was then transmitted through blood to the whole body, conferring immunity. Raynaud therefore anticipated the discovery of cell-mediated mechanisms of specific immunity, and appears to have been the first to have considered immunity from the perspective of the host, as immunologists do.^{21,22} Above all, he was the first who explicitly associated blood and immunity, even though he never tried to do any transfer of immunity.^{21,22}

The French veterinarian Auguste Chauveau (1827–1917), from Lyon, was a great anatomist and physiologist, and considered himself to be an heir of the physiologist Claude Bernard although he never attended his teaching. Chauveau also early devoted himself to microbiology and, in our opinion, he should be considered the real founder of this science, years before Louis Pasteur (1822–1895). Going deeper than Casimir Davaine (1812–1882) (who proved in 1863 the microbial nature of anthrax^{23,24}), Chauveau showed in 1868 the corpuscular nature of the factors responsible of glanders, cowpox and variola, *i.e.*, one bacterial and 2 viral diseases,^{25,26,27} and then developed a theory, which synthesized 2 fundamental epidemiologic concepts, considered to be opposite, contagion and infection (the concept of infection was used to explain the appearance of an epidemic disease without any contagion mechanism). This “*théorie de la contagion médiate ou miasmaticque*” (theory of mediate or miasmatic contagion) redefined infection as a mediate contagion, that is to say a contagion through environment.^{28,29,30,31} Thus, Chauveau built the foundations of microbiology: microbes, depicted as factors of diseases, are involved in contagion as well as in infection. Chauveau was also the author, in the 1880s, of an immunity theory that conflicted with Pasteur's view. Whereas Louis Pasteur thought that immunity was due to an exhaustion of the nutrients that were necessary for microorganisms,³² Chauveau maintained that microorganisms produced, within their host's blood, some substances, which were harmful to themselves.^{33,34} Consequently, although he conceived it exactly in the reverse manner, Chauveau perceived the existence of a humoral immunity. This is an illustration of the main role of the French school of Physiology, to which Richet also belonged, in formulating the basic concepts of immunity.³⁵ To verify his immunity theory, Chauveau tried to transmit immunity against anthrax to sheep, transfusing them with large volumes of anthrax-infected blood whose microorganisms had been previously killed by



Figure 1. Charles Richet (1850–1935) (left) and Jules Héricourt (1850–1938) (right). (Fonds Watier, Rabelais Fundation; University Library of Medicine, Université François-Rabelais de Tours).

heating.³⁶ As the experiment failed, Chauveau abandoned and did not generalize the concept.

Works of Richet and Héricourt before the ones of Behring and Kitasato

Charles Richet and Jules Héricourt

Born in Paris in 1850, son of Prof. Alfred Richet (1816–1891), a famous surgeon who was a friend of Claude Bernard, Charles Richet (Fig. 1A) became professor of Physiology at the Faculty of Medicine of Paris in 1887. During his lifetime, he studied many fields of physiology, such as gastric juice, thermoregulatory mechanisms, dive reflex and psychology. He also discovered anaphylaxis, for which he was awarded the Nobel Prize in 1913. Very cultured and curious, he also devoted himself to literature, theater, and aviation.^{12,37}

Much less known than Richet, Jules Héricourt (Fig. 1B) is however an interesting character. Also born in Paris in 1850, but in a popular milieu, he became friend with Richet while studying together in secondary school, then spent several years as a medical officer in the French Army, where he manifested a deep interest in microbiology. In 1887 he joined Charles Richet at his Physiology laboratory and during 15 y he performed many studies with Richet, particularly in the field of serotherapy. Moreover, Héricourt was a committed physician: at the time of the Dreyfus Affair, he was one of the first “Dreyfusard” intellectuals, and testified in favor of Dreyfus at the Zola trial in 1898. He also co-founded the “*Ligue des Droits de l'Homme*” (Human Rights League) and was one of its Deputy-Presidents. Deeply concerned about social issues, he later dedicated himself to poor people, mainly as director of an anti-tuberculosis dispensary from 1904 to 1934.³⁸

Both Richet and Héricourt were great admirers of Louis Pasteur. As soon as 1883, Richet published a series a scientific papers on fish bacteria with Louis Olivier (1854–1910), a Louis Pasteur's pupil.^{39,40,41,42} He also published a very surprising bacteriology-fiction short story under his writer pseudonym Charles Epheyre in 1890.⁴³ Later in 1914, he anonymously won the competition launched by the French Académie des Sciences with the best poem on the glory of Louis Pasteur.¹² On his side, Héricourt published a

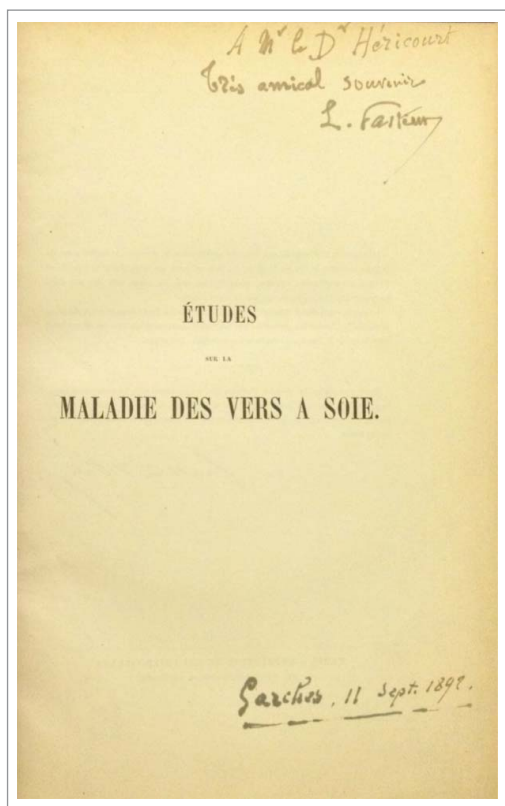


Figure 2. Dedication of Louis Pasteur to Jules Héricourt, at the front of his emblematic book *Études sur la maladie des vers à soie* (Fonds Watier, Rabelais Foundation; University Library of Medicine, Université François-Rabelais de Tours).

first scientific review on the pathogenic role of microbes in 1884,⁴⁴ popularizing the theories of Louis Pasteur, while devoting himself to agents of cholera,^{45,46,47,48,49,50,51} and tuberculosis.^{52,53} It is also established that Héricourt had personal contacts with Louis Pasteur⁵⁴ (Fig. 2).

Formulation of the principle of serotherapy

In 1888, Richet and Héricourt isolated by chance a bacterium they called *Staphylococcus pyosepticus*, probably a strain of *S. aureus*. After a few experiments, they noticed that dogs were naturally resistant to this bacterium, whereas rabbits were susceptible and died.^{55,56} They also showed that it was possible to induce an acquired immunity against *S. pyosepticus* by vaccinating rabbits in accordance with Pasteurian procedures: “*les effets virulents du St. pyosepticus comportent une vaccination*” (“*the virulent effects of St. pyosepticus carry a vaccination*”).⁵⁷

Influenced by Chauveau’s works, and using like him the experimental approaches recalling the ones of Claude Bernard’s school, they hypothesized that immunity could be transmitted from dogs to rabbits through blood. But there was a fundamental difference with Chauveau’s experiments: in contrast to him, Richet and Héricourt decided not to use infected blood, but blood from healthy dogs. Their experiments were described in an announcement read on the 5th of November 1888 at the *Académie des Sciences* by Aristide Verneuil (1823–1895), of whom Charles Richet was a pupil. After having transfused rabbits with dogs’ blood, they inoculated them 36 hours later with *S. pyosepticus* and made 2 observations: canine blood transfusion appeared to confer

immunity against *S. pyosepticus*, and this immunity was stronger if the donor animal had been – accidentally – inoculated by *S. pyosepticus* a few months before. They attached great importance to this second point: “*Il nous semble donc assez probable que le sang des chiens inoculés précédemment avec le Staph. pyosepticus, puis absolument guéris, confère une immunité plus complète que le sang des chiens intacts*” (“*it seems to us quite likely that the blood of dogs that have been previously inoculated by Staph. pyosepticus, then that have absolutely recovered, gives a greater immunity than intact dogs’ blood*”). In other words, the blood of vaccinated dogs conveys an acquired immunity, which can be transmitted. Eventually, Richet and Héricourt did not hesitate to generalize their discovery: “*cette influence du sang de chien [...] s’étend peut-être à d’autres microorganismes (le charbon, la tuberculose)*” (“*this influence of dog’s blood [...] maybe applies to other microorganisms (anthrax, tuberculosis)*”).⁵⁸

The 2 scientists had thus discovered a new immunization method against infectious diseases, based on a transfer of humoral immunity from a resistant animal to a sensitive animal. At this time, Héricourt and Richet believed it was possible to transfer what is now called innate immunity as well as acquired immunity. Nevertheless, it appears undeniable that the general principle of serotherapy, even taken in a restrictive sense of acquired immunity, is settled in this paper published in November 1888.

Application of this new method by Richet and Héricourt

Fully aware of the great importance of their discovery, in spite of their colleagues’ indifference,⁵⁹ Richet and Héricourt quickly decided to apply it to human diseases. After having hesitated between diphtheria, anthrax and tuberculosis, they chose the latter since “white plague” was a huge problem of public health. In hindsight, it is obvious that this was the worst choice: immunity against tuberculosis is now known to be cell-mediated and not antibody-mediated but, more importantly, they had no possibility to induce an acquired immunity, even in animals. Their first experiments (1889–1890) were therefore focused on blood transfer of innate immunity. Considering that dogs were said to be resistant to tuberculosis, Richet and Héricourt first tried to transmit their innate immunity to rabbits, using dogs that had never been exposed to Koch’s bacillus. They found that dog’s blood transfusion seemed to slow the progression of tuberculosis.^{60,61,62,63,64} Shortly after, other French researchers performed similar experiments, attempting in 1890 blood transfers of innate immunity from goats to humans (Fig. 3).

Richet and Héricourt’s area of concern, however, was to find a way to obtain an acquired immunity that could be transferred; in other ways, they had to find a mean to vaccinate against tuberculosis. They first tried to administer into rabbits avian mycobacteria (given by André Chantemesse (1851–1919)), which were killed by heating, in a typical Pasteurian frame of mind.⁶⁵ Then in September 1890, Richet and Héricourt reported having inoculated a dog with virulent bacilli; after a few days, the dog’s blood, supposed to carry an acquired immunity, was injected to rabbits, which seemed to have become more resistant to tuberculosis.⁶⁶

Consequently, at the end of November 1890, Richet and Héricourt had already applied their method to 2 microorganisms,



Figure 3. Transfusion of blood from a goat to a consumptive (tuberculous) woman by Samuel Bernheim (1855–1915) (*L'illustration*. 1891 Mar 7;2506:213. Fonds Watier, Rabelais Foundation; University Library of Medicine, Université François-Rabelais de Tours). Samuel Bernheim, transfusing goat's blood directly to humans, tried a variant of the method of 2 researchers from Nantes (France), Georges Bertin (1833–1916) and Jules Picq.⁸⁹ Bertin and Picq worked on blood transfusion against tuberculosis from 1890.⁹⁰ Like Richet and Héricourt, they focused on this dreadful illness, but contrarily to them, they only tried a transfer of innate (natural) immunity, considering goats as naturally resistant against tuberculosis. Bertin and Picq are the inventors of the word "hématothérapie," which was widely used in France at that time.⁹¹ They were also the first to perform a blood injection (subcutaneously) to a human being with tuberculosis, on the 3rd of December 1890.⁹² This operation caused a sensation worldwide, as witnessed by a *New York Times* article in January 1891.⁹³

S. pyosepticus and Koch's bacillus. Their interpretation of the transfer of immunity is quite interesting. Using reasoning similar to that of German scientists, they put forward a "humoralist" hypothesis: "le sang de chien contient des substances qui passent dans les tissus du lapin et qui, par leur action chimique propre, s'opposent au développement du microorganisme" ("dog's blood contains some substances which pass into the rabbit's tissues, and which by their own chemical action oppose to the development of the microorganism").⁶⁷ However, it is of note that all their experiments were performed with whole blood; Richet and Héricourt reported to have used blood serum instead of whole blood only on December 6, 1890,⁶⁸ which was two days after Behring's seminal publication of serotherapy.⁴ The use of serum was obvious for the German school, since Emil von Behring had shown in 1888 that blood bactericidal activity is borne by the serum.⁶⁹ However, the first researchers who used serum in the context of immunity transfer seem to be Ogata and Jasuhara, from Tokyo, in June 1890 (cited in ref. 70).

Richet and Héricourt's anticancer serotherapy

In 1895, while Behring's serum against diphtheria was highly successful, Richet and Héricourt, discouraged by their failure in tuberculosis, tried to develop a serum against cancer, thought to be an infectious disease.⁷¹ As was mentioned, this episode has already been described by several historians, but it is important to report it here again, not only because it constitutes an original work from Richet and Héricourt, but because it offers the opportunity to make new relevant observations and to formulate bold scientific hypotheses, shedding light on the original scientific approach they adopted.

After having immunized a donkey and 2 dogs with extracts of an osteosarcoma, Richet and Héricourt collected the sera and injected them into 2 patients, one having a cancer of the

thoracic wall and the other having a tumor of the upper abdomen. After a few weeks of daily injections, both patients showed a considerable decrease of their tumor's volume and an improvement of their general condition.⁷² These results were reported to the *Académie des Sciences* in April 1895 and received a warm welcome. Many physicians, in particular René Boureau (1854–1936) from Tours, tried to reproduce Richet and Héricourt's experiments.⁷³ Anticancer serum was shown to improve patients' conditions and sometimes to temporarily reduce the volume of the tumors (facts that were observed by many investigators, rather surprisingly), but not to stop disease progression.^{74,75}

Richet and Héricourt eventually abandoned the field of serotherapy to dedicate themselves to other studies (Fig. 4). It is, however, interesting to point out that Richet and Héricourt's anticancer serum, based on a wrong hypothesis and a lot of naivety regarding such a complex disease, really anticipated the current fantastic successes of monoclonal antibodies in cancer. Very intriguingly, Héricourt's understanding about the way their anticancer serum could be efficient, stated in 1899 and probably inspired by other authors' thoughts (in particular Charles Bouchard (1837–1915),⁷⁶ Elie Metchnikoff (1845–1916) and Emile Roux (1853–1933)⁷⁷), is somewhat visionary: "ce secours dont l'organisme a besoin [pour triompher de la

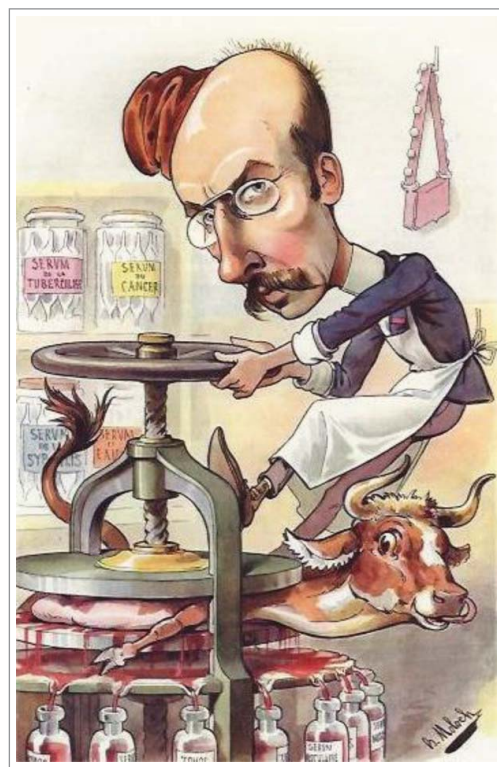


Figure 4. Caricature of Jules Héricourt published in the issue #75 of *Chanteclair* in 1911 (Fonds Watier, Rabelais Foundation; University Library of Medicine, Université François-Rabelais de Tours). Just after their works on serotherapy, Richet and Héricourt set up a raw meat juice-based therapy against tuberculosis, which they called "zomothérapie." This picture shows Héricourt squeezing out raw meat juice with a printing press. In the background, some various sera phials remind his contributions to serotherapy (tuberculosis, cancer, syphilis). A cartridge pouch on the wall (pink-colored because of the "Revue rose," nickname of the "Revue scientifique" for which Héricourt was successively secretary, chief editor and manager, from 1887 to 1903) evokes the military past of Héricourt.

maladie], le sérum le lui apporte; et les phagocytes y trouvent le stimulant nécessaire à leur insuffisante activité. C'est l'appoint qui décide la victoire en leur faveur" ("the serum provides the organism with the assistance he needs [to beat the disease]; and the phagocytes find there the necessary stimulus to their insufficient activity. This contribution determines the victory in their favor").⁷⁸ Indeed, the current use of antibodies targeting cancer cells and recruiting immune effector cells to favor cancer cell killing,^{79,80} or that of immune checkpoint inhibitors waking up these effector cells,⁸¹ are really modern transpositions of Héricourt conceptions.

Anticancer serotherapy also gave Richet and Héricourt the opportunity to describe some adverse reactions of serotherapy. They had first mentioned one case of pain and "two or three" cases of pruritus after serum injection in 1891,⁸² being probably the first to do so. Their description with the anticancer serum in 1895 is more precise: "*Ces injections de sérum [...] produisent vers la troisième ou quatrième injection, rarement plus tôt, quelquefois plus tard, une éruption urticaire, érythémateuse, comme en produisent d'ailleurs tous les sérums [...]*" ("These serum injections [...] induce around the third or the fourth injection, rarely earlier, sometimes later, an urticarial, erythematous rash, as anyway all serums do [...]").⁸³ Richet and Héricourt therefore described typical cases of what will be called later "serum sickness." Type 3 hypersensitivity reactions related to serum were mentioned by several authors as early as the mid-1890s,⁸⁴ but they were clearly characterized in 1905 by Clemens von Pirquet (1874–1929) and Béla Schick (1877–1967) as serum sickness.⁸⁵ Héricourt and Richet also noted: "*Dans quatre cas, l'injection a provoqué des accidents syncopaux (rapidement dissipés) dont la cause nous est encore inconnue*" ("In 4 cases the injection induced syncopal accidents (quickly disappeared), the origin of which remains unknown to us").⁸³ The nature of these syncopal accidents remains more uncertain: anaphylactic shocks or, in this context of anticancer serum, "cytokine-release syndromes" (CRS)? In 1899, Héricourt better developed the clinical symptoms: the dry cough followed by dyspnoea and face cyanosis he described⁷⁸ would rather evoke the laryngeal edema that characterizes CRS.⁸⁶

Discussion

The 2 French physiologists always claimed priority for the discovery of serotherapy, but Behring never acknowledged it and, in a quite discourteous way, quoted their works only to discredit them.⁸⁷ At that time, many scientists agreed that Richet and Héricourt were right, even in Germany, as witnessed by an article written in 1893 by another pupil of Koch, Carl Fraenkel (1861–1915), where he supported Héricourt and Richet's claim for priority.⁸⁸ Of course we cannot rule out the possibility of a rivalry between Fraenkel and Behring, whose successes triggered many jealousies, the most famous being the one from Koch himself. But Fraenkel was right, anyway, as clearly shown in the preceding paragraphs. In Behring's defense, it is conceivable that he never heard of Richet and Héricourt's works before 1890, considering that he reached the discovery of serotherapy with a totally different turn of mind than theirs. Besides, it is undisputable that the first proved clinical success of serotherapy must be attributed to Emil von Behring, and these successes

fully justify his Nobel Prize. He also revolutionized the immunization concept, using toxins instead of microbes, a rupture from the Pastorian mindset, which allowed Paul Ehrlich to develop his famous side-chain theory.³ Nevertheless, Behring did not deserve this award as "the pioneer" of serotherapy, according to the imprecise words of Prof. Mörner pronounced at the Nobel Prize ceremony,¹¹ and therefore unfortunately engraved in marble.

Beyond this question of priority, we have shown the role of the French School of Physiology in formulating the early concepts of immunity, particularly humoral immunity, a role that was neglected due to the radiance of the Institut Pasteur on the one hand, and to the triumph of the German School on the other. The trajectory followed by Héricourt and Richet is indeed probably the best illustration of the "physiologization of pasteurism" theory: they were great admirers of Louis Pasteur and had already some experience in bacteriology when they started addressing questions of antimicrobial immunity with experimental approaches typical of those of the French school of Physiology. In this way, we can consider that their works, and that this movement, led to the birth of a new discipline, Immunology, comprising clinical Immunology with the first descriptions of adverse effects (hypersensitivity reactions) of serotherapy and later of course, for Charles Richet, the discovery of anaphylaxis. They were, however, unlucky in their attempts to translate this knowledge into medical applications, neither with tuberculosis nor cancer, but they already sensed the potential of their discovery in Immunotherapy.

Our study also led to a rather unexpected finding, *i.e.*, that some French physiologists like Maurice Raynaud addressed the question of immunity just a few months after Louis Pasteur formulated his germ theory. Moreover, the physiologist Auguste Chauveau discovered the pathogenic role of microbes before Louis Pasteur, in total conflict with the "physiologization of the pasteurism" theory formulated by Jacques Léonard.^{14,15} It rather appears that Bacteriology like Immunology arose at the interface between Chemistry (Louis Pasteur; German School) and Physiology, and that both probably brought their own specificities.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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