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# Duclaux, Chamberland, Roux, Grancher, and Metchnikoff: the five musketeers of Louis Pasteur.

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**Running Title**: The five musketeers of Louis Pasteur

## ABSTRACT

The Institut Pasteur was created thanks to worldwide generosity with the aim to welcome and treat rabies patients, to provide a place for scientific research and to offer new teaching programs in microbiology. Louis Pasteur invited his main collaborators, who had accompanied him during his previous investigations at École Normale Supérieure, to join him in his new institute. They contributed to the principle discoveries of Pasteur, such as the fight against spontaneous generation, the identification of the ferments of putrefaction, the fight against the silk worm disease, the research on wine and beer, and the set-up of the first vaccines against avian cholera, anthrax, swine erysipelas and rabies. There were two scientists, Émile Duclaux and Charles Chamberland, and two medical doctors, Émile Roux, and Joseph Grancher. In addition, two Russian scientists were invited to join the Institute and to head a research laboratory, Élie Metchnikoff and Nikolaï Gamaleïa, the later will finally never join the institute.

## 1. The birth of Institut Pasteur

In 1857, Louis Pasteur was 35 when he is nominated administrator in charge of the direction of studies at the École Normale Supérieure, rue d'Ulm in Paris. He left his professorship and his position as Dean of the Sciences University in Lille. But in 1867, Pasteur is considered too authoritarian both by his colleagues and by the students, and facing numerous contestations, he resigned from his position as administrator. He then received a professorship at the Sorbonne and at the École Normale Supérieure , where he was entrusted with the direction of the newly created physiological chemistry laboratory. In 1868, Pasteur suffered a severe brain stroke that paralyzed his left side, but he partially recovered.

After his main investigations against the spontaneous generation theory, on silk worm disease, fermentation, wine and beer, Pasteur initiated his investigation on infectious diseases and how to prevent them by prior injection of an attenuated microbe. In 1881, at the international medical congress in London, Pasteur used the word "vaccination": "*I gave the term vaccination an enlarged meaning, that science I hope will consecrate as an homage to the merit and immense services rendered by one of the greatest men of England, your Jenner. What joy for me to glorify this immortal name on the very soil of the noble and hospitable city of London*". But, he could have also paid tribute to Charles-Paul Diday (1813-1894) who had coined the word "vaccination" in 1849, when he reported his amazing works on his anti-syphilitic vaccine. Diday vaccinated 16 patients suffering a genital chancre, by performing an inoculation with the blood from a patient with a tertiary syphilis (Ref. 1). Of course, Diday was also referring to the work of Edward Jenner who prevented human cow pox thanks to the use of bovine vaccinia. In 1879, Pasteur's first vaccine aimed to protect against avian cholera (a bacteria latter called *Pasteurella multicoda*). In 1881, Pasteur designed another vaccine against *Bacillus anthracis,* a major threat in sheep farming. In 1883, he proposed a vaccine against swine erysipelas (*Erysipelothrix rhusiopathiae*). Working then on rabies, he set up a vaccine which was successfully employed for the first time in humans on the 6$^{th}$ of July 1885 on a nine-year-old Alsatian shepherd, Joseph Meister. Jean-Baptiste Jupille was the second child to be treated and saved by the vaccine on the 20$^{th}$ of October 1885. Both would become the door-keepers of the future Institut Pasteur, and Joseph Meister, would eventually kill himself when the Nazis entered in Paris.

The impact of these successes was worldwide. Many doctors and scientists were sent from different countries to learn the technology to prepare such a vaccine against a mostly lethal infection. Anti-rabbies institutes were created all over the world [1]. In 1886, 2,682 people from France and from abroad were treated at rue d'Ulm, with a 1.34% mortality. In 1887, 1,778 people were vaccinated with an improved 1.12% mortality rate (Ref. 2). It was then decided to raise an Institute in Paris which purposes: "the treatment of rabies according to the method developed by M. Pasteur" and "the study of virulent and contagious diseases". In 1887, fundraising

[1] Saint-Petersburg, Odessa, Moscow, Varsaw, Torino, Milano, Palerma, Napoli, Wien, Barcelona, Bucharest, Malta, Constantinople, La Havana, Rio de Janiero, Buenos Aires, Chicago

for the Institut Pasteur began, with donations from many countries. The major donators were namely: Alexandre III, emperor of Russia, Don Pedro II, emperor of Brazil, The Sultan of Constantinople, and wealthy French people such as the baron Alphonse de Rothschild, or Mrs Boussicaut. But many French people, even very modest ones, also contributed to the funding. The subscription ended to 2 586 680 francs, enough to cover the costs to purchase the land, construct the buildings and to fund three years of operating costs, leaving a grand total of 1 022 894 francs founding money. The piece of land, close to the Montparnasse railway station, which belonged to a family of market gardeners for 150 years was finally chosen. It was considered more appropriate than the one offered by the city of Paris. The architects, M. Eugène Petit and Félicien Brébant refused any payment, and designed a Louis XIII stylish building with large windows and brand-new organized laboratories. The apartment of Louis Pasteur was included within the main building. An out-patient clinic was situated on the ground floor with a large waiting room, a room for bandages, a room for inoculation, a room to gather the administrative archives, and a room for preparing the rabbit spinal cords. In addition to the laboratories within the main building, other rooms were dedicated to photographs, surgery, dissection, and to house incubators. Furthermore, on the first floor, two large rooms were designed for teaching, and a spacious library that was also aimed to welcome official events, was situated facing Pasteur's apartment. Annexes to house workers, storage buildings and animal facilities (for dogs, birds, rabbits, guinea-pigs, horses, and for rabid animals) were built or restored on the same campus.

It was decided that six research units would be housed in the main building under the supervision of six renowned scientists, two of them being medical doctors: Professeur Joseph Granger, MD, Dr. Émile Roux, MD, Dr. Émile Duclaux, Dr. Charles Chamberland, Dr. Élie Metchnikoff and Dr. Nicolaï Gamaleïa. Most of them had been collaborators of Louis Pasteur, at the École Normale Supérieure, rue d'Ulm, for many years (**Table 1**), but the two Russian scientists were a more recent encounter and a testimony of Pasteur's love for Russia. Finally, Nicolaï Gamaleïa, although present on the day of the inauguration, and whose name was mentioned during the talks will never join the institute. These five men undeniably participated in the reflection around the design and organization of the institute. In June 1887 the first statutes of the institute, recognizing it of public utility were signed by 16 members including our five musketeers, the first generation of pasteurians. The institute was

created not only with the aim to welcome rabies patients and to play a role in national public health, but also to favor scientific research, as well as to offer new teaching programs, particularly within the emerging microbiology field. Another aim was to position the institute within the international scientific community, and a new journal ("Les Annales de l'Institut Pasteur") was launched the year before the opening of the Institute (Ref. 3). Émile Duclaux was nominated as the Editor-in-Chief and financed the journal. In 1887, the other four French partners of the Institute were members of the Editorial Board (**Table 2**). Very rapidly, the institute extended to different countries: in 1891, Albert Calmette founded the 1st institute abroad in Saigon (Vietnam) where he studied vaccines against smallpox and rabies. In 1894, Alexandre Yersin was sent to Hong Kong, where he discovered the plague bacillus. He later then created a laboratory in Nha-Trang (Vietnam).

## 2. Inauguration of the Institut Pasteur

In the garden, the bronze statue of Jean-Baptiste Jupille fighting with a rabid dog to protect his friends, made by the French Sculptor Émile-Louis Truffot (1843-1895), witnesses the arrival of many ministers, senators, deputies, ambassadors and representatives of foreign countries, journalists, and many medical and scientific celebrities from both Medical and Scientific Academies. The Institute is decorated with French flags. The ceremony takes places in the big library, which can welcome up to 600 people. The room is decorated with the sculptures of the main donators. By half-past-noon, the room is already so full that the guest can no longer enter in the library, and gather in the vestibule and on the steps. Even Dr. Roux, is unable to find a place in the library. By one-thirty, Sadi Carnot (1837- murdered in 1894), the 5th President of the French Republic, arrives in a carriage in front of the steps, welcomed by the Republican Guard which plays the Marseillaise. Mr. Pasteur, after having walked down the steps to meet the President, takes place in an armchair just close to that of the President. The first talk is given by M. Bertrand, General Secretary of the French Academy of Sciences. He recalled a statement by Émile Verdet, a French physicist who worked at École Normale Supérieure, told him a long time ago: "*Pasteur, does not know the limits of science. I fear for his sterile efforts! He loves insoluble problems*." He concluded: "*The problems which, for half a century have tormented your mind without rest, are no longer insoluble nowadays. It is to thank you in the name of science, to rejoice in the name of humanity, to glorify all of*

*us together in the name of France, that we are together today*." Then, Prof. Grancher, the medical doctor who supported and assisted Pasteur in his first rabies vaccine injection in humans gave a long and detailed talk about the rabies vaccination and addressed the different discoveries of Pasteur in the field of infectious diseases. He paid tribute to Pasteur's collaborators, Roux and Chamberland who contributed to his famous investigations on anthrax and rabies. He recalled how an official committee was sent from England to enquiry about the rabies vaccine. Initially incredulous, the main reviewer, Sir Victor Alexander Haden Horsley (1857-1916), an accomplished physician, concluded with his committee that Pasteur had indeed discovered a preventive treatment for rabies similar to the cow pox vaccine. He recalled how his colleague, Dr. Alfred Vulpian (1826-1887) had encouraged Pasteur to apply his rabies vaccine to human beings. And finally, he provided statistics to illustrate the amazing success of the rabies vaccine all over the world. The following talk was given by M. Albert Christophle (1830-1904), governor of a French bank who was the treasurer of the project. He was nicknamed "the enthusiastic fairy", for his glorious national and international effort to gather the funds to raise the institute: He also mentioned how, Pasteur, Chamberland and Roux gave up their own royalties on the vaccines (anthrax and rabies) to contribute to the funding of the institute. He ends his talk claiming his admiration and love for Pasteur.

Too much affected, Pasteur asked his son, Jean-Baptiste, to read his talk. He pays tribute to the international generosity, to his Masters who are not here anymore, and to the six collaborators who will join the institute. About research, he made an interesting statement: "*To believe that we have found an important scientific fact, to have the fever to announce it, and to constrain days, weeks, sometimes years of fighting oneself, striving to ruin one's own experiences, and proclaiming one's own discovery that when you have exhausted all the contrary assumptions, yes, it is a difficult task*." He concludes his talk with a personal thought, illustrating his trauma about the last 1870's war: "*I would say that two contrary laws seem today in struggle: a law of blood and death which, imagining every day new means of fighting, obliges the peoples to be always ready for the battle field, and a law of peace, of labor, of salvation, which thinks only of freeing man from the scourges which besiege him. One seeks only violent conquests, the other only the relief of humanity.*" Warm cheers greet his eloquent speech.

Surprisingly, the President of the French Republic, Sadi Carnot, did not say much and only announced that, after the request of Pasteur, he had promoted Grancher and Duclaux as officer of the Legion of Honor, and Chantemesse, a medical doctor who worked with Pasteur, as a knight of the Legion of Honor. Brébant, the architect was made officer in the order of Academic Palms by Edouard Lockroy, the Minister of Public Instruction (of note the other architect, Eugène Petit, had passed away before the inauguration). Then, Pasteur invited the President to visit the Institute (REF. 4, 5).

## 3. A new conceptual organization of research

The personality of Louis Pasteur has undeniably marked the history legacy of his institution. His initial choices weighed heavily on its destiny. During his teaching career he suffered from administrative red tape and too rigid tutelage of the state. The science of that time was confined to the academic field, to pure theoretical teaching without the experimental complement. Most probably, the creation of a structure like the Institut Pasteur existed for a long time in Pasteur's mind. He wanted to spare his successors the need of "begging" with the public authorities. In a letter of January 12$^{th}$, 1886 to the Comte de Laubespin who had just given him a gift of 4000 francs, he mentioned his intent to founder a model establishment in Paris without recourse to the State, with the help of donations and international subscriptions. For Pasteur, it was important to create an attractive place for French and foreign scientists, linked with medicine and similar to those already existing in Germany.

The statutes of the IP reflect its perspectives and wishes. Before being adopted by the Council of State, they went through very tentative stages of elaboration. Pasteur had a clear vision of what a research laboratory should be, but less about what an institute should be. Under the influence of friends who held high office in the administrative (especially the State Councilor Tisserand, the Ministry of Agriculture), he charged his collaborator Joseph Grancher to negotiate with the government, a recognition of Institut Pasteur as a "public utility" institution. The decree and the statutes were accepted on June 4$^{th}$, 1887. The objectives of the Institute remain those of the Limited Company. In a letter to the Minister of Public Education (Liard, December 22, 1888), he seems to want to use the contribution of the state only in case of budget deficit. The first financial statements mention the

contribution of the State as a regular income finally required for a balanced budget**.** Furthermore, the profits from the sale of vaccines, a point which in the statement of the statutes was not a priority, will gradually steer the Pasteur Institute towards a commercial role.

Beside the statutes, Pasteur also thought about the organization of the staff and entrusted his thoughts to Dr. J. Grancher, in a letter of March 31st, 1887 "*Each head of laboratory will obviously be quite free from his personal work, although obliged however, to certain rules for its expenses. We will need the equivalent of a bursar in a high school. The Assistant Directors will not have to intervene in the works of the head of laboratories, but they will have to adjust and set up the lessons and student work programs in the laboratories, in conjunction with the head of laboratories. We will succeed, I hope, easily to avoid conflicts, by appropriately regulating the attributions and by delimiting the subjects of the studies, either for the young doctors wishing to learn the principles, or for the doctor-professors, scientists, who will want to do personal research and will have distinct and separate investigation rooms.*" So, if Pasteur's first concern was financial, it is clear that he wanted his successors independence and freedom of work. In an article published in the "Revue Scientifique" of 1874, he wrote "*there is no category of science to which we can give the name of applied sciences. There is science and the applications of science, linked together as a fruit to the tree that bore it*."

Thus, quite a new concept emerged, the Institut Pasteur would be a private institute, depending as little as possible on the State financial support, and instead based on donations, and incomes from its own applied research, and providing a teaching activity, independent from the University but offering new areas of courses with practical works. The very first course on microbiology, established by Dr. Emile Roux, started in 1889, and soon became a must for physicians and scientists from all over the world.

4. The musketeers

Pasteur gathered personalities from different origins, backgrounds and disciplines, whose scientific styles have combined their specificities in a beneficial and complementary way. Pasteur had offered to Duclaux, Chamberland, Roux and Grancher, his main collaborators who were working with him at the École Nationale Supérieure, the possibility to head a research laboratory or a medical entity. All had

been closely associated with the works of their Master who had acquired so much fame. The connection with Metchnikoff was far more recent, since it followed a visit that the great Russian Scientist had made in 1887 when he was looking for a place where to work, after he had left the Bacteriology Institute that he had chaired in Odessa. After having met Robert Koch in Berlin, Metchnikoff made the decision to join the new institute. Together, with the putative Gamaleïa, the Russian connection was a great chance for the other members. Both were speaking Russian, German, French, and English while the French partners did not master foreign languages. Amazingly, a common tragedy links Metchnikoff, Roux and Duclaux. All three had lost their first wifes: Metchnikoff lost Ludmilla Fédorovna in 1873 because of tuberculosis (Ref. 6). Likewise, in 1878, Roux lost Rose A. Shedlock because of tuberculosis (Ref. 7). Both died in Madeira, a place commonly visited with the hope to offer better air and sunny days to tubercular patients (A famous scientist, Paul Langherans also died in Madeira in 1888, due to a kidney complication of his tuberculosis). In 1880, Duclaux lost Mathilde Briot, because of puerperal fever, following the birth of their third son (Ref. 8). Most probably these misfortunes have favored the relationship and friendship between them.

a. Émile Duclaux

Émile Duclaux is the first of the five musketeers to have joined Louis Pasteur. After his aggregation of Sciences at École Nationale Supérieure, he joined his laboratory in 1862 at the time the fight against the spontaneous generation was going on (ending to the demonstration of micro-organisms within the environment and the air). He participated to the demonstration on wine making by Pasteur, who had moved in laboratory in Arbois (**Table 3**). Soon he was nominated as professor of chemistry at the University of Clermont-Ferrand (1867), and then as professor of physics in Lyon (1873). Back to Paris in 1878, he taught physics and meteorology, and ran a course of biological chemistry at the Sorbonne (Ref. 9). After the opening of Institut Pasteur, Duclaux transferred his course to the institute as well as the laboratory of physiology-chemistry he headed at Ecole des Hautes études. He was entirely associated with Pasteur's work, even if he was rarely co-author in the publications of his Mentor. He only co-signed two papers with Pasteur, when Roux and Chamberland had co-signed together some 60 papers. He covered a broad range of subjects. His first works were on alcoholic fermentation, which was the topic

of his thesis. He worked on the influence of air and temperatures on the birth and the life of silk worms. He studied grape phylloxera, addressing its geographical spread and the means to prevent it. He investigated molecular balance and capillary tension of liquids. From 1877 to 1883, in response to the request of the Ministry of Agriculture he investigated the preparation of Cantal cheese and on its diseases. He then investigated gastric, pancreatic and intestinal digestion. He also made some personal investigations on the production of enzymes by *Aspergillus* and *Penicilium,* establishing that the production of enzymes is related to added nutrients, known as enzymatic and adaptation observed in bacteria, yeasts, and molds. It was a most important contribution, which was poorly recognized due to its lost within his huge treatise on microbiology (Ref. 9). From May to July 1879, he personally contributed to an important paper of his Mentor on the demonstration of germs in the etiology of some infectious diseases (Ref. 10). He repeatedly provided samples from his own boils! From those, Pasteur identified the presence of *Staphylococcus aureus,* which he also found in bone samples of a 12 year old girl suffering osteomyelitis (Ref. 10).

Due to Pasteur old age and poor health, Duclaux was the master piece, in establishing the Institute, and its running. As mentioned previously, he created the "*Annales de l'Institut Pasteur (Journal de Microbiologie)*", assuming the operating cost from his own money and all the editing work. In addition of being the official channel for the work carried out in Pasteur's house, there were also numerous reports on articles published elsewhere. After his death, Institut Pasteur, under Roux's proposals, bought the journal to his heirs and ensured them a comfortable life annuity (Ref. 11). Duclaux was also playing the role of scientific facilitator, in addition to his own research activities and teaching duties at the Agronomic Institute and at the Sciences University. He organized a cafeteria/restaurant "The golden microbe", a truely scientific and social place. Duclaux would have loved to operate a brewing school and to sell beer yeast. As it was against Pasteur's view, he eventually gave in. Two years after its opening,an extension was built to meet the need to make anti-tuberculosis vaccine. But it was only in 1896, that Duclaux favored the purchase of land just on the other side of the street, thanks to the generous donation of Mrs Lebaudy. On May 1899, a new land was bought, extending the campus until rue de Vaugirard. Duclaux played a key role in the establishment of a hospital specifically designed to host patients with infectious diseases, and a new research building, both

inaugurated in 1900. Thus, Duclaux finalized his dream to open a new research building devoted to biological chemistry

Duclaux logically succeeded Pasteur, after his death on September 28th, 1895, and remained the director until his own death, on May 2nd, 1904. In 1888 he became member of the Sciences Academy, and in 1894, member of the National Academy of Medicine. He was made “Commander” of the Legion of Honor in 1895. Co-founder of the “French League for the Defense of Human and Citizen's Rights", he was the vice-president and took an active part during the Dreyfus affair. Duclaux wrote few books including one on his beloved master published in 1896: "*Pasteur the story of a mind*".

b. Charles Chamberland

Chamberland is the handyman, the inventor and the hygienist in our group of five. In 1875, Charles Chamberland joined the laboratory of physiological chemistry of Louis Pasteur as an assistant one year after receiving his aggregation from the École Normale Supérieure. He was commissioned to repeat an experiment carried out by Henry Charlton Bastian (1837-1915), professor of pathological anatomy at London’s University College Medical School, a supporter of the theory of spontaneous generation, and to demonstrate that the experimental approach and the conclusions were false. Pasteur associated him with his publication on the "Theory of germs and its applications to medicine and surgery" in which they show that each disease corresponds to a particular germ (1878). He was a valuable and recognized collaborator for Pasteur, since he was associated with the works on the etiology of anthrax, on anthrax vaccination, vaccination against swine erysipelas, and anti-rabies vaccination. From 1878 to 1888, he co-signed on 85 papers with Pasteur. Their collaboration soon turned into friendship, and Pasteur even agreed to be his wedding witness in 1889. Charles Chamberland established the rules of the sterilization of culture media, rules which he developed in his thesis of sciences (1879). As a very ingenious and inventive person, he improved the sterilization methods and the laboratory equipment, the Chevallier-Appert water bath with pressure gauge. Furthermore, he has built a disinfection oven, an autoclave, a tool that has become indispensable in laboratories and in industry, not to mention the invention of porous walls made of porcelain clay in the hollow cylindrical shape (candle filters) aimed to retain the particles suspended in the liquids.

Chamberland has played a major role in the preparation of the Pouilly-Le-Fort experiment, which allowed the most successful and convincing demonstration of the anthrax vaccination in front of a general public. The nature of the vaccine against anthrax was never divulged by Pasteur and Chamberland. Pasteur was favoring attenuated vaccine by exposure of bacteria to air, while, in Toulouse, his rival, Henry Toussaint (1847-1890) had prepared an efficient vaccine using an antiseptic treatment with carbolic acid. In fact, Chamberland did use a vaccine that had been chemically treated, but using potassium dichromate. The need to prepare a huge quantity of doses was the pressure leading to create a spin-off vaccine, in addition to the research laboratory. Chamberland was in charge of the vaccine preparation establishing a kind of industrial production unit in a private laboratory, 14 rue Vauquelin, with the participation of four assistant chemists. Then the number of doses went from 164 000 in 1881, to 700 000 in 1882, with a further increase of 900 00 in 1885 (Ref. 12). But in 1882, a crisis occurred after reports of vaccination accidents. Indeed, the quality, the reproducibility, standardization and efficacy of the vaccine was not easily achieved, particularly when the preparations had to be sent abroad, in distant countries.

When the Institute opened, Pasteur entrusted to him the direction of the practical service, that of preparation of vaccines, supported in this task by his brother-in-law Charles Rebour. In this laboratory, he studies the "reports of microbia with hygiene". In fact, Chamberland, in addition to having solid knowledge in physics, had extensive knowledge in chemistry. He published extensively on antiseptic substances to determine the most effective methods for disinfecting objects and premises. He studied the microbicidal action of chlorine in the gaseous state or in solution of chloride of lime, but also the destructive power of essential oils and hydrogen peroxide. With his collaborator C. Jouan, he carried out studies on Pasteurella.

In 1885 he was elected as deputy from Jura and contributed to laws in public health and hygiene. In addition to his duties as head of department, he was also a member of the first editorial board of the Annals of the Institut Pasteur. In 1904, when Duclaux died, he became Deputy Director of the Institute. No doubt he could have had a great scientific and administrative influence for the Pasteur Institute, but disease killed him prematurely at the age of 57 due to lung cancer.

c. Émile Roux

In 1872, Émile Roux started his medical studies in Clermont-Ferrand and became the assistant of Émile Duclaux who was in charge of the chemistry lectures at the University of Science in Clermont-Ferrand. In 1877, Roux moved to Paris and pursued his medical studies at the military school of Medicine (Hôpital du Val de Grâce), but left before defending his thesis (maybe because of his difficulties with the military authority or because of his love affair with Rose A. Shedlock, herself a medical student). Meeting by chance Duclaux, he was asked by his mentor to assist him for the lectures he was giving on fermentation at La Sorbonne. In 1878, Pasteur asked Duclaux if he knew a medical doctor who could assist him in his studies on infectious diseases (Ref. 8); and Duclaux introduced Roux to Pasteur. In 1883, Roux became the deputy-director of Pasteur's laboratory at the École Normale Supérieure, rue d'Ulm. Since 1879, Roux had contributed to Pasteur's investigations on anthrax, then on rabbies. Between 1879 and 1884, Roux would become co-author of 74 papers with Pasteur. In 1883, he was sent to Egypt with Edmond Nocard (1850-1903), Isidore Straus (1845-1896) and Louis Thuillier (1856-1883) to study an epidemic of cholera. There, Thuillier died because of the cholera. During his investigation, Roux conceived that the vibrio of cholera discovered by Robert Koch gains its toxicity through the production of a soluble poison, a "ptomaïne". This concept was key when he undertook his investigation on diphtheria in 1888, together with Alexandre Yersin (1863-1943) (Ref. 13). In 1884, Friedrich Löffler (1852–1915), a collaborator of Robert Koch, isolated and cultured the bacterium identified by Edwin Klebs (1834–1913) an assistant of Rudolf Virchow. Soon after they were convinced that the disease was due to a toxin (Ref. 14). The validation of the hypothesis came from the work of Roux and Yersin. Between 1888 and 1890, they published three reports illustrating that the injected filtrate of cultures of Löffler's bacillus into guinea pigs, rabbits and pigeons would kill them (Ref. 15). In 1890, in Berlin, Emil Adolf von Behring (1854-1917) and Kitasato Shibasaburō (1853-1931) showed that sera obtained against the toxin could protect. Then, Roux introduced the use of horses to prepare the immune sera. A great step forward was taken when Roux at the Pasteur Institute began to use horses for immunization on a large scale to obtain serum against diphtheria toxin, a method that Behring immediately adopted. In 1894 with Louis Martin (1864–1946), his colleague of Institut Pasteur, and Dr. Auguste Chaillou (1866–1915), from Necker Hospital, he published the treatment of 300 children with a 50% decreased in mortality (from 50% to 25%). These results were achieved on a

devastating disease, "the strangling angel of children", as it was called which was killing thousands of young children and had a great impact. The Parisian newspaper 'Le petit journal' published a picture of Emile Roux saving a child on its front page (24 September 1894). The French daily newspaper 'Le Figaro' also echoed this success and launched for a call for donations. The newspaper gathered more than a million francs, which were more than welcomed by the research institute and to buy new horses (Ref. 14). In recognition of the discovery of the protective immunity provided by serotherapy, Emil von Behring was awarded, the first Nobel prize in medicine or physiology in 1901. In his Nobel lecture, Berhing paid tribute to his colleagues Löffler and Roux. Between 1901 and 1932 Emile Roux received 115 nominations for the Nobel Prize, but they were in vain. French medical scientists headed by Emile Roux were particularly far advanced with regard to the production of diphteria antisera and their clinical use. So far advanced, in fact, that some patriotic French journalists got it into their heads that this was a purely French discovery. Behring was quite upset. In this particular case he need not have worried since Roux, a thoroughly honest person, immediately explained the situation and gave all the credit to Behring. That was not all, when Roux was decorated with the Knight's Cross of the Legion of Honor, he refused to accept this honor unless his German colleague also received the same order. Consequently, in 1895, Behring was made Officer of the Legion of Honor (Ref.14). But, the serotherapy was just for therapeutic purpose, a vaccine was highly desired. Together with Gaston Ramon (1886-1963), they came to use an inactivated toxin (by formalin and heat treatment) that has kept its antigenicity. The concept of "anatoxin" was coined by Roux (Ref. 17). Later, Roux will also contribute to investigations on tetanus, tuberculosis, pneumonia and syphilis.

Roux was closely linked with the works associated with the creation of institute Pasteur before and after he headed his own unit "Microbie Technique". Most importantly he created the course. Fifteen students attended it in 1889, 42 in 1896. In addition to the scientist and the teacher, Roux was a technician. He designed aerobic cultures, set up the technique of microbial separation, invented instruments (tubes, boxes, pipettes Roux, ovens with regulators), and was one of the first to apply photography to microscopic preparation (creation of the microphotography laboratory). In a paper published in 1887, he detailed all means to apply photography to the study of microbes (Ref.18). He was also a hygienist. He contributed to disseminate the Pasteurian principles and led the "Higher Council of Public Hygiene"

for 20 years from 1908. Finally, he was an administrator. Deputy-director in 1895 then Director for 30 years from 1904 to 1933 of the IP. He favored the establishment of the international network of Instituts Pasteur worldwide (Algiers, Brazzaville, Martinique, Phnom Penh, Nouméa, Cayenne, Tehran, Hanoi, Athens, Kindia, Dakar, Guadeloupe…).

d. Joseph Grancher

Since the defense of his medical thesis on phthisis in 1872, Joseph Grancher had been working on tuberculosis. In 1880 he was awarded with the Lacaze prize of Medical Academy for this work. When Joseph Grancher met Pasteur, in 1884 at the 2nd international Congress of Medicine in Copenhagen, he was working in Necker hospital. During this congress in Denmark, he listened to Pasteur who was presenting his successful vaccination of dogs against rabies (Ref. 19-21). This event would change his career, as he became the medical advisor of Pasteur. Roux and Pasteur had been working on the rabies vaccine for more than three years, when on the 6th of July 1885, Joseph Meister, a 9 year-old boy was brought to Paris from his Alsatian village, bitten 14 times by a dog. Grancher was supportive to apply Pasteur's vaccine, for the first time to humans which had been proven efficient in dogs. If nothing was done, the child would almost certainly perish. Grancher make all the efforts to convince Pasteur. But Dr. Roux and Dr. Alfred Vulpian (1826-1887) were reluctant. But to save this child, Grancher brought his reputation and career into play, and he made the requested thirteen injections of dried spinal cord of rabid rabbits over ten days. Pasteur was sick and went to rest at his daughter's place near Avallon. Grancher kept Pasteur informed, sending him comforting telegrams about the health of the boy. A second opportunity occurred the same year when Grancher vaccinated Jean-Baptiste Jupille. On March 1886, 350 people had been vaccinated. In 1887, Grancher began publishing monthly detailed statistics of rabies vaccinations in the Annales de l'Institut Pasteur, of which he was a member of the Editorial Board. On January 1887, Grancher read a note in front of the Academy stating that after 1929 vaccinations, the mortality was 0.93% for a disease of which the mortality was at least 16%. But Michel Peter (1824-1893), member of the Medical Academy, conducted the sling against Pasteur while Grancher was in charge of the defense of the work of Pasteur, particularly because Pasteur, convalescing in Italy and then in Arbois, was absent during the rabies debate. During a trial initiated by the father of a

child who died after vaccination, Paul Brouardel (1837-1906), a medical examiner, and Dr. Roux lied about the cause of the death (which was due to rabies) to save the vaccination principle, and indirectly the life of thousands of people who will benefit from the vaccine. Naturally, Grancher was appointed head of the rabies service at the opening of the Institute, however in 1890, for health reasons, he moved away from the laboratory life, and André Chantemesse (1851-1919) supported him in the direction of his service until his death.

Grancher assisted Pasteur in the setting up of the Institution. An abundant correspondence between the two men testifies to his great involvement in the creation of the Institute (field purchases, drafting of statutes, public subscription, recognition of public utility). He was a stakeholder at every stage of the project, and diplomatically greatly facilitated the dialogue with the municipal and state authorities. Pasteur and Grancher were good friends, and Grancher was the godfather of his grand-son (Louis Pasteur Vallery-Radot (1886-1970)). But Grancher always modestly stayed in the shadow of the Master. Despite this retreat, Grancher has followed the evolution of the institute, being the secretary of the Board of Directors, then his Vice-President and President in 1905. He also continued to address the problem of tuberculosis, organizing the screening of the disease in public schools and establishing the rules within the hospital to prevent contagiousness. In 1903, he founded an association ("l'oeuvre de preservation de l'enfance contre la tuberculose") to fight and prevent tuberculosis.

e. Élie Metchnikoff

When Pasteur offered a laboratory to Elie Metchnikoff in his new institute, he was particularly inspired. Among the five musketeers, the most attractive scientist had been Metchnikoff, who, during his 28 years spent at Institut Pasteur, was joined by more than 100 trainees from all over Europe. Because of these foreign scientists working at Institut Pasteur, far right journalists wrote distasteful papers on "the institute of the wogs". Pasteur only met Metchnikoff in 1887, when the Russian scientist came to visit him at rue d'Ulm. He was looking for a place to work after he had resigned from the Bacteriology Institute in Odessa he was leading. His visit in Berlin to meet Robert Koch had been poorly supportive, and Metchnikoff made the decision to move to Paris. He joined the institute on time to attend the inauguration,

and his laboratory was the first to be functional. He was accompanied by his second wife, Olga, who was a gifted artist but who also became his laboratory assistant, publishing some works herself on anthrax vaccine and on germfree tadpoles. Olga was also very helpful to host and in organizing the stays of the foreign trainees. After having initiated his career as an embryologist, Metchnikoff made his main discovery on phagocytosis in 1882 while he was in Messina. The contribution of macrophages and microphages (the name given to the neutrophils) during infectious diseases has been his main conductive thread, and most of his trainees at Institut Pasteur contributed to this research (Ref. 22-24). But he also identified new macrophages such as the alveolar macrophages with Nicolaï Tchistovitch (1860-1926) and microglial cells, then called neuronophages, with Félix Mesnil (1868-1938) and Michel Weinberg (1868-1940). But Metchnikoff had also addressed all the processes associated with the function of the phagocytes. With Arthur Hugenschmidt (1862-1929), and Georges Gabritchevsky (1860- 1907) he studied chemotactism. The later coined the word pinocytosis. With Sir Marc Armand Ruffer (1859-1917), he studied efferocytosis. Of note, after his stay in Metchnikoff's laboratory, Ruffer would be the most fervent advocate of the phagocytosis process in UK. With Constantin Levaditi (1874 - 1953) they observed netosis. But the work of Metchnikoff, once at Institut Pasteur covered far wider field of investigation. Metchnikoff can be considered as the father of the microbiota, which he studied in humans and various animal species. He also promoted the use of probiotics and coined the word "gerontology". He demonstrated the link between certain bacterial metabolites and the occurrence of atheromatous plaque associated with ageing. With Eugène Wollman (1883-1943) and Michel Cohendy (1873-1940), they obtained germ-free flies and germ-free chicks, respectively. Finally, with Roux, he worked on syphilis, introducing investigations on chimpanzees. Their work ended to the proposal of calomel, a mercuric treatment that was proposed by the US army to its soldiers during world war I. The institute became thanks to its links with the Kindia station in Guinea, one of the very first place to investigate on chimpanzees. Furthermore, Metchnikoff wrote two philosophy books on optimism. A sense of life he had acquired later on after two attempts to kill himself, and many other similar ideas when he had to fight for the cellular immunity against the German school who was supporting the humoral immunity. The wise Nobel committee awarded both leaders, Paul Ehrlich (1854-1915) and Metchnikoff in 1908. Admirably, Metchnikoff also favored research on

humoral immunity in his own laboratory, and Jules Bordet (1870-1961) initiated works on alexin, a humoral activity, named “complement” by Ehrlich himself. These investigations of Jules Bordet were awarded with the Nobel prize in 1919. In 1914, Paul h visited the Institut Pasteur. In the Berliner Klinische Wochenschrift on March 16th, 1914, a few months before the war between France and Germany, Roux and Metchnikoff paid tribute to the work of Paul Ehrlich, illustrating the reciprocal consideration between the French and German scientists

In 1890, Metchnikoff joined the editorial board of the Annales de l'Institut Pasteur. Since the beginning of the course organized by Roux, he gave lectures on inflammation. Those gathered in a book published in 1892 were translated in English the following year. Wen, in 1904, Roux became Director of the institute, he nominated Metchnikoff as a deputy-director. But in May 1909, Metchnikoff sent a letter of resignation from this position to the President of the Administrative Council, arguing he had too many collaborators to supervise. It appears that his request was not taken into consideration since he remained deputy-director until his death, which happened in Louis Pasteur’s apartment on July 15th, 1916. For his 70th birthday, Roux said: “The Institut Pasteur owes you much, you brought the prestige of your reputation, and your work and that of your students have greatly contributed to its glory”.

f. The missing sixth: Nikolaï Gamaleïa

Nikolaï Gamaleïa (1859-1949), a Russian physician and microbiologist was present among the 600 people gathered in the library during the inauguration of Institut Pasteur, and his name was officially mentioned to lead the unit entitled “Comparative microbiology” (microbie comparée). However, he will never join the institute. This episode in the history of the creation of Institut Pasteur is rather opaque and the few elements that we address will perhaps offer a begin to explain this intriguing absence.

On February 1886, the Odessa Medical Society had sent him to learn the new anti-rabies treatment developed by Pasteur (Ref. 25). He spent four months in Paris, before contributing to the birth of the first Russian bacteriology station in June 1886, with Metchnikoff as its director. Fluent in French, the links he had established with Pasteur were so good that Pasteur sent him to London to follow the works of the British investigative committee on the rabies vaccine. He contributed to studies on

the different parameters that affected the vaccine preparation. He realized that Russian rabbits were smaller than the French ones, that their spinal cords dried faster, that the protection was dependent of the amounts used for vaccination, and that, in agreement with Roux observation, there was a seasonal influence on the preparation of the rabies vaccine (Ref. 26). He mentioned that there was a need to acquire immunity before the rabies virus reaches the central nervous system. Like Grancher did, Gamaleïa tested on himself the vaccine to demonstrate its safety.

Then, he similarly investigated the parameters that influenced the preparation of the anthrax vaccine. He reported experiments performed on more than 300 sheep, and a few dogs, rabbits, and rats (Ref. 27). He reported that certain preparations could kill the sheep, and established that the fever induced by the vaccine was a prerequisite for the vaccine efficacy. Why such expensive efforts to better define the vaccine. Well, during the summer 1887, it happened that an anthrax vaccination organized by the bacteriology station of Odessa ended to the death of 80% of the vaccinated animals, i.e. 3549 sheeps, for a cost of more than 40 000 rubles. The owner asked Metchnikoff and Gamaleïa to reimburse half the price and went to trial. Of course, the lay press echoed this disaster. No doubt that a major mistake had been made, particularly, the large-scale use of a vaccine not beforehand tested.

Another difficulty arose in Gamaleïa's scientific life. In 1888, studying the sanitary status of the bird market, he identified a new pathology of fowl cholera, he called "choleric gastroenteritis of birds". He reported that this new pathogen was close to that of the avian cholera, but it induced a disease without fever. Gamaleïa isolated and identified the bacteria, he called "*Vibrio metchnikovi*" to pay tribute to his Mentor (Ref. 28). Gamaleïa showed that this bacterium was lethal to chickens, pigeons and also guinea pigs. But Gamaleïa failed to reproduce his results with Parisian pigeons. On April 4$^{th}$, 1889 Pasteur sent him a letter requesting him to be able to reproduce his results. Pasteur precised, that despite the mention of his name in the Annales de L'Institut Pasteur and in the Official Journal of the Republic, the administrative Council of the institute would not yet validate his venue.

From 1886 to 1892, Gamaleïa shared his life between Odessa and Paris. Despite their long collaborative years, the relationship between Metchnikoff and Gamaleïa began to deteriorate. Although, Duclaux reiterated the invitation to join the institute, Gamaleïa pursued his career in Russia, and never joined the Institute where

his venue was scheduled at the very beginning. In 1888, he published a quite fascinating work (Ref. 29). For the first time he showed that bacteria don't need to be alive to induce fever. Furthermore, he showed that filtered alcoholic extracts of spleen from pyretic sheep induced fever within 30 minutes when injected in rabbits. These works led Gamaleïa to write a book on bacterial poisons (1892). Gamaleïa served as director of the Odessa Bacteriological Institute from 1896 to 1908. To fight plague in Odessa, he contributed to a campaign of de-infectation and rat control. In 1910 (till 1913), he published and edited the journal "Hygiene and Sanitation" which welcomed eugenic publications, including his own editorials. He also advocated his eugenic views in different lectures delivered in St Petersburg or Tartu (Ref. 25). In 1912, he was director of an institute in St Petersburg before moving to Moscow in 1930 to take over the Central Institute of Epidemiology and Bacteriology. He was corresponding member of the USSR Academy of Sciences (1939), honorary academician (1940), and academician of the Academy of Medical Sciences of the USSR (1945). Nowadays, the National Research Center for Epidemiology and Microbiology is named after this famous Russian scientist.

## Conclusions

When Pasteur gathered his five musketeers, he contributed to the foundation of an original place where scientists and physicians could cooperate, illustrating the statement of Charles Richet (Nobel Prize, 1913) who was among the 16 founding members: "*To oppose the physician to the physiologist, and the scientist to the clinician, means that one has failed to understand physiology and medicine*". Pasteur invited esteemed colleagues who later had become friends. And for most of them, have been working and supporting his research over a long period of time. He welcomed two Russian scientists, illustrating Pasteur's support for their country. His institution coined a new model favoring the independence of researchers, teaching, applied sciences and its putative incomes, and the offer of an international window within its global network. In 1889, twenty-seven people were listed in the staff of the institute; nowadays around 2500 people are working on the Parisian campus which remains a leading place within the French and international landscape of biological research (Ref. 29).

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Table 1. First encounter of Louis Pasteur with his five associates

| Name | Degree | Year | Age * | Place |
|---|---|---|---|---|
| Emile DUCLAUX (1840-1904) | Agrégation | 1862 | 48 | Laboratory of L. Pasteur, Ecole Normale. Works as a laboratory associate |
| Charles CHAMBERLAND (1851-1908) | Agrégation | 1875 | 39 | Laboratory of L. Pasteur, Ecole Normale. Works as a laboratory associate |
| Emile ROUX (1853-1933) | MD | 1878 | 35 | Contact rue D'Ulm thanks to Duclaux. Works as a laboratory associate |
| Joseph GRANCHER (1843-1907) | MD | 1884 | 45 | International Congress of Medicine, Copenhagen. Called in 1885 to perform the very first human rabies vaccine |
| Elie METCHNIKOFF (1845-1916) | Doctor Sci. | 1887 | 43 | Rue d'Ulm after a visit to L. Pasteur while looking for a job |

** Age at the opening of Institut Pasteur*

Table 2. Responsabilities within the Institut Pasteur

| Pasteurians | Year | Responsabilities |
|---|---|---|
| Emile DUCLAUX | 1887 | Founder of the journal “Annales de l’Institut Pasteur” - Editor-in-Chief |
| | 1888 | Head of Unit “Microbie Général” |
| | 1889 | Deputy-Director |
| | 1895 | Director (succeeded to L. Pasteur) |
| Charles CHAMBERLAND | 1886 | Contributed to set up the organisation |
| | 1887 | Member Editorial Board “Annales de l’Institut Pasteur” |
| | 1888 | Head of Unit “Microbie appliquée à l’hygiène » |
| | 1895 | Technical Director of the Anthrax Vaccine Society |
| | 1904 | Deputy-Director |
| Emile ROUX | 1887 | Member Editorial Board “Annales de l’Institut Pasteur” |
| | 1888 | Head of Unit “Microbie Technique” |
| | 1889 | Created the first Course of microbiology (“Microbie technique”) |
| | 1896 | Deputy-Director |
| | 1904 | Director (succeeded to Duclaux) |
| Joseph GRANCHER | 1886 | Secretary of the subscription committee |
| | 1887 | Member Editorial Board “Annales de l’Institut Pasteur” |
| | 1887 | Secretary of the Administrative Council |
| | 1888 | Head of Unit “Rabies” |
| | 1900 | Vice-president of the Administrative Council |
| | 1905 | President of the Administrative Council |
| Elie METCHNIKOFF | 1888 | Head of Unit “Microbie morphologique” |
| | 1890 | Member Editorial Board “Annales de l’Institut Pasteur” |
| | 1904 | Deputy-Director |

Table 3. Mains scientific contributions of Louis Pasteur's associates

| Pasteurians | Year | Nature |
|---|---|---|
| Emile DUCLAUX | 1862 | Works to the fight the concept of spontaneous generation (with Louis Pasteur) |
| | 1863 | Works on the wine studies (with Louis Pasteur) |
| | 1866 | Works of the silk worms disease (with Louis Pasteur) |
| | 1870 | Works of the fermentation of beer (with Louis Pasteur) |
| Charles CHAMBERLAND | 1878 | Contributes to the theory of germs (with Louis Pasteur) |
| | 1879 | improves the autoclave for medical purposes |
| | | Contributed to the anthrax vaccination (with Louis Pasteur) |
| | 1884 | Designs a filter for sterilization |
| Emile ROUX | 1879 | Contributed to the fowl cholera vaccine (with Louis Pasteur) |
| | 1879 | Contributed to the anthrax vaccination (with Louis Pasteur) |
| | 1881 | Initiated works on rabies (with Louis Pasteur) |
| | 1888 | Identified the diphteria toxin (with Alexandre Yersin) |
| | 1891 | Orchestrated the anti-diphteria serotherapy (with Gaston Ramon) |
| | 1903 | Studied syphilis (With Elie Metchnikoff) |
| Joseph GRANCHER | 1885 | First human vaccine in humans (Joseph Meister) (with Louis Pasteur) |
| | 1888 | Developed prevention against contagiousness of tuberculosis |
| Elie METCHNIKOFF | 1882 | Phagocytosis |
| | 1889 | Alveolar Macrophages (with Nicolaï Tchistovitch) |
| | 1890 | Bacterial chemoattractant factor (with Georges Gabritchevsky) |
| | 1894 | Pinocytosis (with Georges Gabritchevsky) |
| | 1895 | Bacteriolysis and hemolysis (with Jules Bordet) |
| | 1901 | First germ-free tadpoles (with Olga Metchnikoff) |
| | 1902 | Brain macrophages (with Mesnil & Weinberg) |
| | 1903 | Microbiota – Coin the word "gerontology" |
| | 1906 | Calomel as a treatment of syphilis (with E. Roux) |
| | 1910 | Identified indol and paracresol as bacterial metabolites |

Figure legends

Figure 1. On the French banknote of 5 francs (1966), the portrait of Louis Pasteur was shown in front of his historical building and associated with the sculpture of Jean-Baptiste Jupille fighting a rabid dog (by Émile-Louis Truffot)

Figure 2. Portrait of Émile Duclaux by Ernest Bordes (circa 1904)

Figure 3. Portrait of Charles Chamberland (circa 1900)

Figure 4. Portrait of Émile Roux while teaching by Albert Edelfelt (1895)

Figure 5. Portrait of Joseph Grancher

Figure 6. Portrait of Elie Metchnikoff by William Laparra (1911)

Figure 7. Portrait of Nikolaï Gamaleïa


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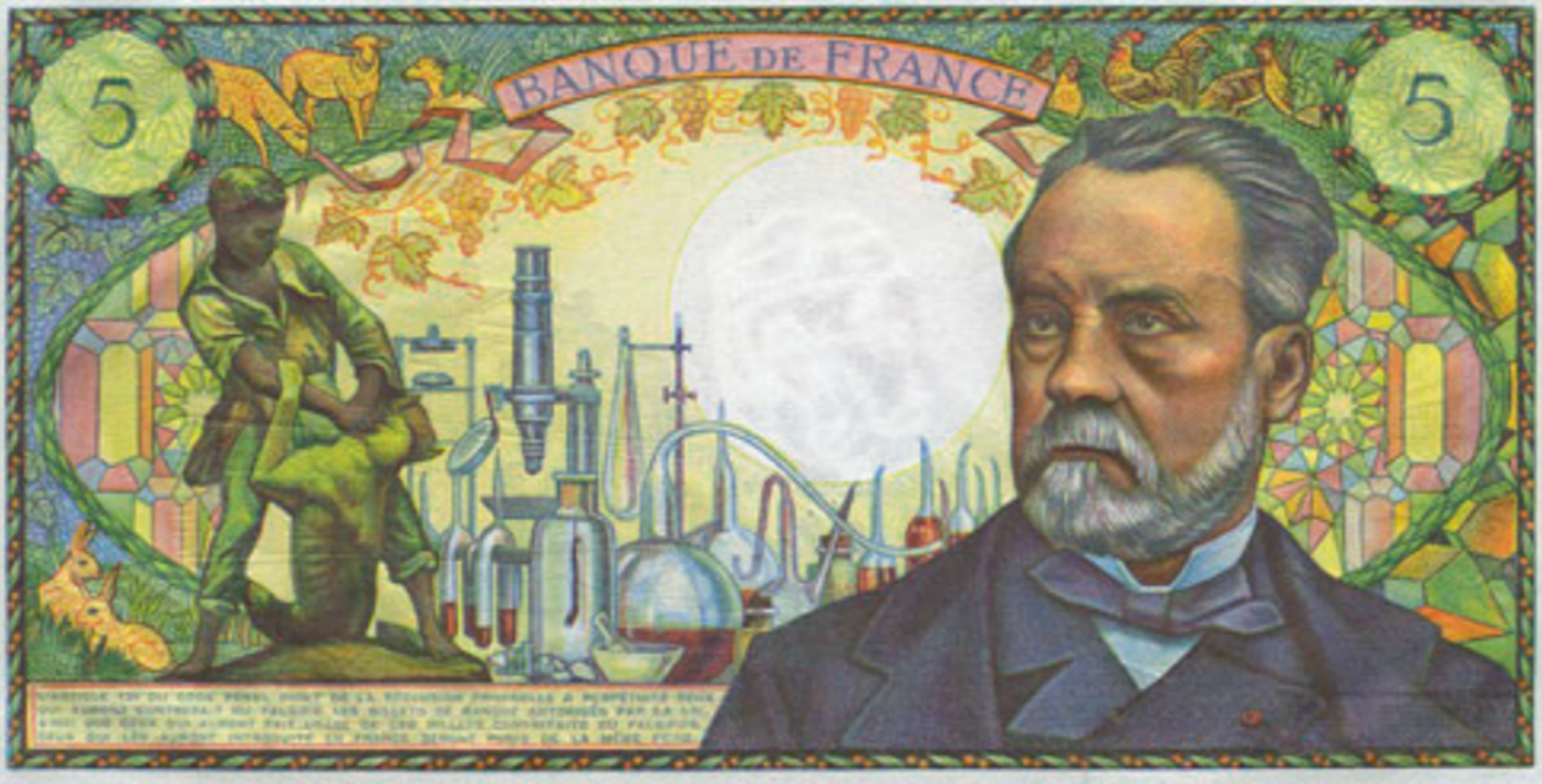
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