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EDITORIAL

Louis Pasteur—The life of a controversial scientist with a prepared mind, driven by curiosity, motivation, and competition

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Brogren C. Louis Pasteur—The life of a controversial scientist with a prepared mind, driven by curiosity, motivation, and competition. APMIS. 2023.

Louis Pasteur, born December 27, 1822 in Dole, France, showed in his childhood and youth great abilities as an artistic painter; however by an age of 19, his interest changed toward science, and he moved to Paris to study chemistry and physics at École Normale Supérieure. During graduation, he initiated research on chiral crystallography and stereochemistry and got his doctorates in 1847 in both chemistry and physics. In 1848, he started as high school teacher in Dijon, but shortly after he became a deputy professor at the University of Strasbourg in chemistry and got married to the rector's daughter Marie Laurent. They had five children, of which only two survived. The family moved to Lille in 1854, where he worked as professor in chemistry and became the dean at the new Faculty of Science at the University of Lille. He initiated his famous research on fermentation in 1855. Louis Pasteur moved back to École Normale Supérieure in 1857, where a major part of his innovative research on fermentation took place ending up with the development of pasteurization in 1864. Through genius experiments, he disputed the spontaneous genesis theory and founded the basis for the germ theory, later confirmed by his enemy Robert Koch and several other research teams, which he for lifetime competed with on the cure and prevention against infectious disease causes by both bacteria such as cholera, anthrax, and virus-induced infections as yellow fever and rabies. However, most of his experiments were done on animals since Pasteur and his colleagues at École Normale Superiére were not physicians but scientists. The first successful attenuated vaccine used in humans against rabies was, when the 9-year-old Joseph Meister was cured or prevented from rabies in 1885 after 13 vaccine injections done by the young pediatrician Joseph Grancher. This worldwide known intervention is both world famous and ethically criticized and disputed. The Pasteur Institute was inaugurated in 1888—now an international prestigious research institute—which has been expanded since in a network of affiliated Pasteur institutes over the whole world. There were multiple links to Danish scientists of the 19th century and to the Danish brewery industry. Most well known is the strong friendship between Louis Pasteur and the Carlsberg brewery and especially to its founder Jacob Christian Jacobsen, who was a great believer on a scientific approach to a cleaner fermentation process and better beer quality. Louis Pasteur stands as a milestone example of the fruitful outcome of scientific competition and collaboration and should therefore be remembered as an inspiration for present and future scientists.

Key words: Fermentation; microbiology; pasteur; pasteurization; vaccination; virology.

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In the 19th century, French art, culture, and science were icons for European lifestyle and innovation. After the French revolution at the end of the 18th century, the 19th century became a light tower for scientific discoveries in bacteriology, physics, chemistry, and medicine. Antoine-Laurent de Lavoisier in the 17th century had shown that nothing disappears in chemistry, and Marie et Pierre Curie in the late 19th century showed oppositely that molecular mass lost can turn into radiation and radioactivity. Pasteur refused the "spontaneous genesis," founded the "germ theory," invented

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pasteurization, and proved the preventive effect of vaccination. In the 20th century, Niels Bohr gave us the atomic model and periodic elementary system and Niels Kaj Jerne proposed the immune network theory. Global pandemics have again and again attacked and challenged our vaccine research and understanding of the immune system, like recently during the COVID-19 pandemic.

Without the discoveries of Louis Pasteur in the 19th century on infection diseases and his understanding that "the role of the infinitely small in nature is infinitely great," the following centuries probably would have been more unsafe and more injured by pandemics due to the increasing global human population and our globalized multicontinental lifestyle with a faster spreading of pathogenic bacteria and virus. Without any understanding and knowledge about an immune system, neither innate nor acquired, Louis Pasteur together with other famous researchers of the 19th century gave the modern world a tool to prevent and cure deadly infections though vaccination. How future generations will look on Pasteur's discoveries still have to be seen, but they will stand forever as an example on how competitive science make progress since "chance favors a prepared mind."

This review on Louis Pasteur and his discoveries was initiated with help from an old Pasteurian colleague Pascal Poncet, and a recent visit to the Pasteur Museum guided by the museum leader Chantal Pflieger in late October 2022. We were also looking on the two Pasteur bicentenary exhibitions at the Pasteur Institute in Paris, the 10 posters at the entrance to the Pasteur Museum on the left side of Rue du Dr. Roux, and another exhibition in the hall of the Èmile Duclaux building on the right site of the street. These recent events plus my many previous working periods at the institute though lifetime being a Pasteurian immunologist has framed this article.

THE RESEARCH LIFE OF LOUIS PASTEUR 1822–1995

Among the most well-known French citizens are not only the emperor Napoleon Bonaparte I, the actor Molière (Jean Baptiste Poquelin), the author Victor Hugo, the president general Charles de Gaulle, but also the chemist Louis Pasteur, who will be remembered in the future, due to his contribution to our understanding of infectious diseases and to the role of hygiene. Attempts have been done to make a united Europe, but those using military power have mostly failed, whereas those based on art, poetry, humanity, and science have been more successful.

In the 19th century, many European scientists contributed to our modern understanding of how the microbial world interacts with our macroscopic world creating both deadly epidemics and healthy symbioses. Louis Pasteur has as one of the brightest shown us, how bacteria and yeast can influence the quality of our wine, beer, and food both negatively and positively. In general, surgery hygiene discovered and developed by Joseph Lister in the United Kingdom, who became a good friend and was inspired of Pasteur, and Pasteur's pasteurization have had impact on both our food quality and our general health. As a pioneer in many fields of research from classical microbiology, to modern virology and forward to the birth of immunology in the coming century, we owe him a great respect both as a famous experimentalist and as a great motivator and inspirator.

For further detailed studies on the scientific and private life of Louis Pasteur, I would like to refer to the multiple book bibliographies [1–6], Internet timeline bibliographies [7, 8], and more recent reviews [9–12], plus the selected references to some of his original scientific publications [13–35], a single translated presentation [36], and to the summaries in Tables 1 and 2 in this presentation. Among all these references, the "timeline" presentation [8] gives the best overview. For further discussion of the competitions and collaborations which is a part of every life of a scientist, please consult the following chapters. One of my aims with this publication is to highlight the importance of both curiosity, competition, and collaboration in creating discoveries, and as quoted by Pasteur, to highlight that "chance favors a prepared mind." Table 3 is a listing of famous quotes from the scientific life of the Louis Pasteur. Most of these expressions are still good to have in mind as a curious scientist.

LOUIS AS CHILD AND TEENAGER IN DOLE, ARBOIS, AND C-CEDILLE (1822–1843)

A promising artist became interested in science

Louis Pasteur was born the December 27, 1822 in Dole in the north-east of France. Soon the family moved to Arbois, also in Jura. The father had served in the army of Napoleon Bonaparte, first as corporal, later as sergent-major, and Napoleon stayed as an idol for him, even after he left the army in 1816 after Napoleon abdicated. In the same year, he married Jeanne Roqui and took up his family profession as tanner in the third generation. Their son Louis entered the primary school in Ambois in 1929. During his childhood, Louis showed a great interest and ability in drawing and

Table 1. Main steps of Louis Pasteur's life and scientific career[1]

December 7, 1822	Birth in Dôle (Jura) (third child of Jean-Joseph Pasteur (1791–1865) and Jeanne-Étiennette Roqui (1793–1848)
1827	The family moved to Arbois
1831–1843	Studied in Arbois, Besançon, Dijon, and Paris
1844–1847	Studied at École Normale Supérieure (ENS, Paris)
1846	"Agrégé préparateur" at ENS
1846–1847	Thesis for his Doctorat ès-Sciences (physics and chemistry)
1848–1853	Taught physics in high school in Dijon and chemistry at the University of Strasbourg
May 29, 1849	Married Marie Laurent, daughter of the Strasbourg university's rector
1850	Birth of Jeanne, first child (deceased in 1859, 9 years)
1851	Birth of Jean-Baptiste, second child (deceased in 1908)
1853	Birth of Cécile, third child (deceased in 1866, 12 years)
1854	Knight of the Légion d'Honneur
1857	Professor of chemistry and dean of the faculty of sciences of Lille
1857	Failure of his application to the Academy of Sciences
1857–1867	Administrator and director of scientific studies at ENS
1858	Birth of Marie-Louise, fourth child (deceased in 1934)
1862	Setup his research laboratory in the attics of ENS Election at the French Academy of Sciences
1863	Birth of Camille, fifth child (deceased in 1865, 2 years)
1863–1867	Professor of geology, physics, and applied chemistry at the School of Fine Arts, Paris
1867–1888	Director of a laboratory at ENS
1867–1872	Professor, chair of organic chemistry at the Sorbonne
1868	First severe brain stroke that paralyzed his left side
1873	Election at the French Academy of Medicine
1875	Failure to be elected Senator for Jura
1879	His daughter Marie-Louise married René Valéry-Radot (1853–1933)
1881	Election at the French Academy; Great Cross of the Légion d'honneur
1888–1895	Director of Institut Pasteur
September 28, 1895	Death in Institut Pasteur annex (Marnes la Coquette), 72 years
December 26, 1896	The coffin of Louis Pasteur was transferred in the crypt of four of 22 Institut Pasteur

[1]Modified from Cavaillon, J.-M.; Legout, S.: Louis Pasteur - Between Myth and Reality. *Biomolecules* 2022, *12*, 596. https://doi.org/10.3390/biom12040596, Latour B. (1994): Louis Pasteur – une Science, in style, un siècle, Perrin, Institut Pasteur, and from Nielsen L. (2013): Louis Pasteur– mikrobejæger og menneskehedens velgører http://www.rostra.dk/louis/andreart/Louis_Pasteur.html.

Table 2. Research discoveries of Louis Pasteur and others in the nineteenth century[1]

1848–1858	Studies on molecular chirality: Crystallography of tartaric and paratartaric acid
1857–1879	Studies on fermentation; First patent on alcoholic fermentation (1857)
1861	Discovery of anaerobic bacteria
1861–1879	Refutation of the theory of spontaneous generations. Discovery of germs
1863–1873	Studies on diseases of wine, vinegar, and beer
1865	Pasteurization of wine; Patent on wine preservation
1865–1870	Study on the diseases of silkworms
1871	Patent on beer preparation and preservation
1877	First observation of antibiosis
1877–1881	Studies on infectious diseases (anthrax, puerperal sepsis, and boils)
1878	Demonstration in a vineyard that isolation of grapes from environmental air prevents fermentation in the further wine-making process
1880	Co-discovery with Alexander Ogston (UK) of *Staphylococcus aureus*
1880–1885	Preparation of vaccines (fowl cholera, anthrax, pig erysipelas, and rabies)
1881	Co-discovery with George M. Sternberg (USA) of *Streptococcus pneumoniae*
1884	First rabies vaccine presented at the Second International Congress of Medicine in Copenhagen
1887	First bacteriological war: Elimination of rabbits by *Pasteurella multocida* over the cellar of Champagne of Mrs. Pommery (Reims)
1902	The State Serum Institut open in Copenhagen with Julius Salomonsen as director

[1]Modified from Cavaillon, J.-M.; Legout, S.: Louis Pasteur - Between Myth and Reality. *Biomolecules* 2022, *12*, 596. https://doi.org/10.3390/biom12040596, Latour B. (1994): Louis Pasteur – une Science, in style, un siècle, Perrin, Institut Pasteur, and from Nielsen L. (2013): Louis Pasteur– mikrobejæger og menneskehedens velgører http://www.rostra.dk/louis/andreart/Louis_Pasteur.html.

painting. Portraits were made in pastel of both his father Jean-Joseph Pasteur (1771–1865) and his mother Jeanne-Étiennette, born Roqui (1793–1848), and a famous painting of the daughter at the hardware store, the 20 years old Sophie Roch (1839), perhaps a secret girlfriend. He painted also the

Table 3. Selected quotes by Louis Pasteur translated to engelsk

1	Chance favors the prepared mind
2	Let me tell you the secret that has led me to my goal. My strength lies solely in my tenacity
3	When I approach a child, he inspires in me two sentiments: tenderness for what he is, and respect for what he may become
4	Do not let yourself be tainted with a barren skepticism
5	There are no such things as applied sciences, only applications of science
6	There does not exist a category of science to which one can give the name applied science. There are science and the applications of science, bound together as the fruit of the tree which bears it
7	Science knows no country, because knowledge belongs to humanity, and is the torch which illuminates the world
8	Science is the highest personification of the nation because that nation will remain the first which carries the furthest the works of thought and intelligence
9	It is surmounting difficulties that makes heroes
10	One must work; one must work. I have done what I could
11	The universe is asymmetric and I am persuaded that life, as it is known to us, is a direct result of the asymmetry of the universe or of its indirect consequences. The universe is asymmetric
12	Never will the doctrine of spontaneous generation recover from the mortal blow struck by this simple experiment
13	To know how to wonder and question is the first step of the mind toward discovery
14	Little science takes you away from God but more of it takes you to Him
15	Wine is the heathiest and cleanest existing drink
16	A bottle of wine contains more philosophy than all the books in the world
17	Life comes only from life
18	The role of the infinitely small in nature is infinitely great
19	The only thing that can bring joy is work
20	Question your priorities make sure God always comes first
21	It is not the germs we need worry about. It is our inner terrain

https://www.brainyquote.com/authors/louis-pasteur-quotes;
https://www.azquotes.com/author/11366-Louis_Pasteur.

more prestigious citizens in Arbois and became locally known as a talented young artist.

In 1838, Louis leaves for Paris in company of a friend for a stay in the boarding school Barbet, but as extreme homesick he returns to Arbois the same year. From 1839, he is student at "Collège Royal" in C-cedille. He received his bachelor's degree in art in C-cedille in 1840. Suddenly, when 19 years old, his interest changed and inspired by his school teacher, he went again to "College Royal" in "Besancon" to study mathematics. In 1841, Pasteur fails examination for a "baccalaureate" in science, and enrolled for a second year in mathematics. He received his bachelor in science from Dijon in 1841. He decided to apply for entrance to École Normale Superiére. After some difficulties for entrance, he starts to studied physics and chemistry at École Normale Supérieure in Paris from 1843 (age 20).

STUDIES IN CHEMISTRY AND PHYSICS AT ÉCOLE NORMALE SUPÉRIEURE IN PARIS (1843–1847)

Initial research in crystallography and stereochemistry

The young science student Louis (Fig. 1) initiated his research carrier at École Normale Supérieure (ENS) during his studies in physics and chemistry by experimenting with tartrate crystals and chiral stereochemistry inspired by Professor Jean-Baptiste Dumas (chemist at Sorbonne University) and Professor Antoine Jérome Balard (chemist at ENS). There is near the old entrance to ENS in Rue d'Ulm a memorial plate (Fig. 2) indicating that Louis Pasteur initiated his earliest research at this location. In 1845, he became Bachelor of Science. In 1846, he was appointed teacher in physics at the Tournon high-school in Ardéche, but refused, in order to stay at ENS as a qualified demonstrator and Master student continuing his studies of various chiral crystals. These studies showed original achievements and should be more enlightened since not done in the path of others as many of his later discoveries [8, 9].

After Pasteur's two doctoral theses in August 1847—one in chemistry and one in physics— he continued 1847–1848 his scientific career as postdoc at ENS by continued studies on the stereochemistry of tartrates and paratartrates, and published his first scientific publications in 1848 [13, 14]. Later in 1851, Louis named his first and only son Jean-Baptiste after his professor at ENS (Table 1).

TEACHER AT STRASBOURG UNIVERSITY (1849–1854)

Continuing research work in Strasbourg on stereochemistry

Louis' first position after university graduation was in 1848 as high school teacher in Dijon near his parental hometown Arbois, but only after

Fig. 1. The young Louis Pasteur—age 21—as student at École Normale Supérire. Drawing by Charles Lebayle 1843 (Musée Pasteur, MP456, Paris).

8 months, he left for a position, which could give him an opportunity to continue his research interests. Therefore, Louis accepted a position as deputy professor in chemistry at the University of Strasbourg (1849–1854). This should soon make a larger change in his life.

In 1849, he married Marie Laurant (1826–1910) —daughter of the rector for the Strasbourg University—and he promised her father in-law Aristide Laurant to make his daughter well-known (Chantal Pflieger, personal communication). His mother had died the year before (1848), so the wedding at Église Sainte-Madeleine in Strasbourg was rather modest. In his marriage to Marie, five children were born, including the only son Jean-Baptiste (1851–1908) and one daughter Marie-Louise (1858–1934) who both survived him, but three other children died at young age, Jeanne (1850–1859) and Cécile (1853–1866), from infectious disease (typhoid fever), and Camile (1883–85) from cancer.

Fig. 2. Memorial plate at rue d'Ulm, indicating that Louis Pasteur started his scientific career at this location (Photo by C.H. Brogren).

This tragedy could very well had initiated his upcoming interest for interventions in infectious diseases caused by pathogenic bacteria and viral agents, which were not yet understood in the early 19th century. His marriage certainly also brought him in contact with the academic world, which would not be easy for a son of a tanner at that time. We were still in a religious period with conflicts between classical Christianity and the "enlightenment" period (1685–1815), and with naturalist Charles Darwin (1809–1889) and his theory of evolution as a crucial dispute. Both Marie Pasteur and Louis Pasteur were both a very religious. However, Louis himself was a more spiritual religious man, who recognized the need for religion, as he many times would rely on faith alone to keep his work going. As quoted by Pasteur, "little science takes you away from God, but more of it bring you to him" (Table 3).

PROFESSOR AND DEAN AT LILLE UNIVERSITY (1854–1857)

Initial studies on fermentation to the discovery of pasteurization

In 1854, Louis Pasteur obtained a professorship in chemistry and became dean for the science studies at Université de Lille. He got motivated to investigate actual fermentation problems in a local beet factory owned by the father of one of his students [7, 8]. This initiated his comprehensive fermentation research

period for the coming 20 years. By simple microscopy, he discovered bacterial contamination in the fermentation process as the major cause of "diseases", which at that time often occurred in production of both vinegar, wine, and beer. Aside from visualizing the "microbial plants" and proving the yeast cell as the cause of fermentation, he also observed other smaller microorganisms as a sign of bacterial contamination. His laboratory worked out a practical way to eliminate the bacteria by heating. This preheating process is still done initially in beer production. Pre- and postheating treatment is now not used any longer in wine production since impact on the aroma profile, but routinely used in the dairy industry—a method now known as "pasteurization", and applied all over the world in the dairy, brewery, and food industry. The more intensive studies on wine and beer fermentation problems and the development of the final pasteurization method first started later after his return to Paris, and elucidate his focus on applied science [20, 21].

During his teaching in chemistry in Lille, he wrote to the rector not to have women as students in his courses, which however were refused. French Universities was among the first worldwide to assign women at their universities, which later motivated Marie Salomea Sklodolowska—later Curie (1867–1934), to travel from Polen to Paris for her chemistry university studies. Pasteur initiated in Lille an intensive study on fermentation, but he failed first to fully understand the fermentation process, in contrast to the French chemist Antoine Béchamp (1816–1908), who already had suggested that both the yeast cells and enzymes (named zymase) were involved in the fermentation process. In this context, Béchamp were on the right track before Pasteur and many others at that time speculating in or investigating the fermentation process [12]. The Béchamp–Pasteur competition became later an issue in the so-called Claude Bernard postmortem affair.

LOUIS PASTEUR RETURNS TO ÉCOLE NORMALE SUPÉRIEURE IN PARIS (1857–1888)

From fermentation to infectious diseases

The ambitious experimentalist decided in 1857 to return to Paris, where he not only established his own research laboratory and taught in chemistry at ENS (1857–1867), but also became professor in organic chemistry at Sorbonne University (1867–1872), and professor at École des Beaux Art (1863–1867) in geology, physics, and applied chemistry. Pasteur was at ENS director of the scientific studies from 1857 to 1867 and from 1867 to 1888 director of his laboratory in Physiological Chemistry, followed by his last period 1888–1895 as director at the newly established Pasteur Institute in Rue du Dr. Roux.

In 1862, he was elected to the French Academy of Sciences, and in 1873, he was elected to the French Academy of Medicine, hereby showing his research movement from chemistry into medicine for a period of 10 years. The period from 1857 to 1888 includes the most important innovative discoveries from the germ theory, over understanding of infectious disease, to the development of attenuated vaccines against cholera, anthrax, and rabies, to understanding of virulence, plus the impact of hygiene on heath.

THE GERM THEORY AND REFUSAL OF SPONTANEOUS GENESIS (1857–1873)

Dispute on the theory of spontaneous genesis to creation of the germ theory for the origin of life

A French colleague Felix Archimède Pouchet (1800–1872) had postulated that microorganisms occurred spontaneously—this theory was called spontaneous genesis and was commonly accepted, but this theory was not in accordance with Pasteur's observations. Pasteur had developed a method to grow yeast and bacteria in liquid media, and setup a brilliant experiment called the "swan bottle neck" experiments (Fig. 3), which definitively were used to prove the theory of biogenesis and the disclosure of the spontaneous genesis theory—claiming through centuries before, that life could be created from nonliving material, which with our time knowledge seems completely innocent [17].

This experiment is an excellent proof for what innovative basic science is and can do for the society. We all know by now, that life comes from life, and living organisms need other living organisms for their creation. It sounds at our time straight, that even intelligent people at that time could believe on "spontaneous genesis," in the public called "heterogeneity," but we were in the 18th and 19th centuries in a strictly religious time, where the common thoughts were, that God has created everything, probably also the invisible microorganisms.

THE DISCOVERY OF PASTEURIZATION (1858–1966, 1970–1974)

From putrefaction to better conservation

The studies of beet fermentation initiated in Lille were continued at École Normale Superiére on both

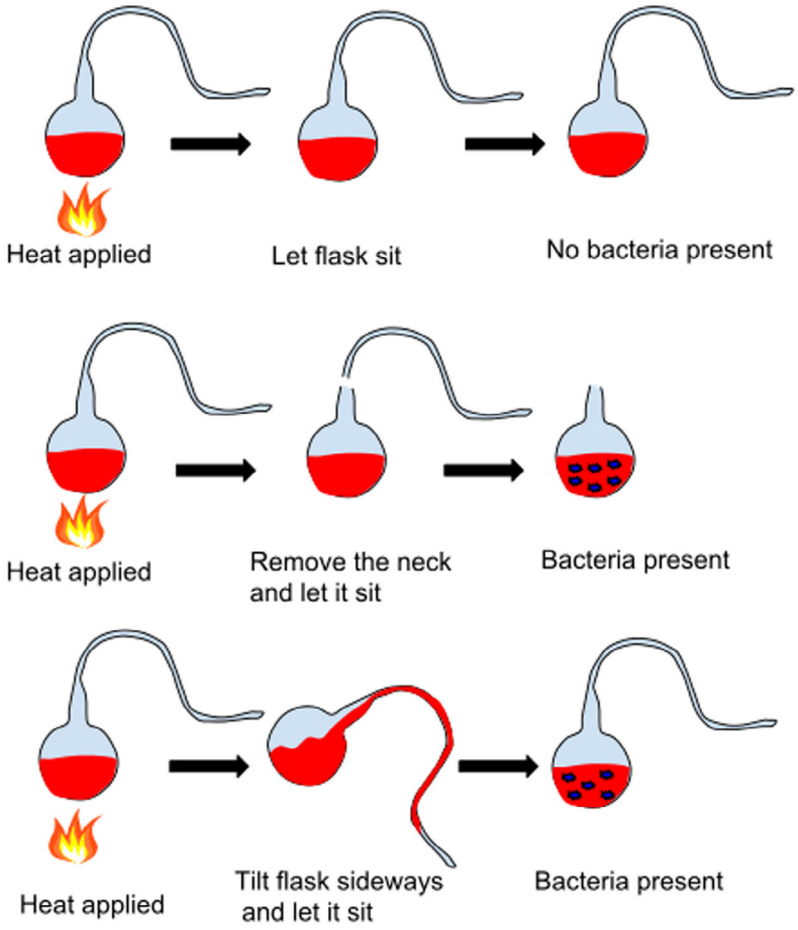

Fig. 3. Spontaneous genesis was proven wrong by the so-called swan bottle neck experiments illustrated here. (ref. Wikipedia**).** Pasteur's test of spontaneous generation*: By sterilizing a food source and keeping it isolated from the outside, Pasteur observed no putrefaction of the food source (top panel). Upon exposure to the outside environment, Pasteur observed the putrefaction of the food source (bottom panel). This strongly suggested that the components needed to create life do not spontaneously arise. Louis Pasteur's pasteurization experiment illustrates the fact that the spoilage of liquid was caused by particles in the air rather than the air itself. These experiments were important pieces of evidence supporting the idea of germ theory of disease. (CC BY-SA 4.0; Kgerow16).*

vinegar, wine, and later also beer fermentation. Two publications on lactic fermentation and on anaerobic alcoholic fermentation were published [15, 16]. A small microbrewery was established in the basement of ENS. One of the rare photos at the Pasteur Museum, where Pasteur is smiling, is where he is together with the rector of ENS in his microbrewery (Chantal Pflieger, personal communication). Hereby, Pasteur's research moved from basic science of molecular chirality to more applied science with obvious direct connection to the industry and economy.

Pasteur's famous heat treatment method to kill pathogenic bacteria and inactivate certain spoilage enzymes in fermented product, known as the pasteurization methods was first time demonstrated for the members of Académie des Sciences on April 20 1862, but actually first published in 1864. It was quickly applied in the dairy and beverage industries. On demand from Napoleon the 3rd with the aim to help the wine industry, the fermentation studies were finally published in 1866 as "Études Sur le Vin, Ses Maladies, Causes Qui Le Provoquent, Procédés Nouveaux Pour Le Conserver Et Pour Le Vieillir" [20]. It will be clarified further on, that Pasteur's initial studies on wine and fermentation will bring him far away from his fundamental studies on fermentation to studies of infectious diseases.

In the next period, Louis Pasteur filed nine patents [37]. Same of these became of great importance for the Danish Carlsberg brewery founded in 1847, which was the first in the world to produce pasteurize beer starting from 1880. In total, three patent were filed in France (No. 91941 Jan. 28, 1871; No. 92505 Aug. 21, 1871; No. 98476, Mar. 13, 1873),

two in Italy (Apr. 8, 1872; Jul. 10, 1873), and two in the United Kingdom (No. 2225, Aug. 24, 1871, No. 1106 Mar. 2, 1873). Furthermore, two US patents were filed (No. 135.245, Jan. 28, 1873, No. 141.072, and Jul 22, 1873). These patents were covering several new technologies for beer production, filtration, use of pure yeast strains, and preservation by pasteurization (No. 134.245). The Carlsberg Brewery started first to use pasteurization in their beer production from 1880. After the patent filing, a general publication on beer production is published first 3 years later in 1874 titled "Études sur la bière, ses maladies, causes qui les provoquent. Procédes pou la rendre inaltérable, avec une théorie nouvelle de la fermentation" [21].

LOUIS HELPS THE SILK INDUSTRIES IN FRANCE (1865–1870)

From microbial causes of disease to preventive hygiene

From the observations that bacteria were the cause of beer and wine "illness", Pasteur was asked to help the silk industry with a current problem, and again bacteria were found to cause the "illness" in the silk larvae. An intervention using better hygiene in the breeding showed again the wanted preventive effect [19]. The impact of hygiene in aseptic surgery had been discovered and highlighted by the British doctor Joseph Lister (1827–1912), who performed the first antiseptic surgery on August 12, 1965, and with whom he became a great friend for the rest of his life. Thomas Anderson, a British chemistry professor appointed Lister to Louis Pasteur's basic discoveries of bacteria causing diseases, and Lister as an amateur scientist started to look after the invisible cause of infections after surgery, which earlier often killed people even after a successful surgery [38]. This is a beautiful example of how international collegial contacts and inspiration can drive scientific innovation. Pasteur will further on move more and more in direction of medical problems and develop vaccines, but before that, a continuous research on fermentation problems now in the brewery industries was in focus in the first half of the 1870ths.

THE STUDIES ON BEER PRODUCTION AND ITS IMPACT ON SUCCESS OF THE DANISH BREWERY, CARLSBERG (1871–1875)

From the pasteurization of France to pasteurization at Carlsberg

During the German–French 1870–1871 wartime, Pasteur escaped from Paris and moved to Pontellier, then Genève, then Lyon, and ended up in Clermont-Ferrand, where his collaborator from ENS Emile Duclaux (1840–1904) had an apartment. Arbois, where Pasteur earlier had established a laboratory for studies on wine in 1858 [8], was in the war zone and not a safe location. In Clermont-Ferrand, Duclaux and Pasteur worked 1870–1871 on beer fermentation in the Brasserie Kuhn, which was the start of the beer fermentation studies period [8].

Pasteur's research on fermentation continued after he returned to Paris at ENS by installing a minibrewery in the cellar at ENS. It was also a few years later in 1875 the Carlsberg Laboratory in Copenhagen was established. A first patent was submitted in 1871 covered a special production method for beer [37]. Multiple other patents related to beer production were filed in this period 1871–1873 [37]. In 1876, he published his "Études sur la bière, ses maladies, causes qui les provoquent. Procédés pour la rendre inaltérable, avec une théorie nouvelle de la fermentation" [21]. The approach was based again on using microscopy for quality control, the use of pure yeast avoiding bacterial contamination, improved hygiene, and employing the recently discovered Barbedienne pasteurization for improving preservation. In general terms, many of the same scientific-based protocols as earlier used to improve wine production [20].

The founder of the Carlsberg Brewery Jacob Christian Jacobsen (1811–1887) was very impressed by Louis Pasteur's research studies on fermentation. Louis Pasteur invited Jacob Jacobsen and his wife Ottilia to Paris in 1880, and later in 1884 Jacobsen invited Louis Pasteur to visit the Carlsberg Laboratory in Copenhagen in August 1884 during his attendance to the 2nd International Medical Congress in Copenhagen. The Carlsberg Laboratory was already established in 1875, and Jacobsen had shortly after in 1878 honored Pasteur with a "marble bust" made by the French artist Paul Dubois [39] place in the entrance hall to the new research laboratory (Fig. 4). It was an acknowledgment for Pasteur's contribution to modernize the brewing process and support the beer industry, in particular of course the Carlsberg brewery. A bonze copy ordered by Carl Jacobsen of the same Pasteur bust was placed in 1884 in the outer wall in a building near the present Ottilia Hotel at Pasteurvej in the old brewery area (Fig. 5). Years later in 1886, Jacobsen asked the French painter Léon Bonnat to make the famous painting of the older Louis Pasteur standing with his grandchild Camille Vallery-Radot (Fig. 6). This painting was given as a gift to Madame Pasteur, and is now at the Pasteur Museum in Paris.

Fig. 4. The marble bust of Louis Pasteur in the entrance hall of the Carlsberg Research Laboratory in Copenhagen (Artist: Paul Dubois, 1878). Photo by C.H. Brogren.

A closer friendship and collaboration were established between Pasteur and Jacobsen [39] and their laboratories, which initiated "the revanche project" [40, 41] aiming to make better beer than the German's. Pasteur's only son Jean Baptiste was enrolled in the French-German war in 1870–1871 and injured, and when the Germans prevailed the French army at Sedan and besieged Paris, why the citizens in Paris ousted the government, it had to escape from the city in balloons.

The correspondence between Louis Pasteur and Jacob Christian Jacobsen—the founder of the Carlsberg Brewery in Copenhagen—is well documented both at the Pasteur Museum in Paris and at the Carlsberg Foundation archives in Copenhagen [39], and their friendship included other members of both families and colleagues in both laboratories. The son of Pasteur Jean Baptiste later had a short job period at the French embassy in Copenhagen (Cavaillon, personal communication);

Pasteur was appointed honorary members and chairman of an art exhibition committee in 1888, illustrated in a painting by Peder Severin Krøyer from 1888 (Fig. 7), where all the most famous French artists are present, including the sculptor, Paul Dubois. The sponsor for the art exhibition Carl Jacobsen is standing just above Pasteur and Dubois, and typically for Krøyer with the painter himself and his co-painter friend Tuxen in the upper right corner.

The Carlsberg Brewery was the first in the world to use pasteurization in its production of beer [40, 41]. Louis Pasteur was impressed by the yeast research of Emil Christian Hansen (1842–1909),

Fig. 5. The bronze bust of Louis Pasteur in the outer wall of a building at Pasteurvej at Carlsberg Brewery in Copenhagen (Artist: Paul Dubois or Barbedienne, 1884). Photo by C.H. Brogren.

physiologist at the Carlsberg Laboratory (Fig. 8), who was the first to isolate a pure strain of yeast, what we now will call a limited dilution cloning. Pasteur's and Hansen's studies on fermentation undoubtfully have had a great impact for the success of Carlsberg Brewery worldwide in making high-quality beer for more than a century. Pasteur's liquid culturing of yeast and bacteria has inspired the Carlsberg Laboratory to develop clean yeast culture in prevention of earlier failures in the beer production mainly due to bacterial contamination. The lager yeast strain *Saccharomyces carlbergensis* was discovered after the Emil Chr. Hansen made the first 100% clean lager yeast culture in 1883, which was voluntarily distributed to breweries all over the world in respect for Louis Pasteur basic discoveries on the fermentation process. Pasteur sets Emil for a French industrial prize "La Societé d'Encouragement pour l'Industrie Nationale," and Emil has now also a bust in a wall at the Carlsberg Laboratory, and a monument in the square in front of the Carlsberg Laboratory, just like Pasteur has in Paris. Interestingly, Emil also expressed both artistic interests in his childhood and also search for a teacher education, just like Pasteur.

Without Pasteur's impact on the development of quality beer at Carlsberg, we would certainly have been without both the New Carlberg Glyptotek art exhibition museum and the philanthropic Carlsberg Foundation, which support our researchers and artists, and hosts The Royal Danish Academy of Science and Letters (Det Kgl. Danske Videnskabernes

Fig. 6. Louis Pasteur and his granddaughter Camille Vallery-Radot. Painting by Léon Bonnat in 1886—A gift from Jacob Christian Jacobsen to Madame Pasteur. (Musée Pasteur, Paris).

Selskab). Larger Danish medical and food related industries like Novo Nordisk, ALK, Christian Hansen and Arla Food, are partly built on the shoulder of Louis Pasteur's research in microbiology and medicine, but certainly first of all our brewery and vaccine industries.

RESEARCH ON VIRULENCE AND ATTENUATED VACCINES (1877–1895)

Enemies and friends in competition and collaboration drive innovation and creates discoveries

The discovery by Pasteur of a vaccine against chicken cholera was his next effort. In 1977, he succeeded to culture the causative agent, *Pasterella multocida*, in a highly virulent form. In 1878, he observed by chance that older cultures had lost virulence, and chickens inoculated with the older cultured were protected against more virulent cultures. The older culture could be used as a protective vaccine. He presented these protective studies in 1878 to Academie des Sciences in a memorandum "Sur les maladies virulentes, et en particulier sur la maladie appelee vulgairement cholera des poules" [25].

Pasteur then became interested in prevention against anthrax, caused by infection of *Bacillus anthracis*, described earlier by the German bacteriologist Robert Koch. This microorganism did not lose virulence in the same way as cholera, but could by oxygen (oxidation) or chemical oxidative treatment be attenuated to a less virulent form and used as a vaccine. In their life time, Robert Koch and

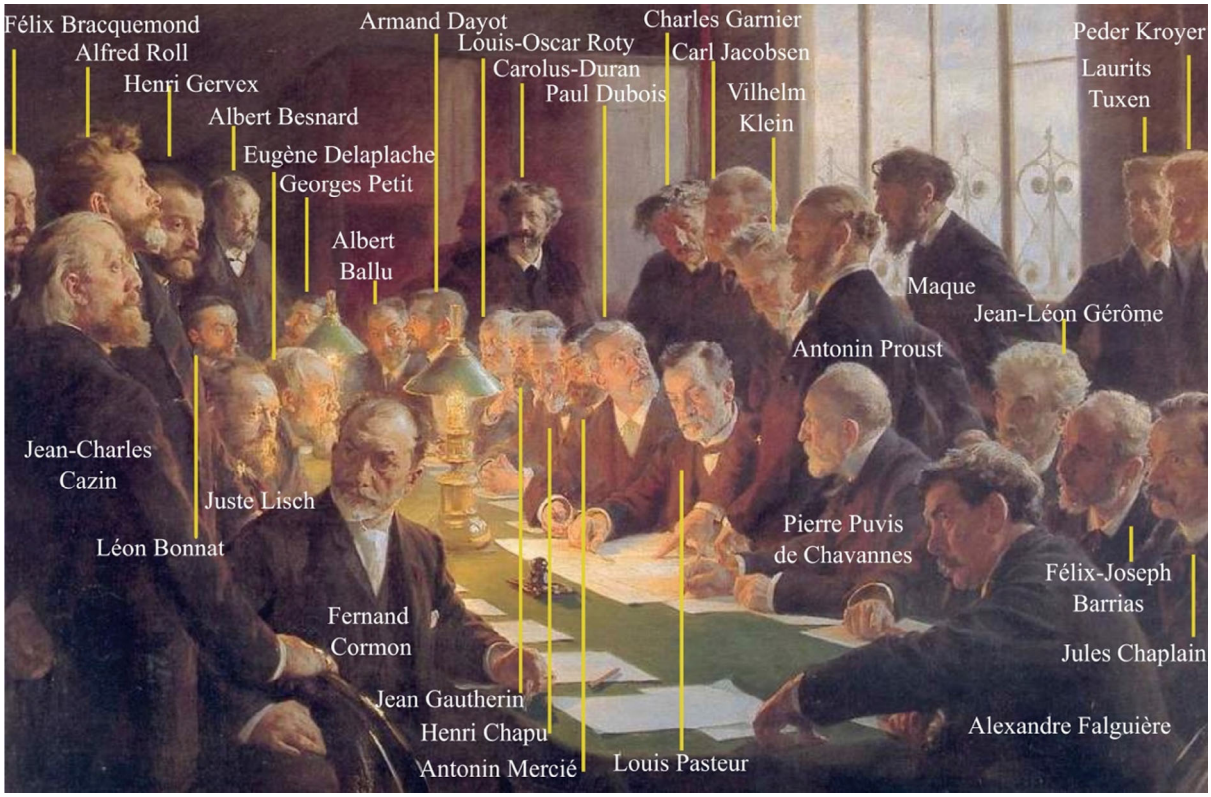

Fig. 7. The French Art Exhibition in Copenhagen committee meeting in Paris 1888 (Severin Krøyer painting. Pasteur in the center was chairman of the art committee; next to him Paul Dubois who created the bust of Pasteur at the Carlsberg Laboratory, and just above them Carl Jacobsen the son of the Carlsberg Brewery founder Jacob Christian Jacobsen. As usual the painting artist Peder Severin Krøyer has painted himself in the upper right corner. (Den Hirschsprungske Samling, Copenhagen). See an annotated version from Le Grand Continent, 2021, France [32].

Louis Pasteur were competitors both involved in the discovery that *Bacillus anthracis* could cause severe illness and cause both animal and human disease [42, 43], as well as on the later development of the vaccine against anthrax.

Perhaps, the antagonism of Louis Pasteur to his younger German colleague Robert Koch was not only scientifically based but also of political origin, since his son Jean-Baptiste was injured during his military service in Germany during the German–French war in 1870–1871 [44]. In protest, Pasteur returned his diploma of *doctor honoris causa* from Bonn University received in 1868. Many years later in 1895, he also refused to accept the Prussian Order of Merit. The dispute with Robert Koch became well-known and is recently published [44], and started out after a paper on attenuated viruses at the Public Health Congress in Geneva in 1882. Dispute between two giants in infectious diseases was even presented in an open letter from Pasteur to Koch published in January 1882 [33].

CHICKEN CHOLERA AND THE BIRTH OF THE FIRST ATTENUATED VACCINE (1877–1880)

Jenner invented vaccination, but Pasteur the vaccines

The infectious bacteria "*Vibrio cholerae*" was first discovered in 1854 during an outbreak in Florence by the Italian physician Filippo Pacini (1812–1883). A cholera epidemic outbreak had also occurred in Paris in 1865, and Pasteur was appointed to a commission charge in investigation of the disease. However, his first report on chicken cholera came first many years later in 1977 after the first experiments with chicken cholera infection were initiated and the microorganism had been isolated and cultured by Pasteur in liquid media. As mentioned above, a vaccine effect of an older (attenuated) culture was observed by coincidence in 1878. This initiated further cholera vaccine studies reported in 1880 [25, 26]. Thus, this first veterinary vaccine against an infectious animal disease using attenuated pathogenic bacteria was developed at École Normale

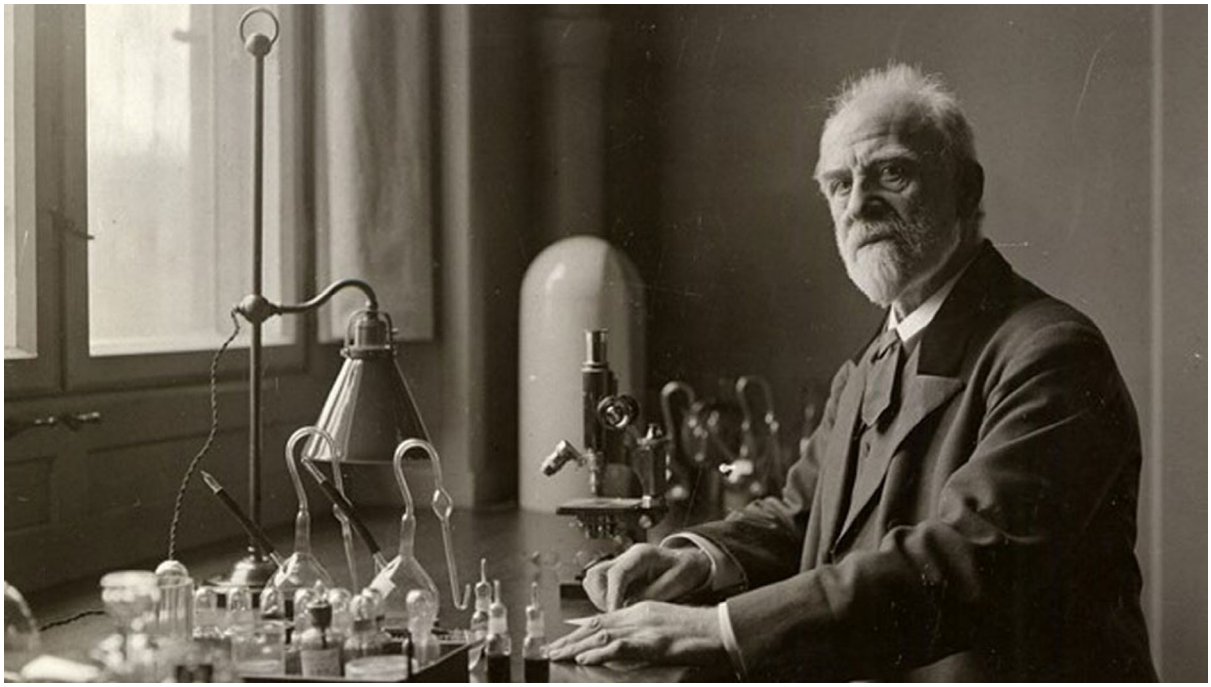

Fig. 8. The Danish physiologist Emil Chr. Hansen at the Carlsberg Laboratory, where he isolated the first pure strain of brewer yeast. His research gave Carlsberg brewery its famous *Saccharomyces carlbergensis* strain (Photo from 1908, Carlberg archives, Copenhagen).

Supérieure in Paris even 10 years before the Pasteur Institute was build, consecrated on June 1, 1887, and inaugurated on November 14, 1888. In 1857, Louis Pasteur had moved back to Paris to become professor at École Normale Supérieure, where he aside from teaching students and supervising researcher and research students, became more and more interested in both animal and human infectious diseases, while continuing research on fermentation. In 1973, he became member of Académie de Médicine. During a visit to London in 1871 to pursue his studies on beer to English breweries, Pasteur met Professor Tyndall who mentioned Joseph Lister (1827–1912) and his work on hygiene to Pasteur. However, the first letter between Pasteur and Lister occurred first in 1874. Another lifelong friendship was established for mutual inspiration, but this time on infectious diseases. What Lister did was to use Pasteur's germ theory in his development of aseptic surgery.

Cholera infection in chicken and household cattle was a raising problem, and in Germany the physician Robert Koch (1843–1910)—his greatest competitor—had already proved a bacterial cause of infectious diseases supporting the germ theory, and shown an effect of hygiene prevention. Pasteur started to infect chickens with a culture extract from diseased hens, and as expected they all died. During a summer vacation, a part of the live cholera suspension culture was left over, and after vacation time given to a new flock of chicken, which surprisingly survived the inoculation. A fresh cholera culture was given in the same flock of chicken, but they surprisingly also survived. They had obtained resistance against cholera, and what we now know been vaccinated and thereby obtained immunity.

This often-told story might however not represent the truth according to Andersen in Science 1993 [45], and Geison's later extensive historical research on Pasteur laboratory notebooks [46], but who created the "vaccination" story is not known. In this time period, many attempts around in Europe were made to create vaccines using different procedures of attenuation, like air drying, air oxidation, or by aseptic chemicals like potassium dichromate, but as elucidated earlier in the "spontaneous genesis" chapter, competition often stimulate innovation in science [17, 18].

Retrospectively, the British physician Edward Jenner (1749–1823) already 100 years earlier had proven a prevention effect of inoculation alias done a vaccination, but without understanding the cause of the observed prevention. Therefore, Jenner was objectively the first to prove a successful vaccination in 1796 against smallpox in humans with a

cowpox generated "Variola vaccinea" (pustules of the cow) extract. The name "vaccination" derives from these human cowpox extract treatments. (Latin "vacco" means cow).

Indeed, Jenner had no idea about bacteria involved in his "vaccination," since bacteriology was first developed half a century later by the next generation of scientists, like Pasteur (1822–1895), Koch (1843–1910), others in Europe, and in Denmark by Carl Julius Salomonsen (1847–1934), who was inspired by both Koch and Pasteur. Salomonsen became the first director of the Danish State Serum Institute (1902–1909). Certainly, they have all been inspired by Edward Jerner's pioneer work in the 18th century, which is how innovation and discoveries occur generation after generation. What inspired Edward Jerner was his observation, that milkmaids in contact with cows were less susceptible to smallpox infection, which with our present knowledge on immunity make sense, since they might have been naturally immunized.

The first cholera vaccine used in humans was developed by the Spanish-French bacteriologist Jaimi Ferran i Cluia (1851–1929) in 1885, contemporary with both Koch, Toussaint, and Pasteur.

ANTHRAX VACCINES PRODUCED AND APPLIED TO CATTLE AND SHEEP (1879–1881)

The definitive proof of concept of preventive vaccination in animals

Anthrax infection of sheep and cattle were another increasing problem in the farming industry. Pasteur and his research team worked out and proposed an anthrax vaccine, and setup a large experiment to illustrate the preventive effect of injected attenuated anthrax bacteria. From a scientific point of view, one of the most famous experiments conducted by Pasteur and his colleagues, is the Pouilly-le-Fort experiment on sheep and cattle with anthrax attenuated vaccines. A risky demonstration for the public and journalists took place on an open field outside Paris on May 5, 1881, where Pasteur and his colleagues arranged a vaccination with attenuated anthrax vaccine on 24 sheep, 1 goat, and 6 cows. On May 17th, a more virulent culture was given as a booster. On May 31, vaccinated animals and a control group were challenged with a high virulent culture, On June 2–3, all sheep and goats in the control group died, and the cows which had received the same challenge were very ill. In contrast, all vaccinated animals survived in good health [30]. The success of the experiment was acclaimed by an enormous crowd including many journalists and government representatives. As a result, 85.000 cattle were vaccinated in 1882 and almost 3.4 million in 1884, thereby reducing anthrax mortality to 0.3% of the French livestock.

Anthrax vaccines were under development also in other research teams, like in the laboratory of the German physician Robert Koch (1843–1910) in Berlin and the French veterinarian Jean Joseph Henri Toussaint (1847–1890) in Paris. In 1880, in fact the year before Pasteur's Poully-le-Fort experiments, Toussaint did a successful experiment on 25 sheeps in the Vincennes region of Paris [12]. Toussaint used chemical treatment with chromate or carbolic acid (phenol) for attenuation, while the Pasteur team used air oxidation. Geison's later research of the original laboratory notebooks has elucidated, that Chamberland in Pasteur's laboratory used the competitor's chromate oxidation for attenuation, instead of Pasteur's air oxidation for the famous experiment at Pouilly-le-Fort. Whether Pasteur himself was involved in this decision, or it purely was a choice made by Chamberland, is not known to my knowledge.

The next even more risky experiment was done on a girl with anthrax infection brought to Pasteur, but the girl died and a claim and criticism could not be avoided. The argument of Pasteur was that the girl already was too sick at the treatment time. Anthrax vaccines for human use was first developed in Soviet Union in late 1930s, due to the fear of biological warfare to be used in World-War II. Human anthrax vaccines have been developed later also in China, the United States, and the United Kingdom. Since then, anthrax vaccines have mainly been used for military protection against biological weapons, like during the Gulf War 1991, where 8000 L anthrax spore suspension was found in Iraq. The anthrax AVA vaccine has been produced in USA since 1970, and used in the AVIP immunization program for US service members established in 1998, vaccinating several millions against anthrax (https://www.cdc.gov/anthrax/resources/anthrax-vaccine-research.html).

THE FIRST VACCINATIONS AGAINST HUMAN RABIES (1885)

From bacteriology to virology with ethically disputed virulent vaccines

Already as a child in Arbois, Louis witnesses several victims of rabies. The epidemic causes 16 deaths in the region, four in the immediate vicinity to Arbois. Pasteur began his research on rabies vaccination already in 1880 [29, 30]. Pasteur's collaborator, the physician Émile Roux (1853–1933)

Fig. 9. The first human vaccination at École Normale Superiéure in rue d'Ulm. The physician Joseph Grancher vaccinates the young boy Joseph Meister with the first human rabies vaccine in 1885. Drawing by Bayard 1886. (Musée Pasteur, Paris, D1638).

inoculated rabies in dogs by trephination. In 1884, a full-scale laboratory to study rabies, complete with animal pens, was setup in Villeneuve d'Etang in the village Marnes-la-Coquettes outside west of Paris. When Pasteur attended the 2nd International Congress of Medicine in Copenhagen in August 1884, vaccination in general and against rabies was presented for the first time, and also preventive methods against rabies in humans were discussed.

The most famous human vaccination story is undoubtfully, when a 9 years old boy Joseph Meister in July 1885 was brought to Pasteur by his mother, who asked Pasteur to try save her son. Joseph had been bitten several times by a rabid dog 2 days before. The boy was vaccinated 13 times with rabbit spinal cord-derived attenuated vaccine with an increasing degree of virulence, given by the pediatrician Joseph Grancher (Fig. 9), and luckily survived. In September 1885, a 15-year-old shepherd, Jean Baptiste Jupille, who had been severely bitten by a rapid dog was also saved by a similar sequence of vaccinations. The first vaccination on Meister was kept secret, but after the second success on Jupille the story was announced and spread quickly. The first scientific article on the human rabies prevention came in 1885 [35]. A third less successful anti-rabies treatment was given to the 11—year-old girl Louise Pelletier later the same year, but she died a few days after the treatment and this initiated arguing that she already had been too ill before the treatment.

Experimental animal study on rapid dogs and rabbits were done over and over again. Various attempts had been done to isolate a pathogenic bacterium from saliva or blood without success. We know now that rabies is a virus-induced disease, but a virus is too small to be visualized by microscopy, and was first described and characterizes by electron microscopy many decades later. We know today that rabies, smallpox, influenza, measles, polio, and many other diseases agents are not caused by bacteria but instead virus induced. Stray dogs were caught and deliberately infected with rabies. It had been noticed that the central nervous system and brain were affected, so attempts to use nervous tissue inserted under the skin were applied with ambiguous results. The surest method was to transmit the disease by drilling a small hole in the

skull of a healthy dogs (trepanning) and injecting disease brain tissue from an infected dog, an unpleased but necessary procedure, that Pasteur did not enjoy using. Finally, multiple experiments were done on rabid dogs given dried spinal cord extract from rapid rabbits, and an increasing success of cure were observed in these dog experiments started in April 1885 and repeated several times in May–June 1885 ([46], p. 244 (fig. 9.1) and p. 251 (fig. 9.2)). A detailed description of these crucial experimental studies can not only be found in the book of Geison [46], but also in the articles of Ham and Ham [47, 48] attempting to link the whole sequence of vaccination experiments together for a better understanding of the progress in the vaccine research done by the team around Pasteur at Ecole Normale Supérieure.

Pasteur and his staff took therefore a risky chance to vaccinate several human victims of rabies already early in 1885. Luckily, the intervention studies done on the rapid dogs with "the other method" of attenuation introduced in May 1885, showed a reproducible successful cure. Therefore, the clinical trials were continued in the summer and autumn 1885. The successful story with Meister's treatment was not immediately released, but after the second success with the second boy Jupille, the news spread quickly all around in the world. In early 1886, four American boys severely bitten by a rapid dog, were send from Newark in New Jersey to Paris for vaccination, and they all survived. During the following years, the rabies vaccine production was escalated, and more than 2500 people were vaccinated. The curative vaccination procedure was hereby proven effective after a recent diagnosis of rabies, a long time before vaccination as a more prophylactic approach were established and introduced many years later.

Since 1876, Pasteur had told his family never to show anyone his laboratory notebooks. For nearly a century these instructions were followed, but Pasteur's last surviving grandson Louis Pasteur Vallery-Radot (1886–1970) donated the majority of these notebooks to Bibliotèque Nationale in Paris in 1964. However, they were not publicly available before his death in 1971, and catalog registration of the documents were first done in 1985. First, several decades after the public release, a few historians were granted limited excess to them [45, 46]. During his lifetime, Pasteur had been criticized for keeping secret his laboratory notebooks and not performing proper preclinical trials on test animals. Pasteur stated that he kept his notebooks and protocols secret for quality control. He later disclosed his procedures to a smaller group of scientist colleagues. One example of discord is, when Pasteur wrote, he had successfully vaccinated 50 rabid dogs before using it on Joseph Meister, but according to Geison [46], Pasteur's laboratory notebooks showed, that only 11 dogs had been vaccinated with random results, but that other trials were ongoing ([46], fig. 9.1 and fig. 9.2). On the other hand, Meister never showed any symptoms of rabies, so the vaccination could not be taken as proof of his "cure," but it could have ended otherwise. One source estimates the probability of Meister contracting rabies to only 10%. Further details of this dispute and on the ethical concerns on the human rabies vaccination can be found both in Geison's book [46] and in many other related debating references [49, 50].

In his book "The private Science of Louis Pasteur" Geison claims, that ethic concerns had not been fully considered and respected by Pasteur, thus revealing deception [46]. These interpretations by Geison have later been debated and questioned by both scientists and other authors [49, 50]. If the vaccination of Meister had gone wrong, the reputation of this intervention had been completely opposite. However, as Pasteur was a chemist without permission to treat humans, it was not Pasteur himself, who gave Meister the attenuated rabies vaccine, but a young pediatrician affiliated to Pasteur' laboratory, Joseph Grancher (1843–1907) (Fig.9), and thereby Pasteur could not be accused directly. Grancher was from 1885 director of Hôpital des Enfants Malades in Paris and from 1900 elected as vice-chairman of the board of directors at the Pasteur Institute.

A highly interesting chapter in Geison's book ([46], page 195–205) describes some initial "clinical" trials, not commonly included in books and articles, which here is carefully and extensively explained. Already on May 1, 1885, a 61-year-old man Girard came to Hôpital Necker in Paris with heavy headache and stomach pain, and refusing to take in food and water or wine, all classical signs of rabies. He explained that he already in March has been bitten by a rabid dog, but the wounds healed and his symptoms of rabies temporarily disappeared. Pasteur received a telegram shortly after his arrival, and came to see the patient with his attending hospital physician. With his acceptance, a vaccination was planned for the next day. On May 2nd 10 a.m., Pasteur arrived again together with his nephew Adrien Loir and his physician colleague Èmile Roux. Girard was given a 1 mL dose of an air-dried attenuated extract from the spinal cord of rapid rabbit. A second injection were planned 10 p.m. the same day, but hospital and health authorities interrupted and Pasteur was told, that Girard could undergo no further vaccine treatment.

After 7 days with various severe illness symptoms, and still refusing both water and food, suddenly Girard's condition became normal and he was released from the hospital without any symptoms of disease on May 25th. Two weeks later, he was declared cured for rabies by Pasteur and the doctors involved. Already on May 23, Pasteur had asked, that this treatment story was not reported further, due to dough on the initial diagnosis.

Within a month, Pasteur treated another case Julie-Antoinette Poughon—an 11-year-old girl—at Hôpital Sct. Denis who in early May had been bitten by her own dog, and suffered with severe headache. Both Pasteur and her hospital doctor agreed that she suffered from rabies. On Pasteur's suggestion, her own doctor gave her two injections, first with the same type of rabies attenuated extract as Girard got, and later the same day at midnight a second injection with a more virulent extract. She died a few days after the treatments.

The second successful vaccination was done on a young 15-year-old shepherd Jean-Baptiste Jupille from Villers-Farley in Jura, bitten by a rapid dog in both his hands on October 15. On initiative from the mayor of the village, Jean-Baptiste was immediately sent to Paris for vaccine treatment initiated on October 20, 1885. Already on the sixth day of daily vaccinations, Pasteur presented a report at the French Academy of Sciences, telling his colleagues how Jean-Baptiste saved six of his younger shepherd friends from attack of a rapid dog, but now was cured from rabies [51].

It is important here to mention, that our days ethical concerns were not existing at that time, so no ethical rules were violated. Retrospectively, diagnosis of rabies was often questionable, for instance in the case of Girard. Perhaps, he was naturally immune before the attenuated virulent vaccination was given. In the second case, the treatment might have been lethally virulent. None of these cases were published. In parallel with these first human clinical trials, several series of experimental experiments on dogs were conducted. One was initiated on 11 dogs on April 13 (before Girard), with ambiguous results, but new series of vaccinations were done on 4 × 10 dogs initiated on May 28th, June 3rd, June 25th, and June 27th (before Meister). These preclinical tests were done with "the other methods"—a new type of attenuation, probably the chromate oxidation method of Toussaint, and now all dogs showed a clear curative effect of the vaccinations (see Geison [46], fig. 9.1 and fig. 9.2). Ethical issues for clinical trials are now far more restricted, but Pasteur's experiments also had to be seen in light of a horrible traumatic lethal disease, also called the "hydrophobia" disease killing many people. Request for more preclinical data are now requested from both toxicological and animal experiments, before vaccines are launched for even initial phase one clinical trials.

LOUIS PASTEUR HAD A STROKE, THEN TWO, THEN THREE (1886–1895)

Buried (1895) in the cellar below his apartment at the Pasteur Institute in the earlier vaccine preparation room

The Pasteur Institute was built in his honor and Louis Pasteur and his family were given a large private apartment in the institute building. During his years there, unfortunately he suffered from several strokes. As the apartment had no elevator, he had difficulties to climb the stairs. As a victim of left arm paralysis since 1886, Louis Pasteur needed help as an experimental scientist. His wife Marie function occasionally as his technical assistant, among many others. Three of his colleagues from ENS, Duclaux, Chamberlain, and Roux also followed him to the Pasteur Institute.

Louis Pasteur's apartment at the first and second floor is now the Pasteur Museum, and the cellar where the rabies vaccines were produced is now his impressive memorial grave site in black marble surrounded with mosaic decorations of his discoveries. He is buried here in the middle of his laboratory vaccine preparation room, where also the grave of his wife Marie is placed, and not at Panthéon as proposed to his family, but after request from Marie Pasteur under their appartment at the institute. It is indeed an impressive grave site, in the basement of the original institute main building. The archive and the museum in the Pasteur Institute house a large collection of books, pictures, and drawings of the older Pasteur from his time as director at the Pasteur Institute. One drawing shows him between the rabbits used for rabies vaccine development (Fig. 10). This drawing has followed me all my life from my first arrival in 1975 and it inspired me to shift from protein chemistry to immunology. In the same way, I could find myself among rabbits since my first stay at the Pasteur Institute as "stagiare" at Service d'Immunologie Cellulaire similarly involved with rabbit vaccinations and antibody development.

From 1888 to his death, Louis Pasteur was the formal director at the Pasteur Institute. The Institute was built on national and international funding to create a new and efficient institute both for production and research on vaccines, and to honor Pasteur and his research team. The institute is still located at both side of the street Rue du Docteur

Fig. 10. The older Louis Pasteur with his rabies-infected rabbits used for vaccine preparation making notes. Drawing by Renourd 1884 (Musée Pasteur, Paris. D1518).

Roux in the 15th arrondissement near Montparnasse. It is continuously expanded and modernized. Latest is the old hospital inside the campus turn into a modern educational center, where now all the many advanced course are hosted. Additionally, a total of 34 affiliated Pasteur Institutes has since been established around the world including one in Hong Kong directed for a time by my French colleague professor Antoine Danchin. See more about the growing Pasteur network in the chapter below. Interestingly, Antoine Danchin wrote recently about Louis Pasteur and his research motivation, driven by our interest to understand the origin of life [52]. This was also the topic of his lecture at the Copenhagen GMO Conference in 2006 [53] and in his interview in the Danish television program Deadline after the conference.

THE PROFOUND SIGNIFICANCE OF PASTEUR INSTITUTE RESEARCHERS (1888–2022)

After Pasteur's death in 1895, his faithful five musketeers, Duclaux, Chamberlain, Roux, Grancher, and Metchnikoff, continued the ongoing vaccine research and added soon new disciplines and research areas to the Pasteur Institute. Cavaillon [11] has carefully reviewed the careers and research work of these five prominent scientists, all of whom were members of the editorial bord of Annales d'Immunologie (IP). The French microbiologist and chemist Emile Duclaux (1840–1904) was the first the join Pasteur at ENS already in 1962, and the French microbiologist and hygienist Charles Chamberlain (1851–1908) was number two to join ENS. He is most known for work on sterilization and development of sterile filtration. Two French physicians, Émile Roux (1853–1933) joined Pasteur's laboratory in 1983 and the pediatrician Jacques-Joseph Grancher (1843–1907) shortly after, that he met with Pasteur at the Second International Medical Congress in Copenhagen 1984.

It was in 1885 that Grancher first applied a rabies vaccine to a human being, namely to Joseph Meister (see above). A total of 13 injections with attenuated dried spinal cord from rabbits with rabies were given over 10 days (Fig. 9). In 1887, Pasteur asked Gancher to lecture about the rabies vaccination at the Académie de Medécine, citing its

successful survival rate. From 1885 to 1909, he was director of Hôpital des Enfants Malades, and from 1900, he was vice-chairman at the board of directors for the Pasteur Institute. He is mostly known for his research on tuberculosis. The Russian-Ukrainian zoologist and immunologist Élie Metchnikoff (1845–1916), who came from Odessa, was the last to join the Pasteur Institute in 1988. He happened to join the institute in time to attend the inauguration of the new Pasteur Institute, and his laboratory was the first to function at the new location. Metchnikoff and Paul Ehrlich got the Nobel Prize in physiology and medicine in 1908. Metchnikoff is known as the father of innate immunity (phagocytosis).

First Duclaux, later Roux became the director of the Pasteur Institute after Pasteur deceased in 1895. Other famous scientists joined the new institute, including the French physician, bacteriologist, and immunologist Albert Calmette (1863–1933), who was the first director for the new Pasteur Institute in Lille and was involved in establishing the Danish State Serum Institute [54]. He is mostly known for his contribution to development of the BCG (Bacillus–Calmette–Guérin) vaccine against tuberculosis. Furthermore, the Swiss-French physician and bacteriologist Alexandre Yersin (1863–1943), who was sent to Hong Kong and later created the first affiliated Pasteur Institute in Vietnam. Up to now, a total of 10 members of the Pasteur Institute have been awarded a Nobel Prize, including the shared prize to André Lwoff, Jacques Monod, and Francois Jacob in 1965, plus the most recent in 2008 to Francoise Barré-Sinossi and Luc Montagnier for discovery of the HIV virus.

The Pasteur Institute (fr. Institut Pasteur) has, since it was established in 1888, been one of the most famous research institutions in the world for a broad range of research disciplines, like microbiology, virology, immunology, and molecular biology. Many French and foreign Nobel Laurates have been affiliated to or visiting this French research center. The Pasteur Institute has also been a considerable factor for scientific development in Denmark. For 150 years, scientists at the Pasteur Institute and the Carlsberg Laboratory have exchanged knowledge and expertise in close collaboration. The connections between the Pasteur Institute and the State Serum Institute are also mentioned above.

In 1975, at an age of 29 years, I had the luck to become a visiting scientist to the Pasteur institute where I worked and studied in Professor Alain Bussard's laboratory for cellular immunology. In this laboratory, my French colleague and lifetime friend Gabriel Peltre and I fractioned antibodies to pure monoclonality by isoelectric focusing and isotachophoresis [55]. The Milstein and Köhler discovery of monoclonal antibodies made with the cell fusion immortalization technology—now known as the monoclonal antibody technology—was published also in 1975. Milstein was a regular visitor in the laboratory of Professor Alain Bussard, so I became inspired by him to work with this technology on monoclonal autoantibodies later in my postdoc period.

I also met the French-Russian scientist Pierre Grabar—innovator of the classical immunoelectrophoresis. Pierre Grabar personally told me about his stay at the Carlberg Laboratory and how Danish scientists from the Carlberg Laboratory regularly visited the Pasteur Institute, which they probably still do. The Danish Pasteur Society granted me my first stay at the Pasteur Institute in 1975 [56], which were followed by many more visits including my postdoc stay for the degree "Diplome d'Immunologie Approfondie" in 1977 [57]. After the immunology course, I stayed another 6 months at the Pasteur Institute with an EMBO fellowship, working in the neurobiology laboratory of professor Jean-Pierre Changeux. In 1979, I organized together with French colleagues an intensive course in quantitative immunoelectrophoresis, an sort of second-generation immunoelectrophoresis, hosted at Ècole Normale Superieure. My friend Gabriel Peltre moved to Unité Immuno-Allergie, and I joint him several times there on FEBS fellowships, grant from the French Embassy in Copenhagen, and on a second time grant from the Danish Pasteur Society. Finally, we both ended up in Ècole Superieurte Physique et Chimie Industrielles and collaborated on microfluidics with me as a visiting professoron on a Joliot-Curie grant.

THE PASTEUR NETWORK AND THE PASTEUR INSTITUTE INTERNATIONAL COURSES (1889–2022)

A food-print to the future research in microbiology and immunology

The creation of 33 associated Pasteur Institutes all around the world started already in 1891 with the first filial in Hô-Chi-Minh (Vietnam) and continue to expand with the latest filial in Sao Paolo (Brazil) in 2019. All these outstations are a part of the international Pasteur Network, significant for scientific progress. Another source for the steadily growing internationalization is the course program at the Pasteur Institut in Paris, open for foreign students, running from the first course in 1889—Cour de Microbie Technique—to the present catalog of courses like

Fig. 11. A vaccination painting by Anna Ancher from 1899. Vaccinations became popular at the end of the nineteenth century and have here inspired the Danish artist Anna Ancher to illustrate the new discovery in a wonderful oil painting. (Skagens Museum, Denmark).

Cours de Microbiologie Géneral, Cours d'Immunologie General, and Cours d'Immunologie Approfondie, and other specializing courses in microbiology, immunology, and virology. This program with numerous Nobel laureates and other top scientists as teachers is also a most significant factor in the global network determining scientific progress.

LOUIS PASTEUR AND HIS CONTRIBUTION AND INSPIRATION TO ART AND SCIENCE

The well-known friendship between Louis Pasteur and the Jacobsen Carlsberg brewery has not only given us the Krøyer painting of the French Art exhibition committee (Fig.7), but might have inspired also another great Danish painter Anna Ancher to create a painting named "A vaccination" from1899 located at the Skagen museum (Fig. 11). The Pasteur Museum in Paris has a large painting with linkage to Denmark, made by the French painter Léon Bonnet in 1886 donated by Jacob C. Jacobsen as a gift to Marie Pasteur showing the older Louis Pasteur with his granddaughter Camille (Fig. 6). Finally, in Denmark, there is not only the sculpture of Louis Pasteur made in marble at the Carlsberg Research Laboratory but also a bronze copy in the outer wall of building near the modern Otilia Hotel at Pasteurvej in the old brewery area (Figs 4 and 6). Multiple French and foreign artist have been inspired both of the anthrax and rabies vaccine stories and created both drawing, painting, and posters now collected at the Pasteur Museum and Archive in Paris.

Many microbial discoveries were done in the nineteenth century mainly based on microscopy, culturing, and exploring of bacteria and yeast, exemplifying Pasteur's quote "the role of the infinitely small in nature is infinitely great" (Table 3). The definition and important role of an immune system was first elucidated in the early twentieth century, starting with the discovery of phagocytosis (innate immunity) by Metchnikoff and Paul Ehrlich (shared Nobel prize 1908), and antibodies (acquired immunity) by Emile von Behring (first Nobel Prize in 1901). The new immunity discipline developed fast in the twentieth century with multiple Nobel laurates [58]. In this way, Pasteur and his coworker can be seen as the progenitors to immunology. From the description of the antibody structure and function, research moved toward the genetic and cellular regulation. Not surprising, many members of the Pasteur Institute have been nominated with a Nobel Prizes—10 in all up to now [59]. New discoveries will according to Pasteur occur when "chance favors a prepared mind" (Table 3).

Concerning my personal relationship to the Pasteur Institute few selected references are included [55–57, 60]. A short Danish bibliography on Pasteur [61, 62] and on the history of vaccination in Denmark are also included [63]. Finally, references to the "chance favors only the prepared mind" quote of Louis Pasteur [64] and to other articles in this issue of APMIS [65, 66]—all in the honor of Louis Pasteur's bicentenary and the centenary of the Danish Pasteur Society. For further reading in the worldwide enormous among of articles and books on Louis Pasteur's private life and research, multiple Internet source can be found like his Wikipedia bibliography, and descriptions from Louis Pasteur homepages from both École Normale Supériere and Institut Pasteur [67–73] but also from the online available articles on his many important research achievements [47, 48].

This article is dedicated to my deceased Pasteurian colleague and great friend Gabriel Peltre [60], who has given me so much inspiration and many opportunities for collaborations within France and warm friendships. Another Pasteurian colleague, Pascal Poncet (pascal@pasteur.fr), to whom I offer my greatest thanks for his historical interests and help to arrange our visit to the Pasteur Museum in October 2022. A planned coauthorship had unfortunate to be canceled due to his acute illness. We thank the museum director Chantal Pflieger (chantal.pflieger@pasteur.fr) for our fruitful discussion and visit to the Pasteur Museum and her guidance to the Pasteur Archives, who gave me permission to use photos for this publication (Fig. 1, 6, 9, and 10). We thank her also for the gifts of Bruno Latour book from 1994—"Pasteur – une science, un style, un siècle." My acknowledgement goes also to a third Pasteurian, Jean-Marc Cavaillon (jean-marc.cavaillon@pasteur.fr), author to a recent review on Pasteur [12] for multiple communications and advices, and for access to his PowerPoint presentation [40]. Finally, my earlier supervisor emeritus docent Thorkild C. Bøg-Hansen from University of Copenhagen is acknowledged for his comments and proposals to the final article.

The Hirschspungske Collection is acknowledged for the permission to use the photo of the Krøyer painting of the art committee 1988 (Fig. 7) now located at the "Ny Carlsberg Glyptotek" in Copenhagen. I also thank Skagen Museum for the permission to use the photo of the Anna Ancher painting 1899 (Fig. 11). The Carlsberg archive has given permission to use the photo of Emile Chr. Hansen in his laboratory from 1908 (Fig. 10). In this connection, I thank Merete Yding (merete.yding@carlsbeerg.com) for her suppoty and contact to the Carlsberg archive, and for her guidance to the Paul Dubois marble bust in the entrance hall in the historical building of the Carlsberg laboratory opened in 1875 (Fig. 4). The photos of the Pasteur marble bust and its copy in the wall at Pasteurvej at the old Carlsberg factory (Fig. 5), plus the memorial plate for Louis Pasteur's first research laboratory at École Normale Supériure in rue d'Ulm (Fig. 2) is my own property.

DISCLAIMER

The author is not a historian of profession, why I apologize for any incorrectness in names and mentioned years. My background is as a researcher in biochemistry, microbiology, and immunology with multiple stays at the Pasteur Institute in Paris, Hôpital Broussais in Paris, Institut d'Embryologie in Vincennes, École Pratique des Hautes Études at Centre d'Oceanologie de Marseille, and École Supèrieure Physics et Chimie Industrielle in Paris. My aim with this publication is to honor a great colleague at his bicentenary birthday and to celebrate the 100 years anniversary of the Danish Pasteur Society, which initiated my specialization in immunology with a travel grant to Service d'Immunologie Cellulaire at the Pasteur Institute in 1975.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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