

The origin of the production of diphtheria antitoxin in France, between philanthropy and commerce

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SUMMARY: 1.—Introduction. 2.—The origins of the serum. 3.—The production process. 4.—Serum at the Pasteur Institute; the pros and cons of media exposure. 5.—The serum and the finances of the Pasteur Institute. 6.—The serum legislation. 7.—French culture and the serum industry. 8.—Conclusion: serum in European cultures.

ABSTRACT: Serotherapy for the treatment of diphtheria represented a major therapeutic innovation at the end of the nineteenth century. The manner in which large-scale production of this medicament was undertaken and the regulations that governed its production and distribution were important elements of public health policy in France as in other European countries. This paper describes the dominance of the Pasteur Institute in this field and, starting from this observation, explores what this event in the history of medicine can tell us about the governance of public health in fin-de-siècle France. The particular organization of this institute and its monopoly of specialist microbiological knowledge allowed it to raise money for serum production from both private and public sources, walking the line between a commercial pharmaceutical venture and a philanthropic enterprise.

PALABRAS CLAVE: seroterapia, Instituto Pasteur, Tercera República, cruz, Salud Pública.

KEYWORDS: serotherapy, Pasteur Institute, Third Republic, Croup, Public Health.

1. Introduction (*)

Histories about microbiology offer fertile territory for puns on the word «culture», but is there more to this trope than simple wordplay? Is there some deeper link between the cultures grown on the laboratory bench

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and the diverse cultures that have developed within human civilization, in particular is there a connection between bacterial cultures and national cultures? Are bacteriological practices and their associated institutional systems themselves akin to the bacteria that are so sensitive to different culture media? Do certain social structures and national predispositions provide fertile ground for one particular form of administration and legislation while inhibiting others? In this paper, I will be arguing for the importance of historical contingencies in determining the form taken by the legislation and production of the diphtheria antitoxin in France at the end of the nineteenth century. Behind this argument however, I want to pass a weaker but broader one concerning the roots of this very configuration in French culture. Thus, behind the accidental form taken lies a deeper structuring influence of a characteristically French approach to medico-legal affairs and the politics of public health under the Third Republic.

This history concerns the introduction of serotherapy, a revolutionary new treatment for diphtheria, at the end of the nineteenth century. This widespread disease had both endemic and epidemic features, and was seen as particularly tragic due to its high mortality rate among babies and children. The symptoms associated with diphtheria were feared across Europe, with babies often painfully suffocating due to the characteristic ‘false’ membrane that formed across the throat. Indeed, the popular name for the disease —croup— was an onomatopoeia for the choking noises issuing from the victims’ throats in the final stages of suffocation. The presence of the disease and its reputation for mercilessly ravaging families, made the promise of an effective treatment particularly charged. It also explains much of the iconography around the disease, with mourning mothers prominent in allegorical representations of both the disease and its cure.

2. The origins of the serum

The development of serotherapy —the use of specific animal-derived blood sera for treating infectious disease— took place around two poles of research, Paris and Berlin, although the bulk of the relevant work leading to the treatment was carried out in Berlin¹. The credit for isolating the bacterium

1. For more on this development and production of the serum in Germany, see THRUM, Carola, *Das*

responsible for diphtheria is usually given to Friedrich Loeffler, who used the techniques of in vitro culture and staining recently pioneered by Robert Koch to prove to his own satisfaction that the bacterium was responsible for the disease. Nevertheless, it was the two French scientists Emile Roux and Alexandre Yersin who in 1888 —the same year that the Pasteur Institute was inaugurated in Paris— first developed a technique (using the porcelain filter developed by Chamberland, another member of the Pasteur Institute) for isolating the deadly toxin produced by the bacteria². Indeed, the disease, characterized by the formation of a membrane in the throat that could cover the larynx and suffocate its victims, more commonly killed by heart attack or other muscular paralysis, which were, unlike the membrane, effects of this toxin. Loeffler was already convinced that just such a soluble toxin was responsible for the high mortality associated with this disease, although he did not isolate it. While the isolation of the toxin would prove a key technique for the later production of the antitoxin, it was not a crucial step in the development of the principle of serotherapy, whose foundations were laid in a publication by Behring and Kitasato that appeared in the *Deutsche Medizinische Wochenschrift* in 1890³. Here, the German and Japanese microbiologists used blood from animals rendered immune to diphtheria and tetanus to cure infected non-immune animals, with Kitasato working on tetanus and Behring on diphtheria. While the results of the experiments were complex and sometimes confusing, the efficacy of the serum as a specific treatment held out much promise, and the authors saw from the outset the potential of this discovery for human medicine. Thus, between 1890 and 1892, Behring worked with another Berlin researcher, Erich Wernicke, to develop a stable system for producing an effective serum against diphtheria in humans⁴. The final process used for large-scale production employed horses to generate the serum for human use. In principle, the technique —inducing immunity in the host animal, and then regularly bleeding it and

Diphtherie-Serum: Ein neues Therapieprinzip, seine Entwicklung und Markteinführung, Stuttgart, Wissenschaftliche Verlagsgesellschaft, 1995.

2. ROUX, Emile; YERSIN Alexandre. Contribution à l'étude de la diphthérie. *Annales de l'Institut Pasteur*, 1888, 629–661.
3. BEHRING Emil; KITASATO Shibasaburo. Ueber das Zustandekommen der Diphtherie-Immunität und der Tetanus-Immunität bei Thieren. *Deutsche Medicinische Wochenschrift* 16, 1890, 49, 1113–1114.
4. See SCHULTE, Erika. Der Anteil Erich Wernickes and der Entwicklung des Diphtherieantitoxins, MD thesis, FreeUniversity, Berlin, 2000.

separating out the serum for intraperitoneal injection into humans— was not too complicated, but serum production depended on many factors that were sensitive and required delicate manipulation.

3. The production process

The first stage, therefore, in the production of serum for the treatment of diphtheria was the immunization of horses, which already implied the mobilization of a considerable amount of microbiology, consisting in the skilful handling of experimental disease in animals, rather than any grand theories about the nature of immunity. Indeed, much of this process deployed the techniques that Pasteur and Koch had used to found the discipline, including the initial step which involved the collection of bacteria from children suffering from the disease to culture it artificially before introducing it into animals, thereby creating the «experimental» disease. For this, the scientists needed a confirmed clinical case of diphtheria, supported by a positive identification of the bacterium under the microscope, whose virulence was in turn guaranteed by the gravity, if not lethality of the symptoms. Thus, we find loose sheets of paper at the archive of the Pasteur Institute from 1894, consisting in a list of horses carrying the names of children who had passed through the wards of the *Hôpital des Enfants Malades*. Abstracted from the dead or gravely sick children, the diphtheria bacilli had to be kept alive and encouraged to multiply in an artificial medium, whose constitution could influence the strength and quantity of the toxin, a vital variable in the process.

While it is probable that immunization was initially achieved in France by injecting a culture of the bacilli responsible for the disease isolated from patients, later the toxin alone was used to achieve immunity. Indeed, the road from the experimental obtention of serum to its large-scale production for nationwide clinical use was no doubt a difficult one, where many variations were tried, and much learned about the practical features of induced immunity. In the context of toxin production, Louis Martin's MD thesis records a whole series of experiments aimed at perfecting techniques for maximizing production in terms of both the quantity and quality of the toxin⁵.

5. MARTIN, Louis. Production de la toxine diphtérique, MD thesis, Faculté de Médecine, Paris, 1897.

Once sufficient toxin had been produced, the bacteria then had to be removed — killed or filtered— before the purified toxin could be injected into the horses, the living producers of the antitoxin. The first injections were done with toxin mixed with an iodine solution, which reduced its toxicity. Over a matter of weeks the regular injection of treated toxin followed by pure toxin led to the full immunization of the horse. Once a horse was immunized, it could be bled (between 4 and 6 litres per bleeding), and the serum separated out from the red blood corpuscles (generally by leaving it to stand). The serum was then transferred into phials, which were sealed ready for distribution to pharmacies or hospitals. In France the standard dose was fixed at 20 cubic centimetres, and the Pasteur Institute introduced its own service for distributing the doses around France and abroad.

4. Serum at the Pasteur Institute; the pros and cons of media exposure

In France, this process of serum production was developed by a group of three researchers in Paris, all associated with the nascent Pasteur Institute. The head of the group was Émile Roux (1853-1933), Pasteur's spiritual successor, although, following Pasteur's death in 1895, he did not become director of the Pasteur Institute until 1904. The other two central figures in this research enterprise were the veterinarian Edmond Nocard (1850-1903) and the physician Louis Martin (1864-1946). Nocard contributed a great deal to the development of serotherapy in France, thus continuing a longstanding collaboration with Louis Pasteur himself. In a commemorative speech, Roux is quite explicit about the importance of Nocard's contribution, as well as the vital contribution of the research facilities at the National Veterinary School at Maisons-Alfort near Paris.

«When serotherapy was introduced, we would never have been able to install a service capable of responding to the legitimate impatience of the public so promptly without Nocard. His qualities as an organizer and leader of men, and his experimental skill saved us in this affair. The laboratory at Alfort became a kind of branch of the Pasteur Institute: here, Nocard prepared the serum and taught the young veterinarians who later became our precious collaborators, animated by the spirit of their master»⁶.

6. Discours de M. le Dr Roux, Directeur de l'Institut Pasteur In: *Edmond Nocard 1850-1903. Discours*

Louis Martin was more important in what followed, and effectively ran the production of serum by the Pasteur Institute starting at the end of 1894. From the beginning, replacing Yersin as Roux's assistant, Martin played a leading role in developing the serum for the Institute. While the French contributed little to the original research on serotherapy, they succeeded in producing experimental quantities of the serum in the period 1893-1894. The first French trials of the serum produced at the Pasteur Institute started on 1 February 1894 at the *Hôpital des Enfants Malades*. On this date, Dr Simon allowed Drs Chaillou and Roux to treat the children on his diphtheria ward for the first time with what was still an experimental product. Roux was soon convinced of the efficacy of the serum, and prepared a paper comparing the results of his experiments with the «normal» mortality of diphtheria as observed at the *Hôpital Trousseau*, as well as the mortality prior to the use of the serum in the same ward. Roux's presentation made at the *Eighth International Conference on Hygiene and Demography* held at Budapest in September 1894 was widely and enthusiastically reported in France, making the front page of *Le Figaro* on 6 September. This press coverage had two consequences that would crucially determine the form taken by serum production in France, and would thus have an influence on the legislation that was introduced to regulate serotherapy. First, the public interest aroused by the announcement of this new cure opened up the possibility of raising funds for French serum production by subscription. It was Gaston Calmette (the brother of the prominent pastorian Albert Calmette) at *Le Figaro* who took the lead, initially appealing for donations directly to the Pasteur Institute before setting up a subscription at the paper, which was echoed by local papers throughout the country. Second, the publicity created an enormous demand, a demand focused on the *Hôpital des Enfants Malades* and the Pasteur Institute⁷.

The fundraising effort launched by *Le Figaro* on 20 September 1894 was very successful, easily surpassing its initial optimistic goals. The target fixed by G. Calmette was to raise 30 000 francs, which would pay for providing serum to the poor, but after only a month the fund had already

prononcés à la cérémonie d'inauguration du monument élevé à sa mémoire. Paris, Masson & Cie, n.d. (p. 46).

7. In October 1894, the *Hôpital des Enfants Malades* was obliged to open more beds in the diphtheria service. See Archives de l'Assistance Publique, *Historique des établissements*, 1894, p. 292.

attained 240 000 francs, reaching 612 000 francs by the end of the year. The publication of the sums donated in the pages of the newspaper encouraged philanthropic competition among the Parisian bourgeoisie, with the donation of horses, particularly retired racehorses, to produce serum garnering further publicity. These generous donations allowed Roux to put into effect a plan for creating a large-scale serum production facility. The site chosen for serum production was Garches, a country house set in a large estate with stables that had formerly been used by the cavalry, and had been made available to Pasteur by the French government for his rabies research. Roux invested much of the subscription money in enlarging and improving the buildings on this estate as well as buying the guinea pigs and horses necessary for producing the serum. Thus, from the dozen or so horses kept at the Institute in September 1894 Roux increased the capacity to some 136 by the beginning of 1895, with nearly all the horses now located at Garches. This increase in the number of horses allowed the Pasteur Institute to produce over seven and a half thousand liters of blood for making serum in the year 1895.

Nevertheless, looking more closely at these dates, we can see a crucial lag that would cost the Pasteur Institute credit in the eyes of many, as well as the possibility of establishing a complete monopoly over serum production. The principal problem was the length of time required to turn a newly acquired horse into a serum producing unit. The initial tests for diseases lasted a week or so, and then there was the variable period of immunization, which was initially estimated at around three months. This three-month lag meant that the horses bought to respond to the pressing demands of September 1894 were not ready to produce serum until the end of the year, or more likely the very beginning of 1895. This led to much frustration and disappointment not only on the part of potential patients, their doctors and local health administrators, but also on the part of the serum producers at the Pasteur Institute. This is how Roux himself retrospectively described the situation in this period from September 1894 to the end of the year in a report written for the Institute.

«Requests for serum came from everywhere, and like a rising tide threatened to submerge the bacteriologists. As for us, we would not have believed such a rapid success possible, we thought that like all good things, the serotherapy for diphtheria would only be introduced slowly, and so we only prepared enough horses to supply the hospital services, and our poor

animals, even at the cost of giving up all their blood, would not be capable of furnishing one hundredth of the required quantity»⁸.

Thus, the early period of serum production at the Pasteur Institute was characterized by a paradoxical situation, in which the Institute was gathering a great deal of money to pay for the production of the medicine, thereby raising expectations that they were unable to satisfy in the short term.

While Roux initially conceived of the Pasteur Institute as the sole producer of diphtheria serum, this dream of a Parisian monopoly was undermined by the Institute's incapacity to produce sufficient serum during this crucial period from September 1894 to January 1895. Indeed, by January 1895, the Pasteur Institute was in a position to supply the whole of France with serum, following the spectacular scaling up of production centred on the new facility at Garches. Nevertheless, this four-month period in which the Pasteur Institute was unable to supply the demand forced Roux to consent to the initiation of serotherapy projects all over France. Looking at the contemporary press, one can read reports of initiatives in Le Havre, Toulouse, Nancy, Marseille and Lyon, among others. To illustrate the consequences of the production problems I have been describing as they affected the regions outside Paris, I will consider what happened at Lyon. Here, following an initiative of the local Public Health Office, an academic veterinarian was able to start supplying the precious serum to Lyon's hospitals starting in February 1895. Following Emile Roux's announcement at Budapest, Dr Gabriel Roux (1853-1914), the director of the Bureau d'Hygiène was charged by Lyon's mayor with obtaining serum for the city. Roux wrote to the Pasteur Institute in Paris, but received a disappointing reply:

«The Pasteur Institute briefly replied to me that the antitoxic serum would not be sent out to the provinces within the next two months, and then would only be delivered to hospitals and patients signed up with the 'Bureaux de bienfaisance»⁹.

8. Archives de l'Institut Pasteur, Direction (1888-1940) File «Création du Service de Sérothérapie».

9. Rapport de M. le Dr Roux soumis à Monsieur le Maire, 6 November 1894, Archives Municipales de Lyon 1125 WP 023 2.

In his report to the Mayor, G. Roux suggested that Lyon should try to produce its own serum like its smaller neighbors St Etienne and Grenoble. The task was entrusted to Saturnin Arloing, a professor at both the medical and the veterinary schools. The project quickly took on a larger scope than simply the production of serum, with Roux conceiving an integrated microbiology laboratory for pathological analysis. Indeed, this was a common feature of the provincial centers I have been able to look at, Lyon and Nancy in particular. While the serum institutes were set up to produce serum for local needs (generally supplying a significant but local region) they also developed a diagnostic capacity, often in the same building. The creation of a microbiology laboratory for diagnosis tempted many into research. The final step taken by Nancy, and possibly other serum producers as well, was to organize courses in microbiology based on the model of the Pasteur Institute, where many of the staff had themselves received their initial training. Thus, the indirect result of Paris's initial inability to supply the provinces was not only the de-localization of serum production with regional centers (usually with only two or three horses) supplying local demand funded by the municipality or public donations, but also the introduction of veritable regional Pasteur institutes. The irony of this situation was that these regional centers found themselves in the same situation as the Pasteur Institute, needing to wait three months to have immunized horses ready to produce the serum. Thus, although he started the immunization process in November 1894, Arloing was only able to supply the Lyon hospitals with locally produced serum in February 1895, by which time a generous supply was available from Paris.

5. The serum and the finances of the Pasteur Institute

The success of the high-profile fundraising campaign headed by *Le Figaro* led to other problems for the Pasteur Institute, although these were not related to any technical difficulties associated with serum production but rather the ambiguous status of the Institute itself. Paid for by a public subscription in the first place, the Institute, like Louis Pasteur himself was never to charge for its rabies vaccine. While this philanthropic side of the Institute was generally the only one that the public saw, it did not prevent the Institute from making money, particularly from its agricultural products. From the beginning, Roux planned to charge for the diphtheria serum, only

consenting to provide the serum free of charge to the indigent. Nevertheless, the Institute expected to be paid even for this free serum, pressuring local government bodies to cover the costs via direct subsidies. While the Institute might have been clear regarding its policy, the fact that they asked for public donations to pay to launch the initial large-scale production and still expected payment for the product was not readily accepted by many citizen-donors. In February 1895, an anonymous reader of *Le Figaro* wrote to Duclaux, in his capacity as director of the Pasteur Institute:

«Is the announcement in the papers true, that on February 10 the Pasteur Institute will be *selling* serum to the pharmacists? Please allow me to ask you on what have you spent the millions that we have given you»¹⁰.

In his reply, Duclaux argued that there had been a misunderstanding, and presented some doubtful statistics to show that the Pasteur Institute needed the revenues from the sale of the serum to pay for its production. In a similar vein, if we look in the archives of the Pasteur Institute, we find letters from local administrators that seem to confuse donations to the subscription with money sent for purchasing the serum. Thus, for example, a finance officer from the town of La Motte-Servolex in the Savoie sent 30 Francs to the Pasteur Institute at the end of 1895, which he described as the «subscription of the Commune of La Motte-Servolex (Savoie) for the purchase of serum»¹¹, suggesting that a number of those who contributed to the fund-raising campaign believed they were buying serum. While the donors may have misunderstood, neither *Le Figaro* nor the Pasteur Institute went to any great lengths to make things clear. This confusion suited the Institute, which continued to capitalize on its image as a philanthropic enterprise, and had no interest in publicizing the fact that it might be able to make money from the sale of the serum. This ambiguity on the part of the Institute and its public perception has been characteristic of the organism throughout its history, and even today its mixed public-private

10. Letter to Duclaux sent to *Le Figaro*, February 1895, Duclaux folder at the Archives de l'Académie des Sciences, Paris. Emphasis in the original.

11. Letter in the Duclaux folder at the Archives de l'Académie des Sciences, Paris. The problem is a failure to distinguish clearly between «subvention»(subsidy), «subscription» (subscription), and payment.

economy is poorly understood by prospective donors¹². Another ambiguity can be seen in the relationship between the Pasteur Institute and local government administrations. While it demanded and received payment from regional and municipal councils for supplying serum to the indigent, it remained staunchly independent. This is in sharp contrast to somewhere like Lyon, where the serum production that was directly supported by the municipality did not pretend to any kind of independence. In light of the size of government subsidies, the Pasteur Institute might be regarded as an «ersatz» government body, performing a function that given slightly different historical circumstances might have been performed by an organism that was officially part of the Ministry of the Interior. We will return to this point in the conclusion.

6. The serum legislation

As we have seen, this serum treatment for diphtheria aroused considerable interest and much hope, but it was introduced into a legislative vacuum in France. If the serum were to be considered a medicament, then in principle it had to be inscribed into the official pharmacopoeia (which it was not) and could only be sold by pharmacists. If it were not considered a medicament, then no specific laws applied to its production and distribution. In light of the publicity surrounding this new treatment, there was a widespread feeling among the elected officials in France that it should be regulated in some way. At the time the serum was introduced, a bill was already under discussion by the government that promised to reform much of the legislation covering French pharmacy, and the French deputies decided to integrate a specific section dealing with the serum and other injectable products of biological origin. As this bill bogged down, however, the legislators took the serum legislation out to pass it rapidly through the Assembly in another form. There were some opponents of the legislation in the Assembly, who argued that such legislation would constrict French innovation by closing down the free market in organic extracts and vaccines, but the urgency of the legislators rapidly overcame any such opposition.

12. For more on the history of the Pasteur Institute's «hybrid» finances, see LÖWY, Ilana. On hybridizations, networks and new disciplines: The Pasteur Institute and the development of microbiology in France. *Studies in the History and Philosophy of Science*, 1994, 25, 655-688.

The justifications for this urgency played on the chord of the tragic fate of children and adults alike killed by unscrupulous dealers in ineffective or contaminated serum.

Thus a new law was propounded on April 25 1895 covering all sera, as well as attenuated viruses, modified toxins and analogous products, and injectable organic extracts.¹³ This legislation responded to a particular problem that the sera posed to pharmacists. Normally, the pharmacist was responsible for the safety and efficacy of everything he sold, but the ordinary pharmacist could not check the quality or even a minimal level of the serum's efficacy. This was due to a lack of both the necessary materials and the appropriate training. Thus, the Ministry of the Interior officially relieved the pharmacist of this traditional duty, and sought to guarantee the quality of the serum by placing a series of restraints on the producer. The new law stated that only authorized institutes could produce and distribute serum in France. This meant that the system for granting such authorizations, which were in principle, but apparently not in practice only provisional, would assume enormous importance in structuring the production and sale of serum. While the authorizations would be granted and enforced by the government (the Ministry of the Interior), the decision would be entrusted to a body that came to be known as the Serum Commission composed of members appointed from the Academy of Medicine and the Ministry's Consultative Committee on Public Health¹⁴.

The composition of the committee was in part dictated by the law, with the secretaries of the Academy of Medicine automatically members as were members of the government's Consultative Committee on Public Health¹⁵. Other members appointed from amongst the membership of the Academy of Medicine included Nocard, Duclaux, Straus and Grancher all active supporters of pastorian science if not active members of the Pasteur Institute itself.

13. *Journal Officiel*, vendredi 26 avril 1895, no. 113.

14. The Serum Commission was appointed by an *arrêté ministériel* from 15 mai 1895. See MINISTÈRE DE L'INTÉRIEUR. *Sérum thérapeutiques et autres produits analogues, législation et réglementation 1895*, Melun, Imprimerie administrative, 1896.

15. The Serum Commission was initially composed of the following members: Brouardel, Monod, Proust, Chantemesse, Bompard, Delaunay-Belleville, Bergeron (Secretaries of the *Académie de Médecine*), Nocard, Duclaux, Straus, Grancher (ordinary members of the *Académie de Médecine*), and Pouchet, Ogier, Thoinot, Netter (Members of the *Comité consultatif d'hygiène*).

With the heavy bias of the commission in favor of the Pasteur Institute, it is unsurprising that the first institution to be approved for production of the diphtheria serum in France in January 1896 was the Institute itself, along with the Pasteur Institute in Lille, an institute in le Havre, one in Nancy, Arloing's laboratory in Lyon and another laboratory in Grenoble. In June 1896, production was approved for laboratories in Bordeaux, Marseilles and Montpellier, with Charles Nicolle's laboratory in Rouen following a year later¹⁶. While the law also allowed for the commission to approve imported serum, this was apparently never done. Thus, despite widespread recognition of the superior efficacy of German serum by the turn of the century, it was technically illegal to sell or use it in France.

This French legislation performed the vital political and public health tasks of organizing the production and sale of the serum, showing publicly that the government was assuming responsibility in such matters, and in turn relieving pharmacists of the unfeasible task of quality control for the serum¹⁷. Nevertheless, the Serum Commission effectively served to delegate the control of sera to the Pasteur Institute in Paris, with prominent pastori-ans more or less directly deciding who could enter the field of potential competitors. Roux's dream of a monopoly was in a sense realized, albeit in an attenuated form. In terms of the amounts of serum produced, the dominance of the Institute was incontestable; while the plant at Garches produced some 100 000 doses in 1896, the production in Nancy for the same year was only 2 000 doses¹⁸. Furthermore, at 2 percent of the Pasteur Institute's production, Nancy was a relatively large institute. Leaving the issue of the scale of production aside, however, it is important to note that none of the institutions approved for producing the diphtheria antitoxin were private enterprises. All the regional producers were attached more or less directly to medical faculties, and none to existing pharmaceutical

16. The list is taken from GEOFFROY, Henri; LEVASSORT, Charles. *Les Sérums et la loi*, Clermont, Syndicat des Médecins de la Seine, 1912, p. 36.

17. The German legislation for serum also relieved the pharmacist of this duty, founding a centralized laboratory to test the serum. See Axel Hüntelmann's contribution to the present volume and HARDY, Anne I. Paul Ehrlich and commercial serum production: on the control of diphtheria antitoxin in the laboratory and in industry. *Medizinhistorisches Journal*, 2006, 41 (1), 51-84.

18. The figures for production at the Pasteur Institute are taken from notes found in Roux's archive at the Pasteur Institute, Paris. The figures for Nancy are from a report for 1896 located at the Municipal Archives, Nancy.

or chemical companies. Thus, while the law did not preclude private production by commercial enterprises, there was none. Why, then, was there no competition from the private sector in what was a potentially lucrative field? As we have already remarked, the question of what kept these competitors out is an interesting one —the reason may well have been the low prices charged by the Pasteur Institute and the relative ease of obtaining the serum free of charge, but in light of the low investment needed to produce the doses (a 20 cc ampoule was sold for 6 francs by the Pasteur Institute), it is quite plausible that private producers were interested, but found their demands rejected by the Serum Commission. Another possible explanation for this lack of competition is the shortage of personnel suitably qualified in bacteriological techniques, skills they could initially only acquire at the Pasteur Institute itself. Whatever the reason, without the records of this commission it is impossible to conclude this issue with any certainty¹⁹.

One can also turn the question around, and ask why the French state did not assume direct control of the production and surveillance of the diphtheria antitoxin, taking the opportunity to set up a National Serotherapy Institute, which could have been at once producer and regulator. In the absence of a Pasteur Institute, this might well have been the response of the French state, fitting a tradition of creating republican organisms to protect the vital interests of citizens. From this perspective, the willingness of the government to delegate the task to the Pasteur Institute (albeit via the Academy of Medicine) reflects the Institute's quasi-public status, as well as its monopoly over the requisite expertise. One can also characterize this response as just another aspect of a traditional culture of the French administration of medicine. After all, the government had formerly delegated responsibility for the contents of the pharmacopoeia, the testing of mineral waters and other pharmaceutical products to the professional bodies concerned, particularly the Academy of Medicine²⁰.

19. Despite searching in many French archives, these records have not been located. Any information concerning their whereabouts would be gratefully received.

20. For a study of the role of the Academy of Medicine in France in the nineteenth century, see WEISZ, George. *The Medical Mandarins: The French Academy of Medicine in the Nineteenth and Early Twentieth Centuries*, Oxford, Oxford University Press, 1995. For a history of the approval mechanisms for medicines in France covering a similar period, see CHAUVEAU, Sophie. *L'invention pharmaceutique. La pharmacie française entre l'Etat et la société au XX^e siècle*, Paris, Institut d'Édition Sanofi-Synthélabo, 1999.

7. French culture and the serum industry

There were a number of important factors influencing the management of serotherapy at the end of the century in France that I have not had the time to explore. One is the popularity of opotherapy, the use of animal organs and their extracts as medicines or stimulants at this time. Inspired by Brown-Séquard, this novel type of medicine had introduced a number of new players into the pharmaceutical or para-pharmaceutical market, including slaughterhouses as well as specialist firms. Thus, the legislation served to put some order into a sprawling and potentially hazardous market, showing that the government was going to distinguish between «legitimate» scientific medicine and the rest. While opotherapy was not outlawed (except for injectable forms), the presence of products from the Pasteur Institute that were distributed through official channels pushed these other therapies to the margins of physician-based medicine²¹.

Stepping back, we also need to consider the particularities of the political and social situation in France under the third Republic. In the wake of the profoundly unsettling Franco-Prussian war of 1870-1871, France was confronted with a vision of (military) modernity as well as what was perceived as a clear demonstration of its own backwardness. One of France's greatest heroes in the struggle to impose its own modern scientific image in the face of Prussian supremacy was, of course, Louis Pasteur. While Pasteur himself did not cure a large number of people with his treatment for rabies, it nevertheless became emblematic of a renewal in French medical science, a return of Paris to the very center of medical innovation in the new age of microbiology. Subsequently, the treatment of diphtheria would come to occupy a crucial position in the prolongation of the Pasteur myth —now centered on the institute that bore his name— being the first major disease to be successfully treated by a microbiological technique²². In a sense, the

21. Indeed, there is an interesting parallel to be made between this configuration and today's flourishing «nutriceutical» industry that operates at the margins of sanctioned (officially recognized by the social security) pharmacy, and includes the much vaunted but unregulated omega-3 family of food supplements.

22. It is important to bear in mind the failed tuberculine treatment for tuberculosis introduced by Koch a few years earlier. While this originally seemed to promise a major success in a very widespread disease, it turned out to be a great disappointment proportional to the hope it had engendered. See Christoph Gradmann, *Krankheit im Labor. Robert Koch und die medizinische Bakteriologie*, Göttingen 2005.

destiny of the Pasteur Institute rode on the serum; this did not necessarily require its success in combating diphtheria —and the evidence for its efficacy is not as convincing as is often presented— but at least required its competent handling. The Pasteur Institute needed to be sure that the practices put in place would ensure the absence of any serious accidents that could be ascribed to any negligence on their part. Furthermore, much effort was invested both on the part of the pastorian scientists and the press in inscribing the diphtheria serum in a continuity of science-based philanthropic ventures associated with Pasteur. In personal terms, it was clear that Roux was the individual who inherited the sacerdotal status of the great, self-sacrificing, modest, life-saving scientist enjoyed by Pasteur even after his death²³. Furthermore, the money raised by the subscriptions and the sale of the serum served as a real boost to the Institute's finances, and it is not clear that it could have easily survived this period without the serum.

While French diphtheria antitoxin production unquestionably invigorated both the finances *and the image* of the Pasteur Institute, therefore, it is important to remember that it also served other nationalist purposes. Indeed, we can see what is at stake more clearly in the case of the Sero-therapeutic Institute of the East (*Institut sérothérapique de l'Est*) founded in Nancy at the very beginning of 1895. Between 1871 and 1918, Nancy was the French city the furthest East, and it surely would have been cheaper in this case to buy serum from Germany rather than producing it. Nevertheless, the city chose to found a dedicated Institute for the production of the diphtheria antitoxin. At the end of the century, Nancy's Institute, under the direction of Eugène Macé (1856-1938), came to occupy its own sizeable purpose-built premises financed by a donation from a wealthy French businessman, Osiris. It is not without significance that the other contribution Osiris made to Nancy during this same period was a statue of Joan of Arc, who had successfully driven out another occupier almost five centuries earlier.

23. In his analysis of Pasteur's success in introducing microbiology into the hearts and minds of the French, Bruno Latour has already suggested how the adoption of this approach by the pre-existing community of public health activists (the «hygiènes» movement) served to integrate it into French culture, providing another link with philanthropic public health ventures. LATOUR, Bruno. *Les Microbes: guerre et paix*, Paris, A.-M. Métailié, 1984.

Moving from considerations of national politics to the more local question of medico-legal culture, what can we learn from the mode of regulation adopted by the French government? In this case, we see the French state effectively delegating responsibility to the medical profession, although under the oversight of the Ministry of the Interior (who would presumably have been held responsible were there any accident involving the approved serum). As I have already remarked, there is nothing unusual about this approach. Indeed, the only case of large-scale direct government intervention into medical affairs is around the period French revolution, where the functions of the faculty of medicine and the pharmacy guilds were brought under direct state control after centuries of autonomous functioning as a guild profession. Nevertheless, what is novel in the case of the sera is that the government delegated its authority to the Pasteur Institute albeit via the traditional route of an elite medical academy. The Pasteur Institute was not, however, a more or less formal professional group of microbiologists, it was somewhere between a philanthropic medical foundation and a for-profit pharmaceutical enterprise. Independent of any direct control by a peer group, it set its own agenda, and managed its own finances, derived from sales and subsidies rather than from members' subscriptions.

Apart from the role of the Pasteur Institute, there is another interesting novelty in this legislation from 1895 that concerns the place of pharmacists in the distribution and quality control of medicaments. Indeed, pharmacists found themselves eliminated from the chain of responsibility with respect to sera, illustrating a new situation with respect to modern microbiological medicaments. While they had been unwilling or unable to verify the content of patent medicines for some time, they were still held nominally responsible in case of incorrect or dangerous preparations provided to them by wholesalers. Nevertheless, with the rise of a pharmaceutical industry, the possibility of ensuring the quality of what they sold became more and more remote, representing a gradual but radical transformation in the role of the pharmacist in modern medical care. While the serum may or may not have been beyond the comprehension of most contemporary pharmacists it was certainly beyond their competence to ensure its quality. The batch of specialized tests on guinea pigs were tricky and required special facilities, leaving no alternative but to rely on some kind of upstream control mechanism, testing the products at the source of production. This situation would be multiplied by the rising tide of chemical pharmaceuticals that would push traditional preparations out of the French pharmacy in

the second half of the twentieth century. Eventually, the situation would demand wider reforms putting a broad system of drug approval into place. Nevertheless, while the regulatory development might have been significant, sera represented a relatively small contribution to the economy of the burgeoning pharmaceutical industry²⁴.

8. Conclusion: serum in European cultures

Despite initial problems of supply, therefore, the French government ended up with a working solution to the problem that triggered the legislation of April 1895; how to insure that those in need of treatment were supplied with effective, safe serum. The solution, as I have explained, was the indirect delegation of the production and supply to the Pasteur Institute, accompanied by a certain amount of funding in the form of subsidies. The government in return received various benefits. First, the bulk of the funding for the project came from charitable donations and so saved them money, and second they were able to ensure adequate internal production of a medicine that was in heavy demand, thereby being seen to respond to public discontent.

We can now return to the initial question of the relationship between French culture and this episode in applied microbiology. We have more chance of identifying the specificities due to French culture if we compare the legislation and production to the case in the German Empire as presented in Axel Hüntelmann's paper. The greatest differences are, first, the German move to monitor the quality of the serum using its own dedicated (and nominally independent) institutions, and, second, the creation of conditions in Germany that would avoid any monopoly over production. In France, there was not so much concern about a monopoly of production, and the job of ensuring that non-dangerous serum was produced and distributed was left to the approved producers. This configuration allowed the Pasteur Institute to dominate serum production, with its only competitors being outriders of provincial medical faculties, and not industrial producers. In the end, I believe that the French government did not have any choice but to adopt this approach. Their habit of delegating to the medical professional

24. For more information on the history of the pharmaceutical industry in twentieth-century France, see CHAUVEAU, note 20.

bodies combined with the practical monopoly that the Institute Pasteur had over specialized microbiological knowledge (and the head-start it had in the area) forced the government's arm when it came to legislate. In both cases, in Germany as in France, the legislation served to reinforce the production situation that was already in place. In France, however, this context had already been shaped by a philanthropic vision of public health that had not only marked the foundation of the Pasteur Institute but had also provided funding specifically for serum production by means of charitable donations. Thus the dominance of the Pasteur Institute represents a continuity in terms of the Institute's image as the provider of a scientific response to infectious disease, and the embodiment of a modern French philanthropic mission. The serum's success also signaled Roux's inheritance of the mantle of savior of mankind from Pasteur. The diphtheria antitoxin was strongly identified with Emile Roux from the beginning, and there is ample iconographic evidence to illustrate how diphtheria became the great perceived success of the pastorian program. Thus, it benefited both Pasteur's



Figure 1. *La sérothérapie*. Allegorical painting by Charles Maurin (1856-1914). Emile Roux is at the centre of the picture. The painting hangs in Lyon's Musée des hospices civils. Image courtesy of the Phototèque, Institut Pasteur, Paris, France.

(posthumous) image and Roux's lifetime success in presenting himself as an (equally) great French humanitarian.

The philanthropic subscriptions to pay for the serum and the image of Pasteur, the Pasteur Institute and Roux are not, however, independent of the way the serum to treat diphtheria was produced and distributed in France. This focus of attention fitted with centralized production, largely financed by subsidies. While the serum was supposed to be sold it was apparently not marketed with any real conviction, and many were able to obtain it for nothing. In a sense, it was enough (financially as well as ideologically) for the Institute to successfully produce and distribute it, something that was not the case for Merck or Schering the other side of the Rhine. It is an interesting question, therefore, why French pharmaceutical or chemical companies such as Rhone did not enter the serum production market. Several explanations seem plausible, all of which turn around the special place assumed by the Pasteur Institute in the story, and so reflect a certain French cultural specificity that I have tried to illuminate in this paper. ■