

# Diphtheria serum and serotherapy. Development, Production and regulation in *fin de siècle* Germany

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**SUMMARY:** 1.—Introduction. 2.—The socio-cultural context of science in *fin de siècle* Germany. 3.— The development of diphtheria serum in Germany. 4.—The production of diphtheria serum in the German Empire. 5.—State control of diphtheria serum. 6.—Serum networks and indirect state regulation.

**ABSTRACT:** The development, production and state regulation of diphtheria serum is outlined against the background of industrialisation, standardization, falling standards of living and rising social conflict in *fin de siècle* Germany. On one hand, diphtheria serum offered a cure for an infectious disease and was a major therapeutic innovation in modern medicine. On the other hand, the new serum was a remedy of biological origin and nothing was known about its side effects or long-term impact. Moreover, serum therapy promised high profits for manufacturers who succeeded in stabilizing the production process and producing large quantities of serum in so-called industrial production plants. To minimize public health risks, a broad system of state regulation was installed, including the supervision of serum production and distribution. The case of diphtheria serum illustrates the indirect forms of government supervision and influence adopted in the German Empire and the cooperation and networking among science, state and industry.

**PALABRAS CLAVE:** suero antidiftérico, Alemania, regulacion estatal, seroterapia, redes entre ciencia, estado e industria, Emil Behring.

**KEYWORDS:** diphtheria serum, Germany, state regulation, serum therapy, networks among science, state and industry, Emil Behring.

## 1. Introduction

At the Tenth International Congress of Medicine in August 1890, Robert Koch (1843-1910) announced that he had found a cure for tuberculosis. In the summer and autumn of 1890 tuberculin was enthusiastically heralded as a breakthrough in modern medicine and its inventor, Robert Koch, as a national hero. Early in 1891, however, it became clear that tuberculin could not really cure tuberculosis, and it had also become obvious that several people had died after being treated with the product. The unbounded optimism of the German population had turned into sour deception and the medical triumph of a year earlier had become a public health fiasco<sup>1</sup>. The public health administration found itself in an embarrassing position. It had done nothing to protect the public from this harmful adventure and had failed to test Koch's new treatment for either its efficacy or its inoffensiveness. The public was quick to criticize the relevant authorities for their impotence and the lack of any appropriate response.

The tuberculin affair had a great deal of influence on subsequent research in bacteriology —especially at the newly founded Institute for Infectious Diseases [*Institut für Infektionskrankheiten*, which would later become the *Robert-Koch-Institut*]. As Barbara Elkeles has pointed out, the experience with tuberculin obstructed subsequent research into serum therapy. The diphtheria serum was only sold in pharmacies after numerous animal experiments had taken place and following monitored trials in children's hospitals<sup>2</sup>. When the diphtheria serum finally started to be sold in pharmacies in August 1894, the relevant medical authorities introduced broad security measures to minimize public health risks.

The present article describes the development, the production and the state control of the diphtheria serum in the German Empire at the end of the 19th century as an example of the cooperation and networking between science, state and industry. Furthermore, the example of the diphtheria serum serves to illustrate the indirect forms of governmental oversight and influence adopted under the German Empire. After the tuberculin affair of

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1. For detailed information see GRADMANN, Christoph. *Krankheit im Labor. Robert Koch und die medizinische Bakteriologie*, Göttingen, Wallstein Verlag, 2005.

2. ELKELES, Barbara. *Der moralische Diskurs über das medizinische Menschenexperiment im 19. Jahrhundert*, Stuttgart, Gustav Fischer 1996, p. 148; and retrospektive WERNICKE, Erich. Zur Geschichte des Diphtherieheilsersums. *Zeitschrift für ärztliche Fortbildung*, 1931, 28, 160-161.

1890, the authorities responsible for public health installed a complex system of control that could be interpreted as a technology of trust to ensure that only pure and effective serum was sold in the German pharmacies.

## 2. The socio-cultural context of science in *fin de siècle* Germany

In the 1890s, Germany was in the take-off phase of industrialisation, with rising steel production and the manufacture of all kinds of machines, chemicals and pharmaceuticals supported by the development of communications as well as mechanical, electrical and optical technology. The universities and science in particular were seen to lie at the base of this innovation and were considered highly prestigious, providing the numerous innovations and discoveries behind economic expansion. The mass production of all kinds of goods also brought with it problems of standardisation and economic linkage, as well as issues of intellectual property rights<sup>3</sup>.

Progress and the rise of a modern industrial society had two sides. The other side of modernity was the utterly devastating living conditions of the working class and a rising underclass, contributing to high mortality rates especially among the poor, as well as generally catastrophic sanitary conditions in the cities. Discussions about the spread of nervous conditions<sup>4</sup>, degeneration, and anti-semitism, as well as criticisms of technology and apocalyptic prophecies painted science and technology in a negative light. Ambiguity was everywhere, although generally covered over with a veneer of chauvinistic nationalism. Following the «glorious» war of 1870/1871 and the largely popular unification, the German Empire experienced a desperate need to get its international place in the sun. This search for priority and for being a world power also operated in the sciences, with the famous race between Robert Koch and Louis Pasteur (1822-1895) to find the pathogenic

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3. For the standardisation of technical, mechanical, electrical and optical devices and high-precision instruments the Physikalisch Technische Reichsanstalt was founded, see CAHAN, David. *Meister der Messung. Die Physikalisch-Technische Reichsanstalt im Deutschen Kaiserreich*, Weinheim, VCH, 1992; legislation and standardisation within the Industrial Revolution in VEC, Milos. *Recht und Normierung in der Industriellen Revolution. Neue Strukturen der Normsetzung in Völkerrecht, staatlicher Gesetzgebung und gesellschaftlicher Selbstnormierung*, Frankfurt, Vittorio Klostermann, 2006.
  4. For example RADKAU, Joachim. *Das Zeitalter der Nervosität. Deutschland zwischen Bismarck und Hitler*, München, Propyläen, 2000.

agent responsible for cholera in 1883 being but one example of national rivalry between France and Germany. Thus, it is unsurprising that a certain medical scepticism accompanied the many innovations seen in the life sciences during this period<sup>5</sup>.

To improve the disastrous situation of large swathes of the population and to minimize the risk of epidemics, several steps were taken. In 1876 the Imperial Health Office [*Kaiserliches Gesundheitsamt*] was founded with the aim of improving public health, and in the 1880s a system of social security was implemented, providing much wider health coverage. Epidemics were not only a human tragedy but by introducing anarchic and destabilising elements represented a risk for society and the political regime in place. This was the socio-cultural background against which Emil Behring started his research on inner disinfection and immunisation around 1890.

The research into a remedy for diphtheria, the large-scale production of sera and the regulation of sera as biologicals occurred at an intersection of these different socio-cultural developments. The ambiguity of that time was also reflected in the bacteriological research. The search for a remedy against the disease was perceived as an urgent social task. At the end of the 19th century, diphtheria was one of the main causes of mortality for children, with 60,000 children dying from diphtheria every year in the German Empire. The serum therapy against diphtheria and other diseases was a major therapeutic innovation in modern medicine<sup>6</sup>. On the other hand, when it was introduced, nothing was known about the side-effects associated with this biological agent or about what the long-term effects of the treatment might be.

### 3. The development of diphtheria serum in Germany

In the first half of the 1880s, Friedrich Löffler (1852-1915) at the Imperial Health Office in Berlin 'discovered' or rather identified the organism that caused diphtheria. But the «discovery» did not explain the disease. He was

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5. DINGES, Martin (ed.) *Medizinkritische Bewegungen im Deutschen Reich (ca. 1870-ca. 1933)*, Stuttgart, Franz Steiner, 1996.

6. WEINDLING, Paul J. From isolation to therapy. Children's hospitals and diphtheria in *fin de siècle* Paris, London and Berlin. In: COOTER, Roger (ed.), *In the name of the child. Health and welfare, 1880-1940*, London, Routledge, 1992, pp. 124-145.

convinced that the bacteria he had found was not the cause of the physical damage associated with the disease, because the clinical symptoms could be found in different parts of the body, while the germ was not found in all these parts. Nevertheless, he could not prove this conjecture<sup>7</sup>. Later on, Émile Roux (1853-1933) and his assistant Alexandre Yersin (1863-1943) working at the newly founded Pasteur Institute in Paris first filtered out a toxin from bacterial cultures, which was able independently to provoke the typical symptoms of diphtheria: massive destruction of cells in the affected parts of the body, mostly in the throat<sup>8</sup>. Death was caused by the membranous inflammations and swelling in the throat or by intoxication of the necrotic cells. The story of the development of the diphtheria serum starts when Emil Behring (1854-1917) entered the Institute for Hygiene in Berlin. He re-examined the research that had been done by Loeffler and Roux and started looking for a remedy for tetanus and diphtheria. When he turned to more immunological questions he found that inoculation with anthrax bacteria did not have the same effect on all animals; rats, for example, were naturally immune to the effects of these bacteria. Behring also observed that serum had immunising and bactericidal properties. The bactericidal impact was not a general attribute of the serum, however, but rather linked to a specific infective organism<sup>9</sup>. In several *in vitro* experiments he noted that the anthrax bacteria did not grow on an agar medium where he had added the serum of rats, which are immune to anthrax, but did grow with the serum of guinea pigs, which are eminently susceptible to anthrax<sup>10</sup>. Based on his experiments on inner disinfection

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7. LÖFFLER, Friedrich. Untersuchungen über die Bedeutung der Mikroorganismen für die Entstehung der Diphtherie beim Menschen, bei der Taube und beim Kalbe. *Mittheilungen aus dem Kaiserlichen Gesundheitsamte*, 1884, 2, 421-499.
  8. ROUX, Émile; YERSIN, Alexandre. Contribution à l'étude de la diphthérie. *Annales de l'Institut Pasteur*, 1888, 2, 629-661; ROUX, Émile; YERSIN, Alexandre. Contribution à l'étude de la diphthérie (2e mémoire). *Annales de l'Institut Pasteur*, 1889, 3, 273-288; ROUX, Émile; YERSIN, Alexandre. Contribution à l'étude de la diphthérie (3e mémoire). *Annales de l'Institut Pasteur*, 1890, 4, 385-426.
  9. Later on, Behring amplified and concluded: "Jede Krankheit verlangt zu ihrer Heilung ein besonders präparirtes Blut [Every disease requires a specially prepared serum to heal it.]" BEHRING, Emil. *Das Tetanusheiserum und seine Anwendung auf tetanusranke Menschen*, Leipzig, Georg Thieme, 1892, p. 37; for more on specificity see MAZUMDAR, Pauline M. H. *Species and specificity. An interpretation of the history of immunology*, Cambridge, Cambridge University Press, 1995.
  10. For an overview see BEHRING, Emil. Die Blutserumtherapie bei Diphtherie und Tetanus. *Zeitschrift für Hygiene und Infektionskrankheiten*, 1892, 12, 1-9; for further details see THROM, Carola. *Das*

Behring found out that laboratory animals who had survived infection with a certain disease were immune to the same disease and also against highly potent bacteria for a certain length of time. In collaboration with Shibasaburo Kitasato (1853-1931), a guest researcher at the Institute for Hygiene from Tokyo University, Behring took blood samples from a rabbit that had been immunized against tetanus and injected the serum into non-immune mice, which themselves were infected a day later with tetanus bacteria. They observed that the pre-treated mice had become immune and did not show any symptoms of the disease while the control animals died shortly after being infected. The immunity, it appeared, could be transferred between animals<sup>11</sup>.

In the following year, Behring advanced to the next step in realising a medical application of this research, and, along with his friend and fellow doctor Erich Wernicke (1859-1928), conducted experiments with diphtheria in guinea pigs. He succeeded in immunizing guinea pigs against diphtheria, and then showed that other guinea pigs injected with serum from immunized ones and then infected with diphtheria bacteria or toxin neither reacted nor became ill. In order to apply this principle in human medicine, Behring had to produce serum of high potency in large quantities. Already in autumn 1891 he started to immunize sheep by injecting small quantities of diphtheria toxin and slowly raising the doses. Initially, they inherited sheep from Robert Koch and then Behring started a cooperation with Wilhelm Schütz (1839-1920) from the Veterinary School [*Tierarzneischule*] so that he could perform trials using animals bigger than guinea pigs, but which were also susceptible to diphtheria. Furthermore, Behring and Wernicke invested their own money. But the experiments were expensive, and after the initial investment in sheep and other animals, they also had to find money

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*Diphtherieserum. Ein neues Therapieprinzip, seine Entwicklung und Markteinführung*, Stuttgart, Wissenschaftliche Verlagsgesellschaft, 1995, pp. 33-38; LINTON, Derek S. *Emil von Behring. Infectious disease, immunology, serum therapy*, Philadelphia, American Philosophical Society, 2005.

11. BEHRING, Emil; KITASATO, Shibasaburo. Ueber das Zustandekommen der Diphtherie-Immunität und der Tetanus-Immunität bei Thieren. *Deutsche Medizinische Wochenschrift*, 1890, Nr. 49, 1113-1114; ZEISS, Heinz; BIELING, Richard. *Emil von Behring. Gestalt und Werk*, Berlin, Bruno Schultz, 1941; for further details see THROM, note 10, pp. 38-40; LINTON, note 10. For Behring's concept of inner disinfection see SIMON, Jonathan. Emil Behring's medical culture. From disinfection to serotherapy. *Medical History*, 2007, 51, 199-217.

to feed them<sup>12</sup>. Laboratory animals could be cured, but experiments with sick children at the university hospital in Berlin at the beginning of 1892 (conducted by Ernst von Bergmann 1836-1907), at the children's ward of the Charité Hospital in Berlin in spring 1892 (conducted by Eduard Enoch 1820-1910) as well as experiments from November 1892 to June 1893 in Leipzig (Otto Heubner 1843-1926) all failed<sup>13</sup>. Nevertheless, the experiments showed the inoffensiveness of the serum and gave reason to hope that more potent serum might be able to cure diphtheria. More money was needed, however, to fund further experiments<sup>14</sup>. At this point, the story transformed from one involving a scientific network into the story of a network involving science, industry, and the state.

In April 1892, Behring received a letter from August Laubenheimer (1848-1904), a member of the supervisory board at the Farbwerke Hoechst, proposing a partnership. The Farbwerke Hoechst would finance Behring's experiments and in return they would have the right, if the experiments succeeded, to produce and distribute the serum. Nevertheless, despite the financial sponsorship, the experiments did not really make any progress. New inspiration and stimuli that pushed the process forward came from a competing research team and the Institute for Infectious Diseases itself. At the veterinary school in Berlin, Hans Aronson (1865-1919) started trials based on the results of Behring and Kitasato. Instead of sheep or dogs he used horses for his experiments because they gave larger quantities of serum. Aronson cooperated with the Berlin pharmaceutical firm Schering that in return financed the horses stabled at the Veterinary School. Later on, Behring also used horses to obtain larger quantities of serum, but the problem of the potency of the serum remained. At this point, Paul Ehrlich, a colleague of Behring's who was also working on immunisation at the Institute for Infectious Diseases, also became involved. In his experiments

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12. For a resume of their experiments see BEHRING, Emil; WERNICKE, Erich. Ueber Immunisirung und Heilung von Versuchstieren bei der Diphtherie. *Zeitschrift für Hygiene und Infektionskrankheiten*, 1892, 12, 10-44. The notebooks of the experiments are in the Erich Wernicke Papers, Staatsbibliothek Berlin, Preußischer Kulturbesitz.

13. THROM, note 10, pp. 50-52.

14. «Wir sind jedoch zu der Ueberzeugung gekommen, dass es die Kräfte und Mittel unserer privaten Thätigkeit übersteigt, den Versuchen eine solche Ausdehnung zu geben, um mit praktischem Erfolge unsere Diphtheriebehandlungsmethode auf den Menschen zu übertragen [...] und so haben wir uns entschlossen [...] weitere Kreise für die Angriffnahme von Versuchen im grossen Massstabe zu interessieren». BEHRING and WERNICKE, note 12, p. 11.

Ehrlich focussed on the augmentation and evaluation of the serum's impact. He observed that the toxin had to be injected over a longer period of time into the test animals in steadily increasing doses in order to obtain a serum of higher value. The enhancement of the serum's potency was not a linear function with respect to time, however, but varied, rising and falling: after a few days of stagnancy, the potency measured in antitoxin-units suddenly began to increase progressively. After reaching at its maximum strength, the antitoxin then declined back to its former level of potency<sup>15</sup>. The trick was to find the point of maximum strength, just before the level of the antitoxin started to decrease. In spring 1894, clinical trials were made with 220 children in Berlin hospitals with considerable success. The mortality rate halved from more than fifty per cent (mortality rate at that time) to 23.6 per cent – even serious and apparently hopeless cases were cured<sup>16</sup>. In March 1894, the company Schering announced that they were able to produce diphtheria serum, but in fact they were unable to offer a very high quality serum –not even attaining the potency advertised on the phial– and they were also unable to supply the quantities needed<sup>17</sup>. Starting in August 1894, phials of diphtheria serum from the Farbwerke Hoechst became available to a wider public via the pharmacies where they were sold. As expected, the sale of diphtheria serum was a great economic success. One month later, at the Eighth International Congress of Hygiene in Budapest in September 1894, the scientific world was introduced to the new therapy against diphtheria, and the serum was greeted as a great breakthrough in the treatment of a terrible disease<sup>18</sup>.

The research involved in the development of the diphtheria serum took nearly four years and involved several scientists. Following a large number of animal experiments, several clinical trials were made in hospitals to ensure the potency as well as the inoffensiveness of the new remedy

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15. BRIEGER, Ludwig; EHRLICH, Paul. Beiträge zur Kenntnis der Milch immunisirter Thiere. *Zeitschrift für Hygiene und Infektionskrankheiten*, 1893, 13, 336-346; THROM, note 10, p. 52-53.

16. EHRLICH, Paul; KOSSEL, Hermann; WASSERMANN, August. Ueber Gewinnung und Verwendung des Diphtherieheilserums. *Deutsche Medicinische Wochenschrift*, 1894, 20, 353-355; WEINDLING, Paul J. From medical research to clinical practise. Serum therapy for diphtheria in the 1890s. In: PICKSTONE, John V. (ed.), *Medical innovations in historical perspective*, Basingstoke, Macmillan, 1992, pp. 72-83.

17. The serum was tested by Paul Ehrlich and he found out that it was not as effective as had been announced, see Bundesarchiv Berlin (Federal Archives, hereafter BA Berlin), R 86/1646.

18. THROM, note 10; ZEISS and BIELING, note 11.



before it started being sold in the pharmacies. We can observe a complex form of networking<sup>19</sup>, with every scientist anticipating research based on the results of other scientists, either indirectly by reading their publications or directly by cooperating in research groups, such as the various research groups at the Institute for Infectious Diseases. The results of the experiments were published rapidly in one of the weekly medical journals like the *Berliner Klinische Wochenschrift* or the *Deutsche Medizinische Wochenschrift*. There was open access to all this information so that every microbiologist or bacteriologically trained physician could predict the research results or reconstruct and improve the published experiments. The price for this openness was that shortly after his publications Behring had to fight off several scientific competitors —especially Hans Aronson— who proclaimed themselves to be the initiators of the innovation of diphtheria serum<sup>20</sup>. Far from the ideal of a cooperative collective enterprise, everybody claimed priority for the discovery. Following Robert Merton, the discovery of something previously unknown or the development of an innovation serves to provide institutionalized anchorage of the inventor's originality as measured by the associated public acclaim. Innovation was seen as the scientist's contribution to the progress that characterized modernity, and in return the researcher could expect some kind of reward like a professorship, funding, or a scientific prize.<sup>21</sup> Behring was part of a scientific network, benefiting from other research results and also sharing the results of his own experiments, while at the same time fighting for priority.

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19. Here I will only talk about the network of human actors and leave out the innumerable non-human actors like host animals, laboratory animals, bacteria cultures, devices and others, although these should be included according to the Actor Network Theory. KNORR-CETINA, Karin D. (ed.) *Science observed. Perspectives on the Social Study of Science*, London, Sage, 1983; LATOUR, Bruno. *Science in context, How to follow scientists and engineers through society*, Cambridge Mass., Harvard University Press, 1987; LAW, John (ed.) *A Sociology of monsters. Essays on power, technology and domination*, London, Routledge, 1991.
  20. The conflicts with Ogata and Emmerich are described in THROM, note 10, p. 45-46; the conflict with Hans Aronson in issue 15 and 17 of the *Deutsche Medizinische Wochenschrift* 1894; ZEISS and BIELING, note 11. In 1903 Emil Behring had a serious conflict with Carl Enoch, partner of the serum producer Ruete & Enoch, concerning the priority of the diphtheria serum. Enoch had written in a draft for a more general overview that Behring and Ehrlich had discovered the diphtheria serum —a claim that provoked a rebuttal from Behring. The correspondence is in the Rochefeller Archive Center, Paul Ehrlich Collection, Box 1, Folder 2.
  21. MERTON, Robert K. Prioritätsstreitigkeiten in der Wissenschaft. In: *Entwicklung und Wandel von Forschungsinteressen. Aufsätze zur Wissenschaftssoziologie*, Frankfurt am Main, Suhrkamp, 1985, pp. 258-300.

Moreover, apart from this typical scientific network, there were other relations involved in the development of the diphtheria serum. Emil Behring was a staff officer [*Stabsarzt*], the protégé of the surgeon general of the Prussian Army [*Generalstabsarzt*] Alwin von Coler (1831-1901), and was working on a remedy against diphtheria at the Institute for Infectious Diseases helped by various different colleagues and assistants. There was a constant circulation of military surgeons in the Prussian army through the Institute for Infectious Diseases, with staff drawn from the armies of all the federal states from the German Empire<sup>22</sup>. The state-run scientific institutions were unable to work without the military surgeons like Emil Behring, Erich Wernicke or Dr. Weisser. Thus, for example, surgeon major Weisser was head of the bacteriological laboratory at the Imperial Health Office for several years<sup>23</sup>. Moreover, Behring cooperated with hospitals and with the veterinary school in Berlin to get the necessary resources and information. Behring was not only excused military service and appointed to the Institute for Infectious Diseases in order to do research, he was also supported by Friedrich Althoff (1839-1908), Deputy Assistant Under-Secretary [*Ministerialdirektor*] in the Prussian Ministry for Cultural Affairs and financed by the Farbwerke Hoechst. In the next stage, the network between industry, state and science was enlarged.

#### 4. The production of diphtheria serum in the German empire

Only two companies had invested in the development of the diphtheria serum in the German Empire. As described above, the Farbwerke Hoechst, formerly known as Meister, Lucius and Brüning, had a contract with Emil Behring, and Schering had supported Hans Aronson. After the first phials became available in the pharmacies and it was clear that this product would be a great economic success, three other companies started producing serum

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22. In comparison to France, for example, this was not very different because several military surgeons from Vâl de Grace were educated at the Pasteur Institute, and the production plant for diphtheria serum of the Pasteur Institute in Garches was a former military stable. The difference was the institutionalisation of this exchange in Germany.

23. The head of the Testing Department [*Prüfungstechnische Abteilung*] of the Institute for Experimental Therapy in Frankfurt [*Institut für experimentelle Therapie*, which would later become the *Paul-Ehrlich-Institut*] was also a military surgeon, cf. the annual reports in the archive of the Paul Ehrlich Institute (Paul-Ehrlich-Institut, Langen – hereafter APEI), Dept. IV, No. 1.

in Germany, all before the end of 1895. In Darmstadt the well-established company E. Merck —producer of pharmaceuticals and chemicals— went into production. In the south of Germany, the Pasteur Institute opened a branch in Stuttgart, and in Hamburg two pharmacists started producing diphtheria serum and set up the company Ruete & Enoch<sup>24</sup>.

The Farbwerke Hoechst not only cooperated with Behring, they also built up a bacteriological research laboratory doing research in parallel to Behring's but with a focus on the problems associated with the industrial production of serum. Arnold Libbertz (1843-1916), a close friend of Robert Koch, became the first director of the research laboratory. After the successful completion of clinical trials in spring 1894, the management of the Farbwerke Hoechst decided to build a new production plant specifically for serum production. The new buildings were officially inaugurated in November 1894. Schering followed in fall 1894 with the installation of its own bacteriological production department, with Hans Aronson as director. Producing serum in an industrial style is, however, a little misleading, as the production plant looked more like farms than factories (fig. 1). The production plant was in general divided into two buildings: a stable where around forty horses were housed and a laboratory for the breeding of the bacterial cultures, the test procedures and the preparation of the serum.

The new 'production plant' at Farbwerke Höchst set the standard for serum production in Germany (see fig. 2). Arnold Eiermann gave an enthusiastic description of his visit to the complex of buildings in the *Münchener Medicinische Wochenschrift*<sup>25</sup>. The process of serum production was complicated, starting with the «production» of diphtheria toxin, using pure cultures of diphtheria-bacillus sown on a special medium. This culture medium was composed of cooked meat with one percent peptone, sodium chloride and caustic soda. The culture heated, filtered, poured into flasks, sterilised and then inseminated with the bacteria. After breeding for several days in the culture-chamber at a constant temperature between 34 and 39° Celsius the cultures were killed using a disinfectant and treated

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24. The official procedure to become a state approved serum producer is documented in BA Berlin, R 86/1646; information about the producer in APEI, Dept. Vd. See also THROM, n. 10, pp. 164-193.
  25. EIERMANN, Arnold. Die Einrichtung zur Darstellung des Diphtherie-Heilserums in den Höchster Farbwerken. *Münchener Medicinische Wochenschrift*, 1894, Nr. 41, 1038-1040.



Figure 1. The Bacteriological Department at the Farbwerke Hoechst after 1900. Emil von Behring Archive, Marburg – Germany.

with carbolic acid for conservation<sup>26</sup>. The production of toxin was difficult because the process depended on the strain of bacteria, the culture medium (agar or nutrient solution), the preparation of the culture medium, the duration and the temperature of the breeding process, and the disinfectant used to kill the bacteria. The precise manner of producing the toxin varied from company to company. The process was important for the fabrication of serum because the value of the serum depended on the strength of the toxin used to immunize the animals. On the one hand, the more potent the toxin, the more powerful the final serum, while on the other hand, a strong toxin could cause inflammations at the injection site, and hinder the process of serum production.

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26. THROM, note 10, pp. 82-86.

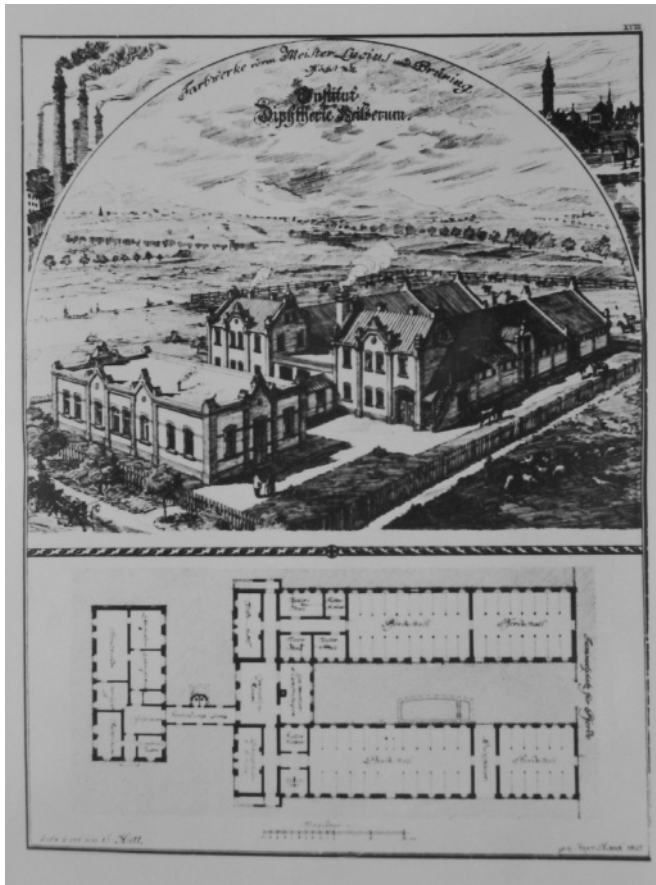


Figure 2. The «production plant». The Bacteriological Department at the Farbwerke Hoechst 1894. Emil von Behring Archive, Marburg – Germany.

The immunisation process itself took a longer period of time; in 1894, it took between four and five months, but by 1900, thanks to the additional experience, the process took only four weeks. During this period of immunisation, the horses were inoculated at regular time intervals —between eight and eleven times— with increasing doses of toxin. Test-bleedings revealed the moment when the antitoxin units in the serum reached their expected maximum. In the new production plant of the Farbwerke Hoechst the bleeding occurred in a separately equipped operation room in the stable

building. When the value of the antitoxin had reached the highest possible point, the horse was brought into the operating room, tied up, the puncture point shaved and disinfected, and a trocar was placed in the jugular vein. The blood came out via a cannula and was collected in a sterilised vessel. The process was used to collect five or six litres of blood per horse providing three litres of serum<sup>27</sup>.



Figure 3. A popular picture of the production of diphtheria serum at the Behringwerke in Marburg, around 1906. On the left side the inoculation of toxin, on the right side the bleeding. Emil von Behring Archive, Marburg – Germany.

According to the report in the *Münchener Medicinische Wochenschrift*, the rest of the 'production process' took place in the laboratory building. The vessels were closed and stored in a cool chamber. After 24 hours, when

27. The production is described in OTTO, Richard. *Die staatliche Prüfung der Heilsera* (Arbeiten aus dem Königlichen Institut für experimentelle Therapie zu Frankfurt a. M. – vol. 2), Jena, Gustav Fischer, 1906, pp. 15-17.

the red blood cells had separated from the serum, the blood was filtered, centrifuged and underwent a bacteriological analysis. If the serum was found to be germ-free, it was treated with 0.5 percent carbolic acid for conservation and to keep it sterile. Every production step was recorded in different registers. After the evaluation procedure had fixed the final value of the serum in terms of immunisation units it was poured into phials that were corked<sup>28</sup>. A label was placed on each phial stating the quantity of serum, its potency in terms of immunisation units, a unique operation number and the date the phial was filled. Finally, the phial was wrapped in paper, packed in a wooden box, and sent out to the pharmacies<sup>29</sup>. Arnold Eiermann remarked at the end of his article that the horses were in excel-



Figure 4. Different serum samples with liquid serum and serum powder, produced between 1897 and 1910. The photograph was probably taken around 1940. Emil von Behring Archive, Marburg – Germany.

28. Later on, the phials were closed with a rubber plug or heat sealed (fig. 4).

29. THROM, note 10, pp. 99-113; EIERMANN, note 25.

lent condition, that they received good care, and looked very healthy. Such care was necessary because after a short period of «holiday» the process of immunization would start again. The experimental system transformed within a short period of time into a production system. Nevertheless, the main problem of this production system was the stabilisation of the different varying factors of production.

## 5. State control of diphtheria serum

The diphtheria serum was an ambivalent object for the medical authorities. On the one hand, the serum offered an apparently effective treatment of diphtheria and other deadly infectious diseases, with the mortality rate for diphtheria significantly decreasing shortly after the introduction of the serum. On the other hand, the new serum therapy presented several public health risks. Furthermore, despite the complexity of the serum production process, any health professional trained in bacteriology could produce serum on the basis of the published research results and the process was not patentable. Furthermore, the production of serum was a profitable business, with Farbwerke Höchst paying off the cost of the bacteriological department described above at the end of 1894 thanks to serum sales, and enjoying an estimated profit of 707,000 Marks by the end of 1895<sup>30</sup>. The evident economic incentives combined with the lack of experience with biological remedies like diphtheria serum and the lack of any information about its long-term effects made the medical administration anxious about unscrupulous producers who might want to imitate Höchst's production process. In the last days of October 1894, the extraordinary members of the Imperial Health Office were invited for a meeting to discuss the new serum therapy and the possibilities of state control.

The easy appraisal of Behring's diphtheria serum by the experts on the basis of its therapeutic success, and the rising demand for the diphtheria serum makes it necessary to discuss government measures concerning the

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30. THROM, note 10, tab. IV in the appendices; LAUBENHEIMER, August. *Zur Geschichte der Serumdarstellung in den Farbwerken* [The history of the serum therapy at the Farbwerke Hoechst], June 1904, Behring Archive, University of Marburg, 8-01, Correspondence with the Farbwerke Hoechst, doc. 678.



production, distribution and use of this new therapy in order to protect public health<sup>31</sup>.

In early November 1894, a conference brought together medical officials from the Prussian Ministry for Cultural Affairs, representatives of the federal states, the Imperial Health Office and the relevant scientists from the Prussian Institute for Infectious Diseases; Paul Ehrlich, Robert Koch and Emil Behring. The conference was organized by the Imperial Health Office, which was the highest medical institution in the German Empire, answerable only to the Chancellor and the Imperial Office of the Interior [the *Reichsamt des Innern*, which became the Ministry of the Interior after 1918]. At this conference, the participants discussed the new serum therapy and the need to protect the public against impure and/or ineffective serum<sup>32</sup>.

Over the course of several meetings between November 1894 and February 1895 a system of state control was drafted. Starting in December, representatives of the pharmaceutical industry were also invited to participate at the meetings<sup>33</sup>. To make sure that the distribution of diphtheria serum was limited to medical specialists, it was decided that, in accordance with an imperial decree from January 1890, the diphtheria serum could only be sold in pharmacies. Secondly, in line with the federal resolution of July 1891, a prescription was required for the diphtheria serum. The imperial law was worked out in November and December 1894 by members of the Imperial Health Office and after a few weeks of consultation put into force in January 1895<sup>34</sup>. In the absence of empirical knowledge about the impact of the serum it was decided to accompany its introduction onto the market by the compilation of a set of medical statistics intended to monitor the effectiveness of the new serum therapy and identify any side effects<sup>35</sup>.

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31. Invitation of the extraordinary members of the Imperial Health Office to a conference on the new diphtheria serum, 3rd November of 1894, BA Berlin, R 86/1646.
  32. The minutes of the meeting from 3rd and 5th of November 1894, BA Berlin, R 86/1646.
  33. The minutes of the meeting from 3rd and 5th of November 1894, BA Berlin, R 86/1646. Background information concerning the importance of the conference is to be found in ZEISS and BIELING, note 11, pp. 153-157; HÜNTELMANN, Axel C. *Gesundheitspolitik im Kaiserreich und in der Weimarer Republik. Das Reichsgesundheitsamt von 1876-1933*, Diss. Phil., University of Bremen, 2006.
  34. *Reichsgesetzblatt* [Law gazette] 1895, 1.
  35. The minutes of the meeting from 3rd and 5th of November 1894, BA Berlin, R 86/1646. The results of the statistics were published as «Ergebnisse der Sammelforschung über das Diphtherieheils Serum für die Zeit vom April 1895 bis März 1896» and sent to every library in

The most significant part of this legislation concerned the state control of the production and distribution of the serum. Until the 1880s, the quality control of the ingredients and the preparation of pharmaceuticals lay in the hands of the pharmacists. With the rising pharmaceutical industry, it became difficult for the apothecary to analyse the ingredients in terms of their purity, meaning that he could no longer guarantee the quality of the tablets or pills<sup>36</sup>. Indeed, the efficacy and potency of the serum could only be determined by a trained expert. The 'industrial' production of serum pushed this same process forward, with the industry instead of the pharmacies increasingly becoming the site of both, production and quality control<sup>37</sup>.

As far as the production of serum was concerned, the state system of supervision combined central and local elements. The process was permanently monitored in the production plant by a medical official, paid by the producer but answerable to the state in the form of the Ministry of Cultural Affairs or the district president. The bleeding took place under the supervision of this medical official. After the value of immunisation units was fixed, the vessel containing the serum was closed, locked and a serum sample sent to a state-run institute for testing the quality of the serum<sup>38</sup>. At the one German serological institute, the serum was tested for purity as well as being evaluated and certified. At this institute, the value of serum

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the German Empire as well as several other institutions. BA Berlin, R 86/1646; and a summary was published in the *Arbeiten aus dem Kaiserlichen Gesundheitsamt*, 1897, 13, 254-292; also see BEHRING, Emil. *Die Statistik in der Heilserumfrage*, Marburg, N. G. Elwert'sche Verlagsbuchhandlung, 1895.

36. The aim of the control was the reduction of sources of error. With the process of industrialization it was easier to control a few producers than to control thousands of pharmacies.
37. HOLSTEN, Jürgen. *Das Kaiserliche Gesundheitsamt und die Pharmazie. Dargestellt an der Entstehung des Deutschen Arzneibuches, fünfte Ausgabe*, Diss. med., Free University Berlin, 1977; HICKEL, Erika. *Arzneimittel-Standardisierung im 19. Jahrhundert in den Pharmakopöen Deutschlands, Frankreichs, Großbritanniens und der Vereinigten Staaten von Amerika*, Darmstadt, Wissenschaftliche Verlagsgesellschaft, 1973; WIMMER, Wolfgang. «Wir haben fast immer was Neues». *Gesundheitswesen und Innovation der Pharma-Industrie in Deutschland, 1880-1935*, Berlin, Duncker & Humblot, 1994.
38. The serological institute was founded in February 1895 as a Control station for Diphtheria Serum [Controlstation für Diphtherieserum]. A year later, in 1896, the field of activity was enlarged to cover all sera, and the institute renamed the Institute for Serological Research and Serological Survey (*Institut für Serumforschung und Serumprüfung*). In 1899, the institute moved from Berlin to Frankfurt and was renamed again, becoming the Institute for Experimental Therapy (*Institut für Experimentelle Therapie*) and was finally renamed after the Second World War as the Paul-Ehrlich-Institut. Hereafter, I will use the abbreviation, serological institute.

proposed by the manufacturer and expressed in immunisation units was verified by means of a complex procedure and the serum was tested for its overall quality. If everything was in accordance with the guidelines, a certificate validating the approved quality and strength in immunisation units was completed and sent to the producer. The medical official on site could now release the relevant vessel of serum for decanting into phials for distribution. Every step of the whole 'production process' was carefully recorded in a register and referred to a single operation number, which made it possible to trace the phial sold in the pharmacy back to the host-animal and the day of bleeding —and vice versa. There were also strict regulations concerning the handling, labelling and packaging of the serum at the end of the manufacturing process, and the sale price was regulated, with special tariffs for social security insurance, welfare institutions and hospitals. Finally, the producers guaranteed the withdrawal of phials from pharmacies after two years or in the case of ineffective or impure serum. The system was implemented within a few months, and the central state institute for serum control set up<sup>39</sup>. After 1 April 1895, only state-certified serum could be legally sold in Germany<sup>40</sup>.

In order to produce state approved serum a company first had to apply for permission and they had to prove their ability to produce serum. Beyond this, the candidate had to pay an «entrance fee» of 1 000 Marks to the serological institute to enable them to submit their serum for testing. As mentioned above, a candidate producer had to recruit a medical official to monitor the production process. Finally, the Ministry of Cultural Affairs, aided by the district president, was to inquire into the company's reputation, as well as carrying out an initial audit covering all aspects of the proposed production process and the associated facilities. The local district veterinary and medical officers inspected the company and its surrounding, examining the condition of the horses, the stables, the laboratory building and the devices, equipment and means for serum production and evaluation.

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39. See the minutes of the meetings from the 17th of December 1894, 17th of January 1895 and 1st of February 1895 and the correspondence between the participants of the meetings in BA Berlin, R 86/1646; Secret Central Archives (Geheimes Staatsarchiv Preußischer Kulturbesitz, hereafter GStA PK), HA 1, Rep. 76 VIII B, No. 3747; for the industry side, see the Histocom archive of the Farbwerke Hoechst, Frankfurt, folder GL 18.1/3. For the foundation of the serological institute see GStA PK, HA 1, Rep. 76 Vc, Sekt. 1, Tit. XI, part II, No. 18, vol. 1.

40. A summary is given in EHRlich, Paul. Die staatliche Controle des Diphtherie-Serums. *Berliner Klinische Wochenschrift*, 1896, 33, 441-443.

The administration procedures also came under scrutiny<sup>41</sup>, with, to cite but one example, the medical adviser of the Ministry of Cultural Affairs complaining about missing registers when he inspected Schering's serum production facilities in January 1895<sup>42</sup>.

The application and the inspection of the company Ruete & Enoch, situated in Hamburg, and their distributor Sthamer, Noack & Co. can serve to illustrate the functioning of the initial audit. In early spring 1895 the owner of a chemical laboratory in Hamburg, Carl Enoch, addressed an inquiry concerning the production and distribution of diphtheria serum to the «Medical Bureau» (the local administrative authority) in Hamburg. In April 1895, this Medical Bureau in Hamburg informed the Imperial Health Office about their transactions with Enoch in the course of the preceding weeks. The Medical Bureau had already gathered information about the reputation of the laboratory to determine whether the company and its application should be taken seriously. The medical official and head of the Hygiene Institute in Hamburg, William Phillipps Dunbar (1863-1922), contacted Richard Pfeiffer (1858-1945), a member of the Institute for Infectious Diseases, where the Control station for Diphtheria Serum was housed during its first year of existence, and discussed the provisional system for serum control. Furthermore, the district veterinary officer had been instructed to visit Enoch's institute. He was to inspect the stables and determine the health condition of the horses. In case of a positive result, the medical councillor of Hamburg would contact the Imperial chancellor concerning the official state control of serum. In its role as the medical advisory board for the Imperial Chancellor, the Imperial Health Office informed the Medical Bureau in Hamburg about the legal requirements concerning serum production: first, after the initial inspection, the serum had to be constantly tested by the Control station for Diphtheria Serum, and second, the city of Hamburg had to enact an order on the basis of the Imperial Decree concerning the diphtheria serum, specifying that serum could only be sold in pharmacies, that a prescription was necessary, and

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41. For instance OTTO, note 27, chap. B and C.

42. In December 1894 there was a meeting between two medical councillors of the Ministry for Cultural Affairs and the director of Schering. A few weeks later there was an inspection at Schering made by one of the councillors and a member of the Imperial Health Office, cf. the notice of Adolf Schmidtman (medical councillor of the Ministry of Cultural Affairs), GStA PK, 1. HA, Rep. 76 VIII B, No. 3748, fol. 208.

that only state-approved, sealed phials could be sold in the pharmacies<sup>43</sup>. In the summer of 1895, the Medical Bureau informed the Imperial Health Office about the inspection, confirming that Hamburg had enacted a law concerning the handling of diphtheria serum in accordance with Imperial and Prussian law. After the successful initial inspection, Enoch was granted permission to contact the Control station for Diphtheria Serum concerning the testing procedures in force. After all the formalities had been taken care of, the company was allowed to produce and distribute state-approved diphtheria serum<sup>44</sup>.

As we have seen, the network of serum control was very elaborate. The reasons for this complexity were first the federal constitution of the German Empire and second the private-public partnership between the private serum producing companies and the state-run institutions. The competences of the German Empire and the federal states were not entirely clear in the case of public health and medical affairs. While the imperial authorities were charged with issues concerning medical police and public health, the federal states were responsible for «medical affairs». There was evidently considerable overlap between these loosely defined spheres. In general, the Empire took control whenever any public health problems arose that concerned more than one state, as in the case of epidemics<sup>45</sup>. Moreover, the imperial officers neither disposed of institutions to execute the decrees or laws, nor did they have any clear authority over local institutions, and therefore depended on cooperation with the federal states, district governments and their respective institutions<sup>46</sup>. This was one of

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43. The «free» city of Hamburg was a federal state in the German Empire. Matters concerning public health and medical police fell within the competence of the German Empire and the federal states.

44. For the complete correspondence see BA Berlin, R 86/1646; and file in APEI, Dept. Vd, No. 4, vol. 1.

45. For further information about health policy in Germany see WOELK, Wolfgang; VÖGELE, Jörg (eds.) *Geschichte der Gesundheitspolitik in Deutschland. Von der Weimarer Republik bis in die Frühgeschichte der «doppelten Staatsgründung»*, Berlin, Duncker & Humblot, 2002, esp. the introduction; public health in the German Empire cf. WEINDLING, Paul J. *Health, Race and German Politics between National Unification and Nazism, 1870-1945*, Cambridge, Cambridge University Press, 1989.

46. The lack of any executive bodies was also a problem for the Imperial (Office) Ministry of Interior, see GROEBEN, Klaus von der, Reichsinnenministerium. In: JESERICH, Kurt G. A. (ed.), *Deutsche Verwaltungsgeschichte*, vol. 4: *Das Reich als Republik und in der Zeit des Nationalsozialismus*, Stuttgart, Deutsche Verlagsanstalt, 1985, pp. 156-168.

the reasons why several conferences brought together imperial and federal medical officials to implement the institutional network of serum control and to ensure continued cooperation.

As a result of the general confusion concerning local and imperial competence and the lack of executive institutions on the local level, the confiscation of out-of-date or ineffective serum —conceived of as a routine operation— proved to be quite complicated. The Empire was responsible for the drug legislation, while the pharmacies were supervised by the Ministry of Cultural Affairs. The confiscation of serum should illustrate the complex interactions between imperial, federal and local authorities. The initial situation was the regular confiscation of serum after two (and later after three) years or after an apothecary had notified the serological institute concerning ineffective serum. In both cases the serological institute informed the Prussian Ministry of Cultural Affairs, providing the operation numbers of the serum that had to be confiscated. The Ministry of Cultural Affairs in turn informed the Imperial Office of the Interior, which in turn sent up the information to the highest relevant authority, the Imperial Health Office. The Imperial Health Office now had to prepare an official decree concerning the confiscation of the serum that was sent back to the Imperial Office of the Interior and the Chancellor who signed and implemented the decree. Afterwards, the imperial decree was sent as a circular to the relevant ministries of the federal states for execution, with the imperial decree being transformed into a state decree. The state decree was published in an official newspaper and finally sent to the district president. The district president and the district medical officer supervised the actual confiscation of the serum in the pharmacies<sup>47</sup>. An urgent and apparently simple demand was, therefore, followed by a long and complex administrative procedure that added as many delays as there were layers of competent administrative bodies involved.

Another reason for the complex system of serum control was the public-private partnership that existed in Germany. When the first phials became available in pharmacies in August 1894 there was no pre-existent blue print for how to introduce a new 'biological' product onto the pharmaceutical market. When the medical officials met at the conference in November

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47. The complete process is documented in BA Berlin, R 86/1646; GStA PK, HA 1, Rep. 76 VIII B, No. 3749-3752; APEI, Dept. Va, No. 2, vol. 1.

1894, they discussed the idea of founding a central state-run institute for serum production, but then withdrew this project. As Schering and the Farbwerke Hoechst had already invested a great deal of money, it was very possible that the two companies would take legal proceedings against the state and sue for financial compensation<sup>48</sup>. Thus the 'easiest' way to guarantee the purity and potency of the serum while ensuring a form of state supervision was the introduction of a central institute for serum control as an obligatory point of passage<sup>49</sup>. Only state-approved serum was allowed to be sold legally on the pharmaceutical market.

## 6. Serum networks and indirect state regulation

This article has given a brief overview of the history of diphtheria serum at the end of the 19th century, covering the «development» of serum therapy, the production of a new remedy of biological origin and the introduction of state control to minimize public health risks. The history of serum production and state regulation is also the history of a network. Numerous (human) actors had been described. Already during the period of research and experimentation, a thought-collective of scientists and laboratory staff was involved, either communicating directly within the research groups or indirectly via the published research results. The scientists concerned came from a variety of different backgrounds: military surgeons, medical officials, veterinaries, laboratory staff, physicians and scientific members of the state-run research institutes and the university laboratories as well as physicians in the hospitals. The network was enlarged when industry became involved in serum research and again with the state control of serum production. In the production plant, medical officials collaborated closely with the staff and the scientists of the bacteriological departments.

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48. See the notes on a meeting on October 19th 1894 in the Imperial Health Office, BA Berlin, R 86/1646; and the minutes of a meeting at the Prussian Ministry of Cultural Affairs on October 24th 1894, GStA PK, HA 1, Rep. 76 VIII B, No. 3747; moreover an undated report from B. Fraenkel about the distribution of diphtheria serum in France, *ibid*; for further information THROM, note 10, p. 71-72. Later on, however, the idea of a state-run institute for serological research and serum production was only raised by medical officials as a bargaining tool when problems emerged with the serum producers.

49. For the obligatory point of passage, see LATOUR, note 19.

For the large-scale manufacturer of a biological product the main problem was the stabilisation of the varying production factors to «produce» a standardized remedy. The production process was steadily improved and monitored by a network consisting of elements from the scientific community, state and industry. Local authorities also featured in this network, as we have seen with the example involving the district medical officer. Beyond this, the network also ensured the indirect state regulation and control of serum production. On the one hand, the network of control was meant to ensure the purity and potency of the serum to protect the public and to avoid any public health scandals of the type seen with tuberculin. On the other hand, the network also guaranteed a remedy of a standardized quality with respect to the standards introduced by the state.

What is the difference between direct and indirect state regulation in the case of diphtheria serum? An indirect model of state regulation might have been, if the serum was produced by companies operating on the free market, probably with safety standards fixed by laws. Under direct state regulation one can probably imagine a situation in that one or perhaps several state-run institution will produce the serum on its own. Such an institute would have been founded by the state and operated by medical officials. The state as serum producer could now guarantee for the quality and potency of the serum. Furthermore, the serum could be stocked in regional serum depots and sent out to the physicians on request, or, in a more market-oriented system the serum could be distributed by the pharmacies. This kind of model was discussed in the first meetings about the organisation of the serum system, referring to the French model, with the idea of founding a single institute to produce and distribute the serum. This idea was soon put aside. In the ongoing discussions concerning an appropriate system of state control the medical officials took into account that there were several serum producers in different locations and for the control of serum production and distribution a central institute for serum control was necessary. The regulation of the diphtheria serum in the German Empire could be characterized as lying somewhere between these two poles: the serum was produced by private competing pharmaceutical companies on the free market, but their freedom was restricted by an initial audit to confirm the company's ability to produce pure and effective serum. Furthermore, the market for diphtheria serum was restricted to companies that could afford the entrance fee of 1,000 Mark and who were able to remunerate a medical official working in the production plant. On



this account only large companies could produce and distribute diphtheria serum on the German market. Finally, a sample of every batch of serum had to be sent to a central state-run control station to guarantee the quality, purity and potency of the serum. Thus, the central institute for quality assurance represented an obligatory passage point for all serum, and could serve to block the business of one or more companies.

To enforce this indirect governmental control a wide network of actors had to be positioned and interconnected. The serum producers had to be involved as well as the scientists and the public health administration to insure a process of control. In the end, however, every actor was bound into this tightly linked network making direct governmental sanctions more or less unnecessary. ■

