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RESEARCH ARTICLE

The globalization of sera evaluation between 1895 and 1925

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Abstract

During the development of an anti-diphtheria serum in the 1890s in France and Germany, the problem arose of how to evaluate the potency of an unstable substance of biological origin. This was solved by developing a complex, relational procedure, centred around standard toxin and sera, with guinea pigs and mice as bioindicators. After the marketing of anti-diphtheria serum in the German Empire in 1894, its production and sale were regulated by the state. The Royal Prussian Institute for Serum Research and Serum Survey soon became the global authority for the control and evaluation of biologicals; that is, substances of organic origin. This study analyses how serum evaluation transformed an unstable biological into an 'objective' remedy with a calculable therapeutic efficacy as measured in rodents.

In 1897, the Danish bacteriologist Thorvald Madsen concluded a comparative study of French, English and German anti-diphtheria sera, suggesting that because of the extraordinary importance of serotherapy, 'the serum's potency should be evaluated on the basis of an international scale unit as the only way to compare and correctly access the successes achieved'.[1] Madsen favoured the German method of measuring efficacy, which he considered to be reliable and easily performed.[2] More than twenty years later, in 1921, Thorvald Madsen noted that the German method of evaluating anti-diphtheria sera had become widely used throughout the world.[3] Now the director of the State Serum Institute (Statens Serum Institut) in Copenhagen and president of the Standardisation Committee of the League of Nations Hygiene Organisation, Madsen recommended that the German method be adopted as an international measure.[4] These two appraisals from around 1900 and the early 1920s hint at a success story. However, the evolution of the method of evaluation was anything but straightforward.

[1] See the summary report about Thorvald Madsen's article written by Wilhelm Dönitz, a member of Institute for Serum Research and Serum Survey, 11 March 1897, Archive of the Paul Ehrlich Institute, Langen (henceforth PEI), Dept. Va, Nr. 1, Vol. 1, original emphasis.

[2] Dönitz, op. cit. (1); and Thorvald Madsen, 'Ueber Messung der Stärke antidiphtheritischen Serums', *Zeitschrift für Hygiene* (1897) 24, pp. 425–42.

[3] On Madsen see, for instance, Anne Hardy, 'Actions not words: Thorvald Madsen, Denmark, and international health, 1902–1939', in Iris Borowy and Anne Hardy (eds.), *Of Medicine and Men: Biographies and Ideas in European Social Medicine Between the World Wars*, Frankfurt am Main: Peter Lang, 2008, pp. 127–43.

[4] Annex 6, memorandum by Thorvald Madsen on the standardization of antitoxic sera, September 1921, PEI, Dept. B, no. 6, vol. 1.

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In this article, I describe the history of the German method of evaluating anti-diphtheria sera. I analyse the method's importance in (1) assessing serum potency, (2) in validating an officially approved pharmaceutical and (3) in implementing a new therapeutic principle. Validating this method helped to establish the standing of German anti-diphtheria serum in global pharmaceutical markets. Indeed, the method itself became a standard international procedure.

The sale of anti-diphtheria sera in the German Empire had been regulated by the state since 1895, and the evaluation of serum (as a defined minimum of so-called immunization units) was a *conditio sine qua non* for pharmaceutical companies to sell their product in domestic markets. The evaluation was an obligatory passage point in various respects. For one thing, every anti-diphtheria serum destined for domestic markets had to undergo an evaluation by a central regulatory agency, the Royal Prussian Institute for Serum Research and Serum Survey (Königlich Preußisches Institut für Serumforschung und Serumprüfung, henceforth IfSS). In addition, the actors involved had to coordinate and synchronize the way they produced and evaluated sera. In the process, an estimated and precarious therapeutic effect had to be translated into a well-defined and exact number of what were called immunization units, thus transforming a biological substance into an official, state-approved remedy. Finally, within this translational and transformative process, the evaluation procedure had to be precisely defined, and all human and non-human actors involved had to be calibrated and standardized – with a specific 'standard serum' playing an eminent role. But how was the method constructed? How did the process work? Which actors were involved? And what were the narrow and broad meaning and function of this method? Although the evaluation was considered to be a complex scientific endeavour, I ask how it was influenced by political and economic factors and how evaluation, validation and regulation influenced each other, how they became fused.

The article is chronologically structured around the historical development of the evaluation method. Anti-diphtheria serum was developed in the first half of the 1890s and first marketed in 1894. Serum evaluation was an eminent part of the production and marketing of the drug, as will be described in the first section. The method was quickly accepted and institutionalized. The subsequent section discusses the role of evaluation in the production, marketing and regulation of anti-diphtheria serum. After the evaluation was established in the German Empire, the third section elaborates the international implementation of the German method after 1900. This success story was interrupted by the First World War, which is summarized in the next section. The fifth section describes negotiations within the Standardisation Committee of the League of Nations' Hygiene Organisation prior to the implementation of universal evaluation methods and 'standard sera'. I will outline the committee's discussions about the development of international evaluation methods for different sera, examining the various premises, conditions and motives. Finally, I will summarize and assess how the German method of evaluation and validation acquired moral authority, and how that method was itself validated, first through a complex system of checks and balances, and later – after the war and the loss of the institute's moral authority – through ongoing collaborations and negotiations.

The production and evaluation of anti-diphtheria serum

Anti-diphtheria serum has been considered to be a major therapeutic innovation in modern medicine.[5] At the end of the nineteenth century, diphtheria was an infectious disease that

[5] See, for instance, Paul J. Weindling, 'From medical research to clinical practice: serum therapy for diphtheria in the 1890s', in John V. Pickstone (ed.), *Medical Innovations in Historical Perspective*, Basingstoke: Macmillan, 1992, pp. 72–83; and Heinz Schott (ed.), *Meilensteine der Medizin*, Dortmund: Harenberg, 1996.

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affected mainly infants and children. They suffered from general symptoms of infection, such as fever and fatigue, as well as more specific symptoms, such as swelling and inflammation of the mucous membranes in the mouth, nose and throat, often to such an extent that there was a risk of asphyxiation. Children often suffocated or died of further complications arising from the infection. The mortality rate among children was about 50 percent, and in the early 1890s around 60,000 persons died annually from diphtheria in the German Empire.[6] Until 1894, there was no effective cure for the disease and anti-diphtheria serum was the first remedy that treated not only the symptoms of the disease but also its causes.

The sale of anti-diphtheria serum yielded enormous profits for serum producers. The chemical company Hoechst Dye Works (Farbwerke Hoechst), for instance, netted a profit of 700,000 marks in 1895 and around 350,000 marks annually over the following ten years from serum sales.[7] Shortly after it went on sale in the summer of 1894, numerous other companies started to produce and sell serum, leading health officials of the federal states and the German Empire to discuss ways of regulating the new anti-diphtheria serum.[8] Why was state regulation considered necessary? Given its novelty, officials viewed it as a thin wedge, paving the way for other sera, like those targeting tetanus, dysentery and other infectious diseases.

The new serum therapy promised high profits for those manufacturers who were able to stabilize the production process and produce serum in large quantities. The research results about the immunization procedure, including detailed information about the production process of the serum, were available in well-known medical publications.[9] Consequently, any medical professional trained in bacteriology could reconstruct the experiments and produce serum without encountering legal problems because there was no patent on anti-diphtheria serum.

At first glance, the production process appeared simple and almost agricultural. Initially, a large animal (preferably a sheep and later a horse) susceptible to diphtheria was injected with small doses of diphtheria toxin that had been extracted from bacterial cultures. This procedure was repeated at regular intervals with constantly increasing doses. Every dose of toxin injected into the animal (called a serum donor, *Serumspender* or *Wirtstier*) stimulated the body's own production of antibodies, in step with the constantly rising level of toxin. When the antibodies in the blood were presumed to have reached their peak, the animal was bled. The blood was then stored to allow for coagulation. The serum, separated from the coagulated portion of blood, was poured into sterile vials and prepared for sale. The entire process was extremely delicate; in their efforts to maximize the production of antitoxins, producers had to carefully calibrate each step and variable: the strain of bacteria, how it was cultivated, the production and strength of its toxin, and the serum donor's health. All of these factors influenced the immunization process and the potency of the serum.[10]

[6] See Carola Throm, *Das Diphtherieserum: Ein neues Therapieprinzip, seine Entwicklung und Markteinführung*, Stuttgart: Wissenschaftliche Verlagsgesellschaft, 1995.

[7] Cf. Throm, op. cit. (6), Table IV.1 (p. 206).

[8] Cf. Throm, op. cit. (6); and Axel C. Hüntelmann, 'Diphtheria serum and serotherapy: development, production and regulation in *fin de siècle* Germany', *Dynamis: Acta Hispanica ad Medicinae Scientiarumque Historiam Illustrandam* (2007) 27, pp. 107–31.

[9] See, for instance, Emil Behring and Shibasaburo Kitasato, 'Ueber das Zustandekommen der Diphtherie-Immunität und der Tetanus-Immunität bei Thieren', *Deutsche Medizinische Wochenschrift* (1890) 16, pp. 1113–4; Emil Behring, 'Die Blutserumtherapie bei Diphtherie und Tetanus', *Zeitschrift für Hygiene und Infectionskrankheiten* (1892) 12, pp. 1–9; Emil Behring and Erich Wernicke, 'Ueber Immunisirung und Heilung von Versuchsthieren bei der Diphtherie', *Zeitschrift für Hygiene und Infectionskrankheiten* (1892) 12, pp. 10–44; Ludwig Brieger and Paul Ehrlich, 'Beiträge zur Kenntnis der Milch immunisirter Thiere', *Zeitschrift für Hygiene und Infectionskrankheiten* (1893) 13, pp. 336–46; Paul Ehrlich, Hermann Kossel and August Wassermann, 'Ueber Gewinnung und Verwendung des Diphtherieheilserums', *Deutsche Medicinische Wochenschrift* (1894) 20, pp. 353–5.

[10] Cf. Throm, op. cit. (6); Hüntelmann, op. cit. (8).

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The production of such sera entered the market in uncertain legal and scientific circumstances. A few years earlier, the introduction of tuberculin had triggered a public health scandal. Robert Koch, the prominent German bacteriologist, had proclaimed at the international medical congress in August 1890 that he had developed tuberculin as a cure for tuberculosis. The public and the medical community welcomed this news enthusiastically. In the face of rising international scientific competition and an intense Franco-German rivalry, the Prussian state pressured Koch to release the drug as early as possible. Koch himself had high hopes that the drug could be successfully marketed. Although tuberculin had been sufficiently tested in neither animal experiments nor clinical trials, Koch released the drug to the public in November of 1890. Critics complained that he had not disclosed any information about the manufacturing process: neither the ingredients nor the composition of the drug, which comprised extracted bacteria cultures dispersed in glycerine, were known to the public. It soon became apparent that tuberculin had no therapeutic effect, and indeed reports surfaced of numerous cases involving severe side effects and death.[11] Nevertheless, Prussian officials continued to endorse Koch's work, establishing a state institute in Berlin in 1891 to promote research on infectious diseases, the Royal Prussian Institute for Infectious Diseases (Königlich Preußisches Institut für Infektionskrankheiten, today's Robert-Koch-Institut), and making Koch its director.

Against the backdrop of these developments, many bacteriologists remained sceptical about the newly developed anti-diphtheria serum, not least because it had been developed by Emil Behring and Paul Ehrlich at the Institute for Infectious Diseases.[12] In addition, serum therapy was a completely novel concept and so there was still no information about its long-term effects. Given the prospects for reaping high profits, but also the risks of another public-health mishap, the new serum therapy attracted the attention of imperial officials. Not least because the German Empire was a federation of states, with health legislation differing from state to state and serum producers located all across the country, officials in Berlin argued that centralized control was necessary.

In the German Empire, state regulation of the production as well as the distribution of anti-diphtheria serum began in 1895. The production process had to be supervised, and there was centralized control of the purity and potency of all serum sold domestically. The evaluation procedure modelled an infection and its cure within a laboratory setting using test animals. It assessed the ability of the active (and as yet unknown) ingredients of the therapeutic serum to neutralize the bacteria or the bacterial toxin and was expressed in immunization units (*Immunisierungseinheiten*, IE for short). Various methods of evaluation existed: for instance, during the development of the serum, Emil Behring evaluated

[11] Cf. Bernhard Opitz and Herwarth Horn, 'Die Tuberkulinaffäre: Neue medizinhistorische Untersuchungen zum Kochschen Heilverfahren', *Zeitschrift für die gesamte Hygiene und ihre Grenzgebiete* (1984) 30(7), pp. 731–34; Barbara Elkeles, 'Der "Tuberkulinrausch" von 1890', *Deutsche medizinische Wochenschrift* (1990) 115, pp. 1729–32; and Christoph Gradmann, *Krankheit im Labor: Robert Koch und die medizinische Bakteriologie*, Göttingen: Wallstein, 2005.

[12] Emil Behring, a military surgeon who worked at the Hygiene Institute of the Friedrich Wilhelms University in Berlin and later at the Institute for Infectious Diseases, both under the direction of Robert Koch, was appointed professor of hygiene in Marburg in 1894. In 1902 Behring received the first Nobel Prize in Medicine or Physiology for the development of the anti-diphtheria serum. Paul Ehrlich was appointed director of the newly founded Institute for Serum Research and Serum Testing in 1896 and received the Nobel Prize in 1908 (together with Ilya Mechnikov) for his theory explaining immunological processes. On Behring see Derek S. Linton, *Emil von Behring: Infectious Disease, Immunology, Serum Therapy*, Philadelphia: American Philosophical Society, 2005; Ulrike Enke, *Emil von Behring 1854–1917: Immunologe – Unternehmer – Nobelpreisträger*, Göttingen: Wallstein, 2023. On Ehrlich see Axel C. Hüntelmann, *Paul Ehrlich: Leben, Forschung, Ökonomien, Netzwerk*, Göttingen: Wallstein, 2011.

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the serum's efficacy in proportion to the weight of the guinea pigs that remained free of symptoms after they had been injected with the diphtheria toxin.[13]

The official testing and state approval of anti-diphtheria serum was initially carried out in a department (called Preußische Controlstation für Diphtherieheilserum) within the Institute for Infectious Diseases, but already in 1896 the Controlstation was separated as the IfSS. In 1899, the IfSS moved from Berlin to Frankfurt and was renamed the Institute for Experimental Therapy (Königlich Preußisches Institut für experimentelle Therapie, henceforth IET), underscoring the shifting focus from testing to research and from serum therapy to medical therapies in general. Shortly after the establishment of the IfSS, a specific, new method of evaluation was implemented. The method involved a complex reference system based on a 'standard' or so-called 'normal serum', and a corresponding 'standard' or 'normal toxin' which served as measures for the serum samples sent to the institute by manufacturers. The definitive measure in this control regime, the 'standard serum', was an arbitrary serum with a fixed value of immunization units that was preserved by vacuum drying and sent to serum producers at regular intervals.[14] Richard Otto, an IfSS medical officer, stated that in the field of biometrology the 'standard serum' was comparable to the prototype of the metre or kilogram in Paris.[15] The 'standard serum' was in turn used to calibrate a 'standard toxin' that was used to measure the efficacy of batches of serum. The value of the immunization units was linked to the serum's prophylactic – or therapeutic – effect on a biological organism: the guinea pig. In practice, a mixture of serum and toxin was injected into a guinea pig (weighing approximately 250 grams) so that the laboratory animal would die after four days – clearly indicating an expected 'objective' (+) effect.[16] In order to objectify the procedure, it was conducted simultaneously by two medical officers.[17] This method was discussed by Madsen and compared with alternative methods used in Britain and France.

The aim of the German method of evaluation was to create an 'objective' procedure that would produce the same results regardless of the time, place or person performing the test. As a precaution, every working step and the exact evaluation procedure were defined and

[13] Behring's research involved various approaches and sequences: the infection with diphtheria bacteria (cultures) or the injection of diphtheria toxin; the serum was injected twenty-four hours before bacteria cultures had been administered or fifteen minutes after pure toxin had been injected in order to test its prophylactic effectiveness; or the other way around: serum was administered after the guinea pig had been infected in order to test its therapeutic effectiveness. For an overview of these matters see Ulrike Klöppel, 'Enacting cultural boundaries in French and German diphtheria serum research', *Science in Context* (2008) 21, pp. 161–80, esp. 174–5.

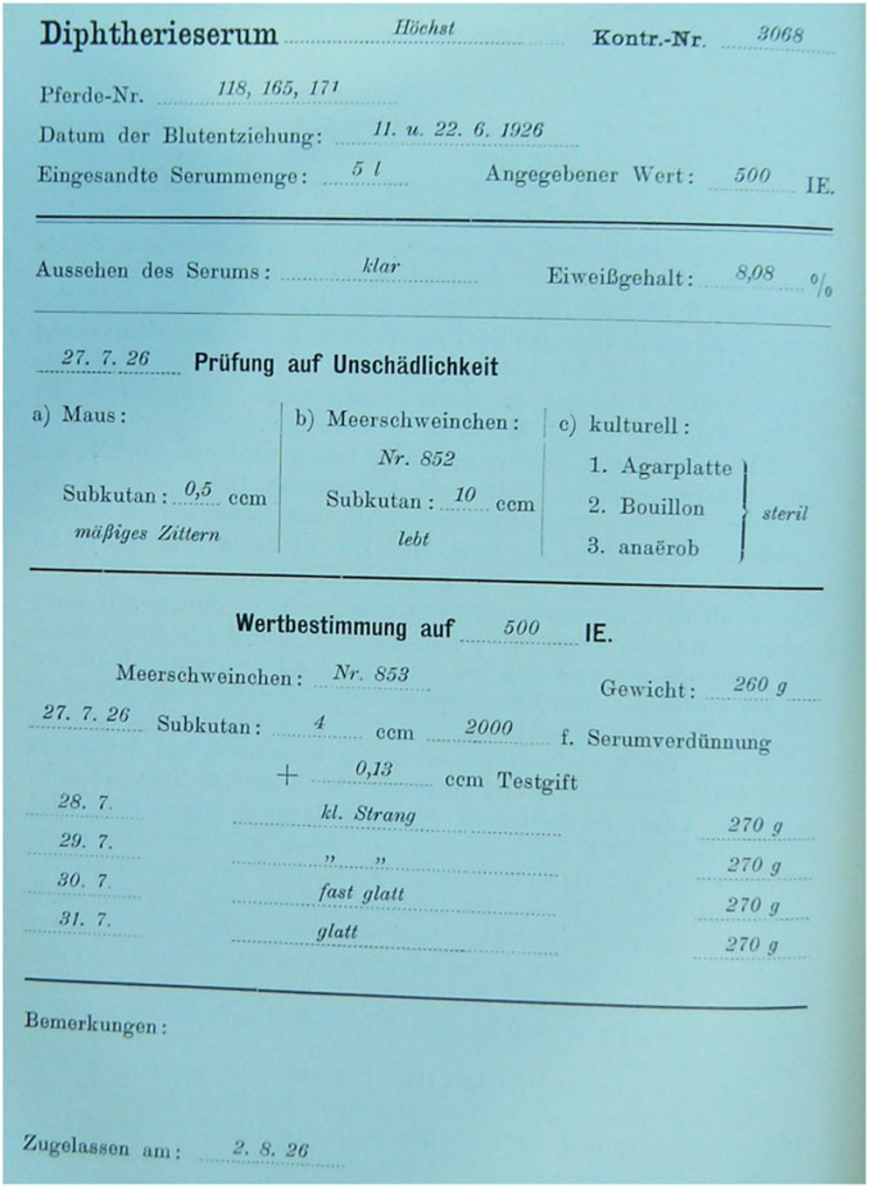
[14] Previously, the reference system had been less complex and there had been only a 'standard toxin'. A diphtheria toxin, produced according to a fixed procedure, that had been stocked for some time was considered to be stable. But it turned out that the toxin weakened at a slow and constant rate. After fifteen months of trials on the preservation of sera and toxins (and theoretical work on the composition of diphtheria toxin that led to the side-chain theory), a 'standard serum' was introduced as a new reference base. It was produced in a large batch, vacuum-dried and bottled in small phials that could be opened individually. The efficacy of the standard serum was also tested at regular intervals. See Richard Otto, *Die staatliche Prüfung der Heilsera* (Arbeiten aus dem Königlichen Institut für experimentelle Therapie zu Frankfurt a. M., vol. 2), Jena: Gustav Fischer, 1906; Axel C. Hüntelmann, 'The dynamics of *Wertbestimmung*', *Science in Context* (2008) 21, pp. 229–52.

[15] Otto, op. cit. (14), p. 29.

[16] Aside from the introduction of the 'standard serum', this was another novelty of the new method: previously, the proportion of serum and toxin injected into the guinea pig was such that the animal merely survived in order to show any signs of illness or infection. But it turned out that there were many misunderstandings and disagreements (with the serum producer) about the 'signs of illness' because the test animals showed different reactions, such as weight loss, atypical behaviour, anaerobic contractions or widely varying secretions. By contrast, the death of the test animal was considered a reliable criterion.

[17] Cf. Otto, op. cit. (14); Throm, op. cit. (6); Hüntelmann, op. cit. (8).

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Diphtherieserum Höchst **Kontr.-Nr.** 3068

Pferde-Nr. 118, 165, 171

Datum der Blutentziehung: 11. u. 22. 6. 1926

Eingesandte Serummenge: 5 l Angegebener Wert: 500 IE.

Aussehen des Serums: klar Eiweißgehalt: 8,08 %

27. 7. 26 **Prüfung auf Unschädlichkeit**

a) Maus:	b) Meerschweinchen:	c) kulturell:
	Nr. 852	1. Agarplatte }
Subkutan: 0,5 ccm	Subkutan: 10 ccm	2. Bouillon } steril
mäßiges Zittern	lebt	3. anaërob }

Wertbestimmung auf 500 **IE.**

Meerschweinchen: Nr. 853 Gewicht: 260 g

27. 7. 26 Subkutan: 4 ccm 2000 f. Serumverdünnung

\+ 0,13 ccm Testgift

28. 7.	kl. Strang	270 g
29. 7.	„ „	270 g
30. 7.	fast glatt	270 g
31. 7.	glatt	270 g

Bemerkungen:

Zugelassen am: 2. 8. 26

Figure 1. The certificate of state approval issued after evaluating anti-diphtheria serum in 1926, the same way it was done around 1900. An anti-diphtheria serum from the Hoechst Dye Works company had been tested. The submitted serum quantity (five litres of batch no. 3068) was obtained from horses (nos. 118, 165, 171) and tested using five hundred immunization units. The test for innocuousness (in the middle part of the certificate) was carried out on a mouse and a guinea pig (no. 852). The lower part of the certificate documents the evaluation process using a guinea pig (no. 853). After the guinea pig had been injected with a mixture of the manufacturer's serum and the equivalent amount of 'standard toxin', the guinea pig's behaviour was observed for four days. After initial infiltrations, the guinea pig showed no more symptoms; that is, the serum contained at least the specified value or even more. Richard Otto and Heinrich Hetsch, *Die Prüfung und Wertbemessung der Sera und Impfstoffe mit besonderer Berücksichtigung der bei der staatlichen Prüfung in Deutschland angewendeten Methoden* (Arbeiten aus dem Staatsinstitut für experimentelle Therapie und dem Georg Speyer-Hause zu Frankfurt a. M. 19), 3rd edn, Jena: Gustav Fischer, 1927, p. 68.

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documented in official guidelines and instructions.[18] A life scientist, appropriately trained in bacteriological methods, who followed the instructions and was provided with the 'standard serum' could, in principle, perform the evaluation. In this respect, the German method was transferable to other countries and foreign institutes.

Evaluation and its importance for the development, production, marketing and practical use of anti-diphtheria serum

The German term *Wertbestimmung* – translated here as 'evaluation' – has two denotations. More generally, valuation implies an ideal or moral value of, for example, knowledge, concepts or ideas, for society. Second, evaluation means an objective and quantifiable value of something, for example a valuation in monetary terms, or of a chemical compound, toxin or disinfectant.[19] As a practical method, evaluations were used in pharmacies to assess the effectiveness and potency of medicines.[20] Their purpose was to transform an undefined, imponderable agent into an objective, quantifiable, comparable factor with an exact mathematical value.[21] Evaluations were designed to be objective processes that determined the precise 'value' of a remedy's effect and overcame less accurate qualitative descriptions such as 'potent', 'highly potent', 'curative', 'preventive', 'weak' or 'ineffective'.

In Norton Wise's words, the value of precision refers to accuracy of measurement and also to certainty, objectivity and rationality – 'it shows quality'.[22] In order to compare (experimental) drugs, a specific (ideally precise) value was needed as an 'objective criterion' to measure the different results yielded in one's own research, as well as that of competing scientists or companies.

When anti-diphtheria serum was developed, neither the composition of diphtheria toxin nor that of its antitoxin was known (or visible). In the late 1880s, Emil Behring had observed that the blood serum from an animal that had survived a specific infection (or an artificial immunization) and been transferred to another animal was able either to cure that animal of the same disease (if it had been previously infected in the test setting prior to serum therapy) or to prevent the outbreak of the disease (if it had been infected after the serum had been applied). In the absence of an identifiable substance, Ehrlich arbitrarily defined the amount of diphtheria toxin capable of killing a 250-gram guinea pig in just four days as the single lethal dose ('Ehrlichs physiologische Gifteinheit' – 'einfache tödliche Dosis').

[18] 'Instruktion für den Betrieb der Controlstation für Diphtherieheilserum', dating from February 1897, dealt with the evaluation process in paragraphs 7 and 8. See PEI, Dept. Va, no. 1, vol. 1. This information was also published in Paul Ehrlich, 'Die Wertbemessung des Diphtherieheilserums und deren theoretische Grundlagen', *Klinisches Jahrbuch* (1897) 6, pp. 299–326; and Otto, op. cit. (14).

[19] E. Hailer, 'Zur Frage der Prüfung und Wertbestimmung der Desinfektionsmittel', *Arbeiten aus dem Reichsgesundheitsamte* (1924) 54, pp. 347–54.

[20] For example, on the evaluation of the effects of digitalis see Alexander Berghaus, *Die Entwicklung und Methoden zur Physiologischen Wertbestimmung von Digitalispräparaten*, Husum: Matthiesen, 1982.

[21] The need for accuracy and quantification arose out of the transformation of medicine into a statistical and empirically based science along the lines of the natural sciences. As medicine became an increasingly evidence-based science, test-arrays, empirical knowledge and an awareness of epistemological concerns became necessary. Cf. Georges Canguilhem, *Grenzen medizinischer Rationalität: Historisch-epistemologische Untersuchungen*, Tübingen: edition diskord, 1989; J. Rosser Matthews, *Quantification and the Quest for Medical Certainty*, Princeton, NJ: Princeton University Press, 1995; and the contributions in Norton M. Wise (ed.), *The Values of Precision*, Princeton, NJ: Princeton University Press, 1995; Graeme Gooday, *The Morals of Measurement: Accuracy, Irony, and Trust in late Victorian Electrical Practice*, Cambridge: Cambridge University Press, 2004, Chapters 1, 2; and the contributions in Gérard Jorland, Annick Opinel and George Weisz (eds.), *Body Counts: Medical Quantification in Historical and Sociological Perspective*, Montreal: McGill–Queen's University Press, 2005.

[22] Wise, 'Introduction', in Wise, op. cit. (21), pp. 3–13, esp. 3.

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And Behring later defined 'normal toxin' as a hundredfold dose of toxin, diluted in one centilitre.[23] And one hundred immunization units were set arbitrarily as the minimum dose for serum sold in pharmacies in Germany after 1894. Everything else, later on, involved upscaling. In particular, a precise dosage was required for therapeutic success. This meant that the method of evaluation had to meet several preconditions: it had to be quantitative, regular, reliable, traceable and repeatable. As an 'objective' method, the evaluation of the serum had to be independent of local circumstances – all contingencies had to be ruled out – and of the person performing the test. Thus the person carrying out the evaluation procedure had to follow a fixed set of instructions governing the sequences and technical arrangements.[24]

Last but not least, all the other actors in the chain of events from initial production to treatment – including test animals and microbes – had to be fixed and defined in order to attain the same results everywhere and every time. In this case, this involved the bacterial cultures, the horses producing the serum, the guinea pigs or mice used as bioindicators, the human scientists, the applying physicians, and the patients. If processes were not quantifiable, they had to be regulated, and the actors had to be calibrated, unified and normalized. The strain of bacteria and the method used to produce the diphtheria toxin for the immunization procedure influenced the production of the serum and the outcome. Therefore, when the toxin was more toxic, the serum donor produced more antibodies. The serum donor also had to be standardized; a horse with a differing (i.e. poorer) health status would produce fewer antibodies than a healthy horse, or the process would take longer, or the horse could die. All the experienced reactions had to be translated into knowledge or know-how for producing serum.[25] Furthermore, the manufacturer and the scientists executing the process at the IfSS had to be trained in the evaluation technique and in how to standardize the evaluation process in order to achieve the same results as the medical officials at the IfSS.[26] The laboratory animals used as bioindicators also had to be standardized so that they would react similarly.[27] The main steps within the production and evaluation processes were documented to control the production process, to clarify differences in the evaluation process between the manufacturer and the IfSS, and to ensure traceability, meaning that every vial of serum sold in pharmacies can be traced back to the serum donor.[28] Ultimately, to determine whether a drug was effective or whether complaints about its ineffectiveness were related to its potency, the disease had to be standardized. While clinical symptoms were sometimes ambiguous and unclear, only bacteriological laboratory testing provided

[23] Cf. Otto, op. cit. (14), p. 27. Laboratory animals – killed in legions in test arrays – played a decisive role, as they indicated the impact of the serum. And for economic and practical reasons, the evaluation procedure had to be accomplished using small test animals like mice, rats or rabbits.

[24] 'Instruktion für den Betrieb der Controlstation für Diphtherieheilserum', op. cit. (18); Ehrlich, op. cit. (18); Paul Ehrlich, 'Die staatliche Controle des Diphtherieserums', *Berliner Klinische Wochenschrift* (1896) 33(20), pp. 441–3; and Otto, op. cit. (14).

[25] On the standardization of the pharmaceutical manufacturers see Jean-Paul Gaudillière and Ilana Löwy (eds.), *The Invisible Industrialist: Manufactures and the Production of Scientific Knowledge*, Houndmills: Macmillan Press, 1998.

[26] See the contributions in Christoph Gradmann and Jonathan Simon (eds.), *Evaluating and Standardizing Therapeutic Agents, 1890–1950*, Basingstoke: Palgrave 2010.

[27] On the standardization of laboratory animals see, for instance, Karen Rader, *Making Mice: Standardizing Animals for American Biomedical Research, 1900–1955*, Princeton, NJ: Princeton University Press, 2004; Robert G.W. Kirk, '"Wanted – standard guinea pigs": standardization and the experimental animal market in Britain, ca. 1919–1947', *Studies in History and Philosophy of Biological and Biomedical Sciences* (2007) 39, pp. 280–91.

[28] On the importance of protocols in the process of standardization in medicine see Stefan Timmermans and Marc Berg, 'Standardization in action: achieving local universality through medical protocols', *Social Studies of Science* (1997) 27, pp. 273–305.

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consistent results.[29] And so the standardization of all actors and processes played a major role in the evaluation procedure, which in turn helped to ensure a standardized outcome.[30]

During the 'production process' (that is, during the immunization of serum donors) a precise value was needed to define a point in time when the serum donor was ready for bleeding. Objectifying the value of the serum served to stabilize the industrial process. Furthermore, for the serum producer, state approval had a legal, an economic and a marketing value. When responding to litigation or public scandal involving the serum's efficacy or safety (such as the case of Ernst Langerhans, who died in April 1896 after the application of anti-diphtheria serum), the manufacturer, in cooperation with the state institute, could prove that the serum had been produced in accordance with the official guidelines.[31] In competition with other manufacturers, companies like Hoechst Dye Works, Schering or Merck could save money on test fees and gain a cost advantage by increasing the number of immunization units. In addition, government approval was seen as a mark of quality, and increasing the number of immunization units became a marketing tool and sign of 'good quality'. On the serum market, the evaluation was also a criterion for comparing different sera. Finally, general practitioners and hospital doctors needed a quantitative criterion such as 100 or 200 IE to assess a serum's effectiveness before administering it to the patient.

Sera evaluated by the same method enabled manufacturers, consumers and physicians to assess and compare the potency of different sera and manufacturers. As marketed products, the serum and the production process were standardized by the state approval of the evaluation procedure in two ways: first, every serum sold on the German market had to have a minimum efficacy of one hundred immunization units (guaranteeing a standardized minimum quality); and second, the definition of certain standards for the production process was intended to guarantee a valid and safe pharmaceutical: a physician had to supervise the process, and prior to state approval a district physician inspected the production plant and the documentation of the evaluation process as well as the health status of the animals used as serum donors. Finally, the evaluation process itself was standardized by establishing rules about how the evaluation should be carried out.[32] These rules, and the practical know-how associated with them, were adopted by serum manufacturers (such as through practical training at the IfSS), ensuring that one hundred immunization units at the production plant were equivalent to one hundred immunization units at the IfSS. These measures proved helpful in the international implementation of the German method of evaluation.

[29] On the standardization of diseases see, for instance, Olga Amsterdamska, 'Standardizing epidemics: infection, inheritance, and environment in prewar experimental epidemiology', in Jean-Paul Gaudillière and Ilana Löwy (eds.), *Heredity and Infection: The History of Disease Transmission*, London: Routledge, 2001, pp. 135–79.

[30] The importance of standardization and standards in science, and in modern life, is highlighted in the contributions in Martha Lampland and Susan Leigh Star (eds.), *Standards and Their Stories: How Quantifying, Classifying, and Formalizing Practices Shape Everyday Life*, Ithaca, NY: Cornell University Press, 2009; Lawrence Busch, *Standards: Recipes for Reality*, Cambridge, MA: MIT Press, 2011.

[31] After Ernst Langerhans died in April 1896 following a prophylactic course of anti-diphtheria serum, his father, Robert Langerhans, a renowned physician himself, declared in a public announcement that his son's death had been caused by the serum. An official investigation tracked all vials of the same batch of serum, their production, their control and their use in hospitals. This traceability became possible after the introduction and documentation of serum control in 1895. After no further deaths or illnesses were reported, the official report concluded that the death of Ernst Langerhans was simply an unfortunate mishap. Some years later it was described as one of the first cases of death from anaphylactic shock. The report was published in Ehrlich, op. cit. (24). See also Axel C. Hüntelmann, 'Das Diphtherie-Serum und der Fall Langerhans', *Medizin, Geschichte und Gesellschaft* (2006), 24, pp. 71–104.

[32] 'Instruktion für den Betrieb der Controlstation für Diphtherieheilserum', op. cit. (18); Ehrlich, op. cit. (18); Otto, op. cit. (14).

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The evaluation procedure was intended to underscore the rationality and scientific basis of the new serum therapy, especially following the tuberculin scandal in 1890–1.[33] In addition, the mysterious mixing and dilution of serum, which was treated almost like a homeopathic substance, made it necessary to establish an objective value. In the eyes of one official, the evaluation and state control of the serum was intended to strengthen confidence in the new serum therapy; in other words, it functioned as a technology of trust.[34] The serum's potency, announced by the manufacturer, was validated by IfSS approval and certification. Evaluation, regulation and validation were inextricably intertwined.

The global rise of the German method of evaluation and its institutionalization

As Madsen contended in 1897, establishing an objective and precise method of serum evaluation was the starting point for the German method's wider use. Disagreements between the IfSS and local serum producers were aired in writing or clarified by joint practical work at the institute's laboratory. From the late 1890s, serum manufacturers and foreign scientists visited or were invited to the IfSS, where they received training in the (correct) method of evaluation.[35] Further disagreements were resolved by inspections of the production site by medical officers of the IfSS, and finally by shipping standard serum and standard toxin until the evaluation of serum at both sites matched. In this way, the evaluation itself regulated serum production.

The exchange and dissemination of knowledge about the evaluation method at the IfSS was soon institutionalized and a training programme for staff of serum manufacturers and for scientists from other hygiene institutes (such as Thorvald Madsen, William Welch, Henry Dale and Theobald Smith) was established at the beginning of the twentieth century.[36] Graduates of the programme helped to implement the German method once they had returned home and to spread the method worldwide.[37]

Dating back to the 1880s, the Kaiserliches Gesundheitsamt (Imperial Health Office) had hosted foreign scientists for longer periods of time, and the Institut Pasteur in Paris had

[33] Cf. Opitz and Horn, op. cit. (11); Elkeles, op. cit. (11); Gradmann, op. cit. (11).

[34] Cf. Otto, op. cit. (14), p. 40. On the technology of trust see Theodore M. Porter, *Trust in Numbers: The Pursuit of Objectivity in Science and Public Life*, Princeton, NJ: Princeton University Press, 1995.

[35] See Hüntelmann, op. cit. (14). Problems arose, for instance, due to cold winter temperatures (see Paul Ehrlich to Angelo Knorr, 21 February 1897, PEI, Dept. Va, no. 1, vol. 1) or to technical inaccuracies arising from the different ways in which the toxin–antitoxin mixture could be administered, i.e. the different sites of the injection (subcutaneous, intramuscular, intraperitoneal), the bacterial strain used in the production of the toxin, or the animal species used as a bioindicator. All of these factors influenced the evaluation process. In one case, problems arose in the evaluation of erysipelas serum because employees of the company, Ruete & Enoch in Hamburg, had used grey mice to evaluate the serum, while white mice, whose organisms absorbed the antitoxins more quickly, were used in the state-run institute. See Otto, op. cit. (14), pp. 66–7; and the correspondence between the institute and the serum producers in PEI, Dept. IX, no. 1, vol. 1.

[36] The US pathologist and bacteriologist William Welch had visited Germany several times, initially during his medical studies in the 1870s. Welch went on to help establish Johns Hopkins Medical School and soon became a leading medical figure in the United States and the founding president of the Rockefeller Institute for Medical Research. See Simon Flexner and James Thomas Flexner, *William Henry Welch and the Heroic Age of American Medicine*, New York: Viking Press, 1941. Theobald Smith was also a leading bacteriologist in the United States whose research focused on animal diseases, public health and comparative pathology, and who had taught at Harvard University since 1895. Henry Dale had just finished his medical studies in Cambridge when he visited the IET for a couple of months. He later became a prominent physiologist and biochemist who was awarded the Nobel Prize in Medicine or Physiology in 1936.

[37] See the correspondence with the superior institution, the Prussian Ministry of Cultural Affairs (Prussian Secret State Archive Berlin (GStA PK), 1. HA, Rep. 76 Vc, Sekt. 1, Tit. XI, part II, no. 18, vol. 1) about foreign guest researchers and the file 'Laboranten' (laboratory workers) in PEI, Dept. I, no. 6, vol. 1.

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done the same since the 1890s.[38] These exchanges fostered an international scientific community. Aside from technical training, the evaluation of serum abroad also required the 'standard serum' as a reference to obtain a comparative result. Thus some foreign institutes (whose staff had previously worked at the German state institute) requested samples of the 'standard serum' from the IET.[39] At first, the institute responded informally, sending samples of the 'standard serum'. But soon the supply was organized on a subscription basis. German serum producers regularly received a tube of 'standard serum' every two months (as they were obliged to test their sera). Producers, researchers and testing institutes in Europe and the Americas also began to be supplied with serum at the same two-month interval.[40] The wide geographic reach of this system is underscored by the IET's collaboration with the Imperial Institute for the Study of Infectious Diseases in Tokyo (later renamed the Kitasato Institute for Infectious Diseases after its founder, Shibasaburo Kitasato, who collaborated with Robert Koch and Emil Behring).[41]

In 1913, the institute's annual report proudly announced that fifty-six foreign producers and regulatory agencies had subscribed to the German 'standard serum', making the IET the biometric 'master of measurement'.[42] The subscribers were located in Europe (especially Eastern Europe, Britain and Italy), North and South America (Brazil) and Japan, as well as British and French colonies in Africa and parts of Asia (especially India). Not only did the German method of evaluation become an obligatory passage for manufacturers who wanted to sell serum on the German market, but also the 'standard serum', the central core of that method, became a boundary object, connecting numerous actors in science, government and the economy at the intersection of various processes of scientification, bureaucratization, industrialization and standardization.[43]

The globalization of evaluation required some understanding (and acceptance) of bacteriology, as well as bacterio- and serotherapy in the respective countries, where serum production followed similar principles and processes. Furthermore, the globalization of evaluation was embedded in the context of the 'Age of Empires'. At that time, Germany, France and Great Britain fought for hegemony in all fields of science and metrology: natural and life sciences, mathematics and geography. While France prevailed with the establishment of the decimal system and both the International Bureau of Weights and Measures

[38] For the Imperial Health Office see the complaint in November 1883 that, due to (foreign) guest researchers' numerous requests for an internship/laboratory slot, the staff lacked the time to do their regular work. See Federal Archive (Bundesarchiv) Berlin, R 86, no. 752; and Axel C. Hüntelmann, *Hygiene im Namen des Staates: Das Reichsgesundheitsamt 1876–1933*, Göttingen: Wallstein, 2008, Chapter 4.1.2. For the Pasteur Institute, prominent guest researchers were Constantin Levaditi from Romania, Elias Metschnikoff from Russia and Alexandre Yersin from Switzerland – to cite only the best-known, who later also became staff members. On the scientific networks of the Pasteur Institute see Ilana Löwy, 'On hybridizations, networks and new disciplines: the Pasteur Institute and the development of microbiology in France', *Studies in History and Philosophy of Science* (1994) 25, pp. 655–88; and Anne-Marie Moulin, 'The Pasteur Institute's international network: scientific innovations and French tropisms', in Christophe Charle, Jürgen Schriewer and Peter Wagner (eds.), *Transnational Intellectual Networks: Forms of Academic Knowledge and the Search for Cultural Identities*, Frankfurt am Main: Campus, 2004, pp. 135–64.

[39] See the first requests from Britain and Russia for standard toxin in 1896 in GStA PK, 1. HA, Rep. 76 Vc, Sekt. 1, Tit. XI, part II, no. 18, vol. 1; and the file 'Abgabe von Testgift u. Standardserum an ausländische, wissenschaftliche Institute', PEI, Dept. Vc, no. 5, numerous volumes, starting in 1896.

[40] See PEI, Dept. Vc, no. 5, vol. 1.

[41] See Jane-Hsiu Chen, '*Eine strenge Prüfung deutscher Art': Der Alltag der japanischen Medizinausbildung im Zeitalter der Reform von 1868 bis 1914*, Husum: Matthiesen, 2011.

[42] Annual Report 1913, in PEI, Dept. IV, no. 1, vol 2. The German term (*Meister der Messung*) refers to David Cahan's monograph *An Institute for an Empire: The Physikalisch-Technische Reichsanstalt 1871–1918*, Cambridge: Cambridge University Press, 1989.

[43] Cf. Susan L. Starr and James J. Griesemer, 'Institutional ecology, "translations" and boundary objects: amateurs and professionals in Berkeley's Museum of Vertebrate Zoology, 1907–39', *Social Studies of Science* (1989) 19, pp. 387–420.

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and the International Health Office in Paris, Great Britain succeeded in dividing the globe according to a system of hours and longitudes and fixing the prime meridian at the Royal Observatory in Greenwich.[44] Given these French and British successes, the establishment of the Imperial Physical Technical Institute (Physikalisch-Technische Reichsanstalt) and the IET was seen as a matter of paramount national importance.[45] While the IET globalized the German method of evaluation by sending 'standard serum' around the world, the Pasteur Institute set up a worldwide system of subsidiary institutes to help establish French standards.[46] By 1914, the IET enjoyed international supremacy in the field of serology and immunology, and the institute was the pioneering authority on the evaluation and standardization of sera and vaccines.

The decline of German dominance

The success story of the globalization of the German evaluation method was disrupted by the outbreak of the First World War. Shipments of 'standard serum' into the countries at war became impossible. The decline is clearly reflected in the dwindling number of subscribers. In the first year of the war, the number of foreign institutes receiving 'standard serum' decreased to twenty-four, and by 1918 the number of subscribers had fallen to five.[47] There were also technical difficulties. Under the conditions of a wartime economy and the rising demand for sera and vaccines, especially from the German Army (315 litres of tetanus serum in 1913, rising rapidly to 2,124 litres in 1914; by the end of the war 16,471 litres had been tested in 1,200 batches), it became more difficult for the institute to meet its own quality standards and to carry out serum tests as officially required (not least due to a lack of test animals). In addition, the institute's duties and responsibilities increased and shifted away from evaluation: during the war, the institute itself became a manufacturer, producing vaccines against typhoid fever and cholera for the army. However, the increasing workload had to be borne by reduced staff numbers, as many members of the institute were conscripted into the army. Further, during the war, the institute conducted only war-related research on sera for dysentery and gas gangrene or on the serodiagnosis of typhoid fever.[48] Over the course of the war, the IET first lost its technical–scientific supremacy, and soon also its moral authority as a reference system. For not only had it produced serum for the German Army, but also its director, Paul Ehrlich, had signed the so-called Manifesto of the Ninety-Three (Aufruf an die Kulturwelt) which sought to justify the German invasion of neutral countries (Belgium) and war crimes against the civilian population.[49]

[44] Cf. Peter Galison, *Einsteins Uhren, Poincarés Karten: Die Arbeit an der Ordnung der Zeit*, Frankfurt am Main: S. Fischer, 2003.

[45] Cf. Cahan, op. cit. (42). For Britain and similar discussions about the introduction of the ohm as an electrical standard see Simon Schaffer, 'A manufactory of ohms: late Victorian metrology and its instrumentation', in Susan Cozzens and Robert Bud (eds.), *Invisible Connections: Instruments, Institutions, and Science*, Bellingham: SPIE, 1992, pp. 23–56; Schaffer, 'Rayleigh and the establishment of electrical standards', *European Journal of Physics* (1994) 15, pp. 277–85; and Schaffer, 'The accurate measurement is an English science', in Wise, op. cit. (21), pp. 135–72.

[46] See Löwy, op. cit. (38); Moulin, op. cit. (38); and Bruno Latour, *The Pasteurization of France*, Cambridge, MA: Harvard University Press, 1988.

[47] The figures were extracted from the files in PEI, Dept. Vc, no. 5, vol. 1–2; and from the annual reports in PEI, Dept. IV, no. 1, vol. 2.

[48] See the figures in the annual report for 1917 in PEI, Dept. IV, no. 1, vol. 2. The institute's decline is described in Wilhelm Kolle, 'Das Staatsinstitut für experimentelle Therapie und das Chemotherapeutische Forschungsinstitut "Georg Speyer-Haus" in Frankfurt a. M.: Ihre Geschichte, Organisation und ihre Arbeitsgebiete, nebst vollständigem Verzeichnis der in den Jahren 1896–1926 veröffentlichten Arbeiten', *Arbeiten aus dem Staatsinstitut für experimentelle Therapie und dem Georg Speyer-Hause zu Frankfurt a. M.* (1926) 16, pp. 1–67.

[49] Jürgen von Ungern-Sternberg and Wolfgang von Ungern-Sternberg, *Der Aufruf 'An die Kulturwelt!' Das Manifest der 93 und die Anfänge der Kriegspropaganda im Ersten Weltkrieg*, Stuttgart: Franz Steiner, 1996.

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Regaining influence

Paul Ehrlich's successor as head of the IET, Wilhelm Kolle, was appointed in 1917 and began reviving research and implementing a sweeping structural reorganization of the institute from the end of the war in 1918 during the post-war chaos lasting until 1923.[50] Kolle was faced with many problems. First, the financial pillars of the institute, which rested on test fees paid by serum producers, began to collapse. In the economic crises following the war, the whole system of test fees was called into question by the serum producers.[51] Second, as an institution that tested sera and vaccines, the IET encountered new competitors in Germany: the Imperial Health Office and the Prussian Institute for Infectious Diseases. During the war, both institutions had not only produced serum but also developed serum evaluation methods.[52] Third, the death of a whole generation of German bacteriologists between 1910 and 1918 (Robert Koch, Paul Ehrlich, Friedrich Loeffler, Emil Behring, Georg Gaffky) led to the collapse of long-standing personal networks. In a way, Kolle was somewhat excluded from the German scientific community because from 1906 (until 1917) he held a professorship in Switzerland at the Swiss Institute for Infectious Diseases (Institut zur Erforschung der Infektionskrankheiten) in Bern. Finally, the life sciences witnessed a paradigm shift from bacteriology and sero- and bacterio-therapies to epidemiology, hormones and endocrinology, and to eugenics and genetic concepts of disease.[53] All these factors weakened the position of bacteriology as a scientific field and of the IET.

After the war, the Allies agreed that Germany (and German science) should not regain its old strength and should be excluded from all international positions and committees.[54] On the one hand, German scientists were shunned by British, French and Belgian colleagues and excluded from conferences. On the other hand, German bacteriologists and immunologists were leading experts in their field, and their knowledge was almost indispensable in the post-war period when infectious diseases such as tuberculosis, typhoid fever, cholera, venereal diseases or influenza broke out on an epidemic or pandemic scale. Such outbreaks spawned efforts to reintegrate German scientists into the international community.

But many German scientists were ambivalent about international cooperation with former 'enemy' scientists, their perceptions oscillating between national rehabilitation and shame. The League of Nations' Hygiene Organisation, whose members professed allegiance to objective scientific truth, began providing a neutral framework for international

[50] See Kolle, op. cit. (48).

[51] See the financial files in PEI, Dept. II, no. 6, vols. 2–3; and Kolle, op. cit. (48).

[52] The Institute for Infectious Diseases had already produced sera before the war, but only incidentally was there any discussion of evaluation. Since the 1920s, the testing of foreign swine fever/swine erysipelas or gas gangrene sera had been conducted by members of the Imperial Health Office. See for instance H. Zeller and K. Beller, 'Erfahrungen bei der staatlichen Prüfung ausländischen Schweinepest-Serums', *Arbeiten aus dem Reichsgesundheitsamte* (1930) 61(1), pp. 113–24; Hans Schlossberger and W. Menk, 'Die Wertbemessung der antitoxischen Gasödemsera', *Arbeiten aus dem Reichsgesundheitsamte* (1931) 62(1), pp. 51–62. This institutional 'competition' became possible because members of the IET (e.g. Hans Schlossberger or Hermann Dold) had moved to the Imperial Health Office.

[53] This paradigm shift found its personal counterpart in the departure of Martin Kirchner (bacteriologist) from the Prussian Ministry of Interior and the nomination of Adolf Gottstein (social hygienist) as ministerial director at the new Prussian Ministry for Public Health. On public-health policies in Germany see Axel C. Hüntelmann, 'The shifting politics of public health in Germany between 1890s and 1920s', in Barry Doyle and Hannah-Louise Clark (eds.), *Imperial and Post Imperial Healthcare before Welfare States*, special issue of the *European Review of History* (2021) 28(5–6), pp. 636–62.

[54] On the efforts to 'keep Germany down' cf. Margaret Macmillan, *Paris 1919: Six Months That Changed the World*, New York: Random House, 2003.

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collaboration ('in the silence of the laboratory' and including German scientists) in 1921, long before Germany became a member of the League of Nations in 1926.[55]

As head of the organization's Standardisation Committee, Thorvald Madsen proposed a work schedule for various sera in autumn 1921. For the international standardization and evaluation of anti-diphtheria serum, he suggested proceeding with the pre-war system because the German method of evaluation was well known, reliable and accepted throughout the world. For tetanus serum, the situation was more complicated. Tetanus occurred less frequently than other infectious diseases, such as diphtheria, mostly after an injury when the tetanic pathogens entered the wound. But its characteristic rigid spasms were terrifying and its outcome was almost always fatal. Because it was relatively rare, tetanus serum had long played only a minor role. But during the war tetanus serum was administered prophylactically to wounded soldiers – and horses – and needed in large quantities. However, an international standard for the evaluation of anti-tetanus serum had not gained acceptance in the early 1920s and Madsen saw a need to overcome the different methods used in Germany, France, Italy and the United States. For dysentery and other sera, a standardized method of evaluation did not even exist and had to be developed from scratch. The necessary examinations were executed at different national institutes – including German research institutes – and discussed by experts at international conferences.[56]

During a private visit to Frankfurt, Thorvald Madsen presented his proposal to Wilhelm Kolle and invited him to attend the second meeting on the standardization of sera, scheduled for December 1921 in London.[57] Because Madsen enjoyed good relations with both German and allied scientists (during the First World War the Danish Serum Institute had produced serum and vaccines for the German as well as for the Allied armed forces), he was well suited as a mediator between both parties. And beyond this, the Danish institute was not suspected of pursuing Danish national interests.[58] The difficult post-war situation allowed small states like Denmark, Poland, Belgium and Switzerland to play important roles as international mediators via 'back-channels' (*Hintertüren der Macht*).[59]

Madsen's invitation was followed by a diplomatic balancing act that exemplified the difficulties, entanglements and ambivalence that arose whenever German scientists participated in international conferences in the post-war period. For example, Kolle – who as Ehrlich's successor thought he had a 'natural' right to participate – on the one hand resented not being invited to the first meeting of the Hygiene Organisation in October 1921 in Paris, and on the other hand was uncertain about what to expect in London.[60] In correspondence with his superiors at the Prussian Ministry of Cultural Affairs, German motives were clearly articulated. Kolle feared that the Hygiene Organisation might agitate against and/or reject the widely used German method of evaluation of anti-tetanus serum. This would end up weakening the 'dominant position of German science esp. concerning the

[55] See Pauline M.H. Mazumdar, '"In the silence of the laboratory": the League of Nations standardizes syphilis tests', *Social History of Medicine* (2003) 16, pp. 437–59.

[56] League of Nations, Provisional Health Committee, Minutes of 2nd session, Paris, 20th to 22nd October 1921, Annex 6, memorandum by Dr Madsen on the standardization of antitoxic sera, etc. A copy is in PEI, Dept. B, no. 6, vol. 1.

[57] Thorvald Madsen to Wilhelm Kolle, 17 November 1921, PEI, Dept. B, no. 6, vol. 1.

[58] Henrik Tjornelund, 'The Copenhagen vaccine: the collaboration of the State Serum Institute and the Robert Koch Institute 1941–44', in Marion Hulverscheidt and Anja Laukötter (eds.), *Infektion und Institution: Zur Wissenschaftsgeschichte des Robert Koch-Instituts im Nationalsozialismus*, Göttingen: Wallstein, 2009, pp. 188–205, 191.

[59] Cf. Madeleine Herren, *Hintertüren zur Macht: Internationalismus und modernisierungsorientierte Außenpolitik in Belgien, der Schweiz und den USA, 1865–1914*, Munich: Oldenbourg, 2000.

[60] Pauline M.H. Mazumdar, 'The state, the serum institutes and the League of Nations', in Gradmann and Simon, op. cit. (26), pp. 118–38, 122–3.

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method of the evaluation of sera' and hence also weaken the competitive position of the German serum producers in international markets.[61]

In Madsen, the German Empire had a good friend who would help to restore the scientific relationship between German bacteriologists and those of the 'victorious powers' and would give 'neutral' advice about immunological matters. Kolle believed that the proceedings in London would probably not boil down to a 'replacement of the German methods of evaluation but to a formal verification'.[62] Here again, the relation between regulation, evaluation in the sense of standardization, and validation in the sense of verification became explicit. In principle, Kolle expressed his readiness to cooperate with Madsen and the Hygiene Organisation, simply to defend German methods (and to re-establish contact with his foreign colleagues).

One problem identified by Kolle involved financial compensation. Thorvald Madsen offered a considerable sum of money to cover the costs for examinations and experiments (500 pounds, or 600,000 marks), money that would benefit Kolle's institute. On the other hand, Kolle explained to Madsen that the German institute could not accept these 'meagre alms' from the League of Nations while Germany was simultaneously paying fifty billion marks in annual war reparations and hence unable to adequately fund its research institutes.[63] Further consultations and correspondence between Kolle, Madsen, the Ministry of Cultural Affairs and the Foreign Office followed. Finally, they found a pragmatic arrangement: Kolle would attend the conference of the Hygiene Organisation as a private person. And he would be reimbursed not directly from the League of Nations but from an intermediary: the Danish Serum Institute. This again illustrates Madsen's importance as a key international mediator.[64]

At the conference of the Hygiene Organisation held in December 1921, the participants decided to adopt the existing evaluation methods for anti-diphtheria and anti-tetanus sera. The IET and the Hygiene Laboratory in Washington, DC, the precursor of the National Institutes of Health, would exchange German and American anti-diphtheria 'standard sera' and then send them to research institutes in Paris, Rome and Copenhagen for comparison. All of the institutes agreed that the German and the American 'standard' produced the same results.[65] The Danish Statens Serum Institut coordinated the comparison, distribution and adjustment of the results. After the completion of all examinations the results were discussed at a conference in September 1922, where the German method of evaluation of anti-diphtheria serum was declared the standard for all countries. The 'standard serum' would be kept in Frankfurt, while the Danish serum institute would do an annual 'meta' control audit to test the equality of different sera.[66]

Coordinating a standard evaluation method for anti-tetanus serum turned out to be more difficult (see Figures 2 and 3). Although the method itself (vacuum-dried standard serum, two different series of tests) was in principle the same, there were different 'standard sera'. Madsen complained that the 'units by which this anti-toxic value is expressed vary so much that, for instance, a phial of serum which in Germany would be said to contain 20 anti-toxic units would in the United States, be said to contain about 1,000 anti-toxic units.

[61] Wilhelm Kolle to the Prussian Ministry of Cultural Affairs, 8 November 1921, PEI, Dept. B, no. 6, vol. 1.

[62] Kolle, op. cit. (61).

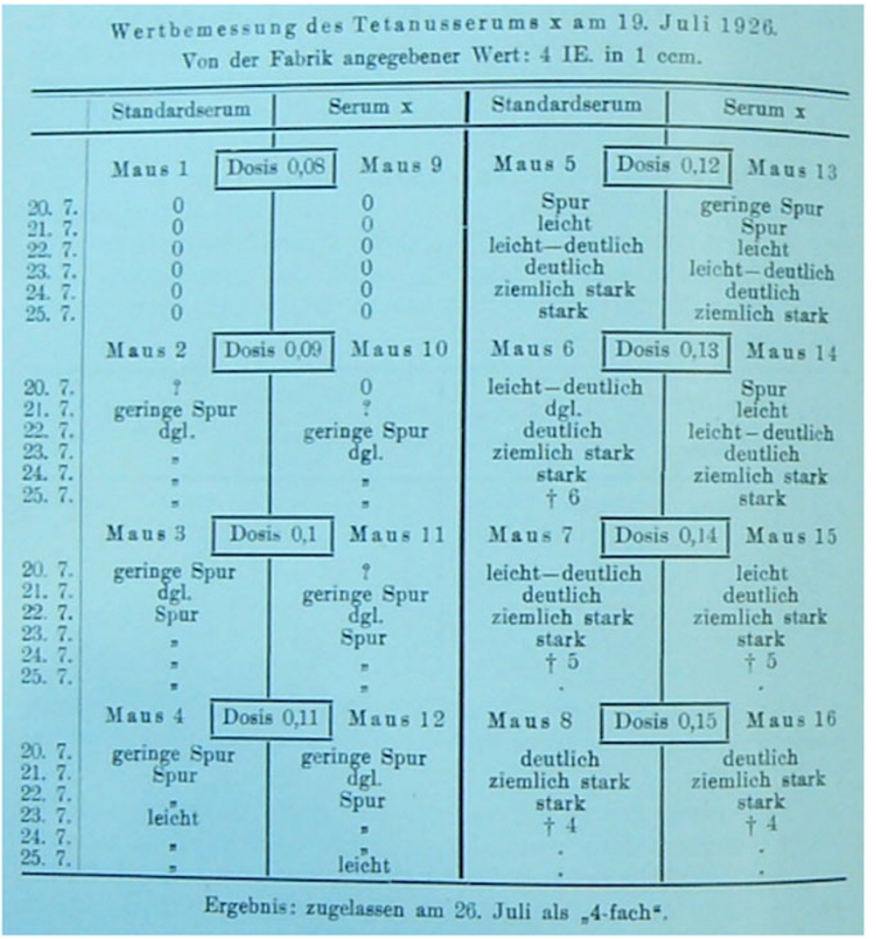
[63] Wilhelm Kolle to the State Secretary in the Prussian Ministry of Cultural Affairs, Hugo Krüss, 14 November 1921, PEI, Dept. B, no. 6, vol. 1. I have cited the main points of Kolle's argument because many of them were repeated in the correspondence between the Ministry for Cultural Affairs and the Foreign Office.

[64] See the correspondence in advance of the conference in PEI, Dept. B, no. 6, vol. 1.

[65] The comparison was completed at the IET in July 1922.

[66] See the correspondence and resolutions in PEI, Dept. B, no. 6, vol. 1; and Archive of the United Nations, League of Nations – Hygiene Organisation, (Permanent) Standardisation Committee, Cart. 858, 903–15, 5989.

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Wertbemessung des Tetanusserums x am 19. Juli 1926.
Von der Fabrik angegebener Wert: 4 IE. in 1 ccm.

	Standardserum	Serum x	Standardserum	Serum x
	Maus 1 Dosis 0,08	Maus 9	Maus 5 Dosis 0,12	Maus 13
20. 7.	0	0	Spur	geringe Spur
21. 7.	0	0	leicht	Spur
22. 7.	0	0	leicht—deutlich	leicht
23. 7.	0	0	deutlich	leicht—deutlich
24. 7.	0	0	ziemlich stark	deutlich
25. 7.	0	0	stark	ziemlich stark
	Maus 2 Dosis 0,09	Maus 10	Maus 6 Dosis 0,13	Maus 14
20. 7.	?	0	leicht—deutlich	Spur
21. 7.	geringe Spur	?	dgl.	leicht
22. 7.	dgl.	geringe Spur	deutlich	leicht—deutlich
23. 7.	"	dgl.	ziemlich stark	deutlich
24. 7.	"	"	stark	ziemlich stark
25. 7.	"	"	† 6	stark
	Maus 3 Dosis 0,1	Maus 11	Maus 7 Dosis 0,14	Maus 15
20. 7.	geringe Spur	?	leicht—deutlich	leicht
21. 7.	dgl.	geringe Spur	deutlich	deutlich
22. 7.	Spur	dgl.	ziemlich stark	ziemlich stark
23. 7.	"	Spur	stark	stark
24. 7.	"	"	† 5	† 5
25. 7.	"	"	.	.
	Maus 4 Dosis 0,11	Maus 12	Maus 8 Dosis 0,15	Maus 16
20. 7.	geringe Spur	geringe Spur	deutlich	deutlich
21. 7.	Spur	dgl.	ziemlich stark	ziemlich stark
22. 7.	"	Spur	stark	stark
23. 7.	leicht	"	† 4	† 4
24. 7.	"	"	.	.
25. 7.	"	leicht	.	.

Ergebnis: zugelassen am 26. Juli als „4-fach".

Figure 2. What started with the evaluation of anti-diphtheria serum and two guinea pigs as bioindicators (see Figure 1) became more difficult with the evaluation of anti-tetanus serum and seventeen mice as bioindicators (sixteen plus at least one control). The illustration shows the evaluation of anti-tetanus serum. In principle, the potency of the serum submitted by the manufacturer (serum x) was compared with that of the standard serum and the results would be the same (as they were in this case). Increasing doses of tetanus toxin (from 0.15 to 0.08 cc) were added to the sera and the effect on the bioindicator 'mouse' was measured qualitatively over a period of days (20 to 25 July). The effect was classified as slight/mild, distinct, severe (convulsions), death (+), or none (0). Otto and Hetsch, op. cit., Table 7, p. 78.

Such a state of affairs has resulted in a good deal of confusion'.[67] Again, it was agreed that the evaluation methods and the 'standard sera' needed to be validated. Henceforth, all the standards from Germany, Italy (Laboratori Scientifici della Direzione di Sanità – Scientific Laboratory of the Public Health Service), Poland (Warsaw's Panstwowego Zakladu Higieny – National Institute of Hygiene), the USA (Hygienic Laboratory in Washington) and Japan (Kitasato Institute for Infectious Diseases in Tokyo) would be exchanged and compared with

[67] League of Nations, Provisional Health Committee, Minutes of Meetings held in Paris, October 20th–22nd, 1921, Annex 6, memorandum by Dr Madsen on the standardization of antitoxic sera etc., p. 48, PEI, Dept. B, no. 6, vol. 1. After a closer investigation, it was noted that one unit in Germany correlates with 60 to 66 American units and 2,500 French units.

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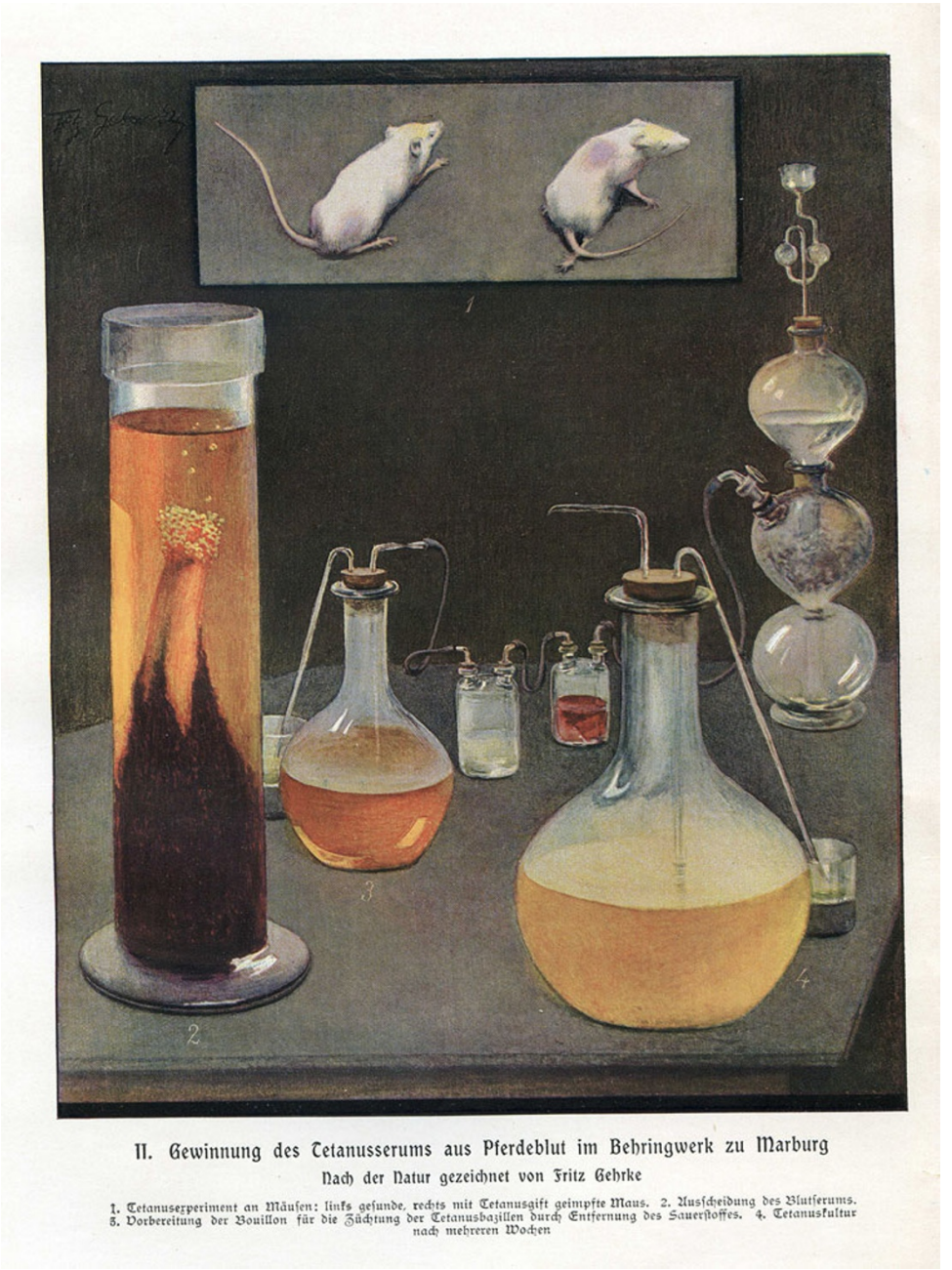


Figure 3. The production of tetanus toxin and anti-tetanus serum. Above: two white mice used as bioindicators: the mouse on the left shows no symptoms; the one the right (with a coloured mark on its back) shows the typical symptoms of tetanus. The large glass vessel on the left shows the coagulation process of serum 'production', while the glass bulbs show the cultivation of tetanus bacteria and the 'production' of tetanus toxin. Emil Behring, *Therapeutische Tierexperimente im Dienste der Seuchenbekämpfung*, offprint, Archive of the Emil Behring Library, Marburg.

each other in order to establish *one* method by which the potency of the serum could be reliably evaluated. The Danish Institute would again coordinate the exchange and comparison of standards.

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The compromise produced at the conference for the standardization of biologicals in July 1923 clearly demonstrated the spirit of cooperation. In adjusting the measure, it was agreed to use the American unit as an average value between the German basic reference unit (1), the US unit (50–66, which means that 1 German unit was equal to 50–66 American units) and the French unit (2,500, hence 1:50–66:2,500). It was also suggested that the German method developed by Paul Ehrlich (two series of tests on mice injected with a mixture of tetanus toxin and anti-tetanus serum, whereas in the series the quantity of anti-tetanus serum was diminished gradually (see Figure 2) should be used as a universal standard method of evaluation. The prospective 'standard serum' was to be kept at the Hygienic Laboratory in Washington, DC, and finally a meta-assessment would be organized by the Danish institute (see Figure 4).[68]

Establishing a method for the evaluation of anti-dysentery serum was even more laborious, for there was no uniform method of evaluation, nor was the mode of action of bactericidal sera generally understood.[69] This research was divided between the national institutes in Poland, Japan, Germany and France, which had already conducted research on anti-dysentery serum. Results were to be discussed at regularly held conferences.

With the development of an international 'standard serum' and evaluation method in the second half of the 1920s, the IET seemed to have re-established its standing in the field.[70] However, the institute was now only one of many members of the Standardisation Committee. For example, studies on the standardization of the diagnostic tuberculin had been undertaken by Albert Calmette at the Pasteur Institute in Lille, and tests on a sero-diagnostic like the Wassermann reaction or on biological testing methods for the chemotherapeutic Salvarsan against syphilis had been performed by Hans Sachs in Heidelberg.[71] Other therapeutics and diagnostics had been standardized in similar collaborations, with the objective of establishing stable and standardized methods of evaluation.[72] At the centre of this collaborative research stood the Danish institute and its director, Thorvald Madsen, who as chairman of the Standardisation Committee of the Hygiene Organisation coordinated the various tasks and conferences. Another indication of the waning role of the IET was the declining importance of the standardization of sera as such. Immediately after the war, discussions on the standardization of sera predominated, but by 1923 the standardization of other drugs, such as adrenaline, Salvarsan and digitalis, or later of vitamins, insulins or hormones, had become more important. Indeed, Henry H. Dale, one of the leading British biochemists, remarked in 1925 that the regular conferences

[68] A summary of the correspondence and resolutions of the Standardisation Committee of the Hygiene Organisation can be found in PEI, Dept. B, no. 6, vol. 1; and Archive of the United Nations, League of Nations – Hygiene Organisation, (Permanent) Standardisation Committee, Cart. 870, 903–15, 5989, 5991.

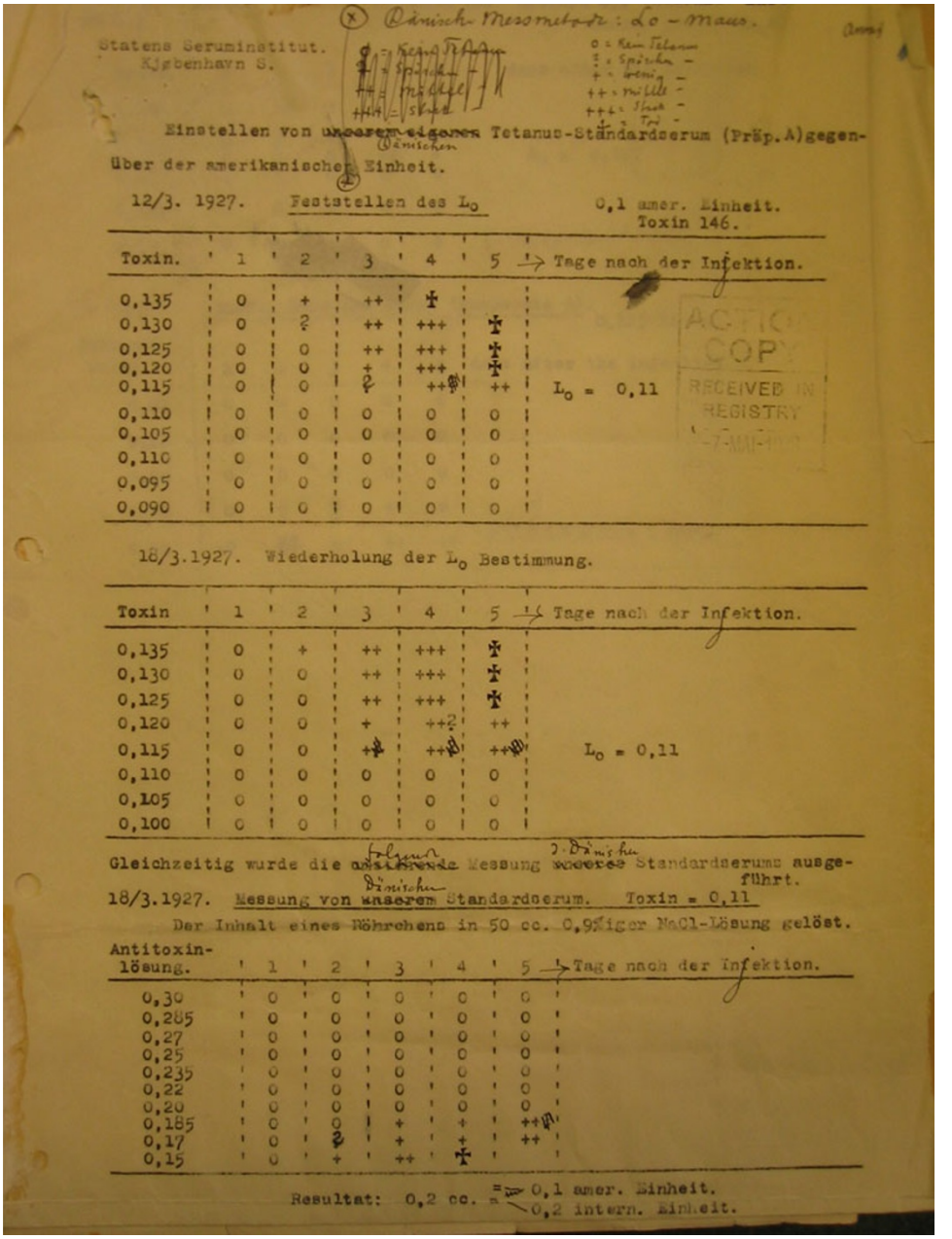
[69] On the difficulties standardizing the BCG vaccine at the Pasteur Institute during the 1920s see Christian Bonah, 'The "experimental stable" of the BCG vaccine: safety, efficacy, proof, and standards, 1921–1933', *Studies in the History and Philosophy of the Biological and Biomedical Sciences* (2005) 36, pp. 696–721.

[70] In 1929, the Standardisation Commission met in Frankfurt. In his short summary about its work, Carl Prausnitz concluded, 'It is a gratifying thought for us Germans that full agreement was reached on several important problems at this historically important place of serological research ... Thus we observed how a [new] scientific ediface is gradually growing thanks to friendly cooperation among scholars of all countries.' ['Es ist für uns Deutsche ein erfreulicher Gedanke, daß gerade auf diesem für die serologische Forschung historischen Boden für eine Reihe der wichtigsten Probleme der Kommission die volle Einigung erzielt worden ist ... So sehen wir, wie allmählich ein wissenschaftliches Bauwerk erwächst durch freundschaftliche, verständnisvolle Zusammenarbeit der Gelehrten aller Länder']. Carl Prausnitz, 'Die Standardisierung der Heilsera, Bakterienpräparate und serologischen Methoden durch das Hygienekomitee des Völkerbundes', *Klinische Wochenschrift* (1929) 8(46), pp. 2152–4.

[71] On the role of the IET see PEI, Dept. B, no. 6, vol. 1–2; on the working groups for anti-dysenteric serum or syphilis see Archive of the United Nations, League of Nations – Hygiene Organisation, (Permanent) Standardisation Committee, Cart. 862–3, 903–15, 5987, 5989–90.

[72] On the Wassermann reaction for syphilis, see Mazumdar, op. cit. (55).

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Statens Seruminstitut.
Kjøbenhavn S.

(x) Dänisch-Mesometer: Lo – Maus.

Einstellen von unserem eigenen Tetanus-Standardserum (Präp. A) gegenüber der amerikanischen (Dänischen) Einheit.

12/3. 1927. Feststellen des L_o 0,1 amer. Einheit. Toxin 146.

Toxin.	1	2	3	4	5	→ Tage nach der Infektion.
0,135	0	+	++	†		
0,130	0	?	++	+++	†	
0,125	0	0	++	+++	†	
0,120	0	0	+	+++	†	
0,115	0	0	?	++	++	L_o = 0,11
0,110	0	0	0	0	0	
0,105	0	0	0	0	0	
0,110	0	0	0	0	0	
0,095	0	0	0	0	0	
0,090	0	0	0	0	0	

18/3.1927. Wiederholung der L_o Bestimmung.

Toxin	1	2	3	4	5	→ Tage nach der Infektion.
0,135	0	+	++	+++	†	
0,130	0	0	++	+++	†	
0,125	0	0	++	+++	†	
0,120	0	0	+	++?	++	
0,115	0	0	?	++	++	L_o = 0,11
0,110	0	0	0	0	0	
0,105	0	0	0	0	0	
0,100	0	0	0	0	0	

Gleichzeitig wurde die folgende dänische Messung unseres Standardserums ausgeführt.

18/3.1927. Messung von unserem dänischen Standardserum. Toxin = 0,11

Der Inhalt eines Röhrchens in 50 cc. 0,9%iger NaCl-Lösung gelöst.

Antitoxin-lösung.	1	2	3	4	5	→ Tage nach der Infektion.
0,30	0	0	0	0	0	
0,285	0	0	0	0	0	
0,27	0	0	0	0	0	
0,25	0	0	0	0	0	
0,235	0	0	0	0	0	
0,22	0	0	0	0	0	
0,20	0	0	0	0	0	
0,185	0	0	+	+	++	
0,17	0	?	+	+	++	
0,15	0	+	++	†		

Resultat: 0,2 cc. = 0,1 amer. Einheit.
= 0,2 intern. Einheit.

Figure 4. Comparison of American and Danish standard (anti-tetanus) sera, calibration according to the US unit. The table shows the reaction of mice after 1, 2 […] 5 days of infection with a decreasing dose of tetanus toxin. Archive of the United Nations, League of Nations – Hygiene Organisation, Standardisation Committee, Dossier 3551.

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were no longer dealing with the 'standardisation of biological products', but with 'Biological Standardisation of Certain Remedies'.[73] The standardization of these products fell outside the remit of the IET.

Conclusion

The paper has examined the globalization of the evaluation of sera (as part of a history of standardization) between 1895 and 1925. The globalization of (serum) evaluation took place in two phases, the first lasting until the First World War. Methods of evaluation were dominated and controlled by the IfSS and the IET, in part because its director, Paul Ehrlich, was a key figure in relevant international networks. Validation and serum evaluation were related in various ways: the evaluation process influenced the serum itself as a market product. Official evaluation transformed the serum into a standardized product with a quantifiable efficacy. The state's approval of its potency and of the production process was governed by well-defined and detailed instructions.

Prior to the First World War, the German method of evaluation gained acceptance for several reasons. Given the empire's federal constitution, an 'objective' method of evaluation was deemed necessary to overcome differences between serum producers in different states and maintaining high quality standards required that testing be done by a central institution. Furthermore, the tuberculin disaster helped to promote a style of thought that emphasized the prevention of worst-case scenarios and the regulation of unfettered markets. The German institute's key role in the global framework of cooperation was further enhanced by the fact that a standard serum was sent to producers as well as to regulatory institutions at regular intervals and the complex system of quality control and evaluation was taught to colleagues around the world. The result was a complex method of evaluation that was intended to be independent of person, place and time, which aimed to expand global markets and improve industrial mass production. By contrast, the French method of evaluation was based mainly on the reputation and trust enjoyed by semi-public or regional producers, who would guarantee standards and thus obviate the need for quality controls.

During these early years, the production of anti-diphtheria (and other) sera was stabilized, validated as a marketable drug because it had been evaluated and approved by state authorities. Initially, the evaluation process transformed an unspecified effect into a precise, quantifiable value. Official evaluation of the serum gave the impression that its efficacy, as claimed by the manufacturer, and its quality were objectively guaranteed by the state. In this sense, the evaluation method acted as a technology of trust for a new form of therapy. By validating such a (stable) method and control system, the IET – and especially its director, Paul Ehrlich – became a moral authority, proclaiming itself the master of measurement.

The second phase began in the early 1920s. Between 1920 and 1925, and especially after Germany had joined the League of Nations in 1926 and up until 1933, the heyday of cooperation between Germany and the League of Nations began.[74] The IET's new director, Wilhelm Kolle, was willing to cooperate with the Hygiene Organisation and international life scientists, although his motives were influenced by the politics of the post-war period. Nevertheless, it seems clear that the integration of individual scientists like Kolle was surprisingly unproblematic, especially given the political turmoil of the early 1920s, for example the occupation of the Rhineland by the French Army, which further exacerbated

[73] See PEI, Dept. B, no. 6, vol. 1–2; and Archive of the United Nations, League of Nations – Hygiene Organisation, Standardisation Committee, Cart. 983, Doss. 3551 and 6489; and Hüntelmann, op. cit. (14).

[74] Cf. Iris Borowy, 'Wissenschaft, Gesundheit, Politik: Das Verhältnis der Weimarer Republik zur Hygieneorganisation des Völkerbundes', *Sozial.Geschichte* (2005) 20(1), pp. 30–56.

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the international political tensions. Reviewing the international cooperation of the IET and the globalization of evaluation, we find a transition from a kind of national internationalism, in which national groups and institutes cooperated and competed with each other, to an institutionalized internationalism, in which national groups of researchers worked together in international committees, albeit without precluding the pursuit of national goals by individual actors.

The position and importance of the IET were threatened by the consequences of the war and the problems of the post-war period. The motivation for international cooperation arose from national interests (such as the prevention of epidemics) and from domestic and foreign-policy concerns, as well as from narrower scientific research agendas. Furthermore, as in the pre-war era, a standardized method for the evaluation of sera (and biologicals) was necessary for their international exchange and, more broadly, for the developing global market for new therapeutics of biological origin. Germany had to cooperate, subordinating itself to international institutions like the Hygiene Organisation. Otherwise, state officials feared losing influence and contact with the international scientific community. The example of the international standardization of methods for evaluating sera also shows that the 'objective' evaluation of sera had less to do with a scientific process than with cooperation and negotiation between scientific and political actors. For, in general, the evaluation of sera worked well in all countries and comparisons of the respective national 'standard serum' produced the same results. So it was rather a process of power sharing which ensured that no one nation would have a prerogative of interpretation over the system of evaluation, and in this respect it decentralized serum control. As coordinator and auditor of the whole fragile system of quality control, the Danish institute secured its influence through the 'back doors of power'.[75]

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[75] Thus Herren, op. cit. (59).

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