Science in Context **21**(2), 229–252 (2008). Copyright © Cambridge University Press
doi:10.1017/S0269889708001701 Printed in the United Kingdom

The Dynamics of *Wertbestimmung*

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Argument

The procedure of *Wertbestimmung* played a vital role in the implementation of serum therapy and the standardization of mass-produced pharmaceuticals. In fin-de-siècle Germany, a legal framework was put in place to guarantee serum quality and safety and to minimize any associated public health risks. Because the sera were biological remedies, it was difficult to produce them in uniform quality and the procedure of *Wertbestimmung*, i.e. determining the potency of the serum based on an objective and comparable value, was extremely complex. Various agents such as bacteria cultures, serum hosts, or test animals had to be regulated. In the years after 1895, numerous efforts to stabilize the procedures of *Wertbestimmung* were undertaken by serum producers and members of the state-run survey institute responsible for overseeing serum production. Despite efforts to stabilize the framework and to generate a reliable reference system, the framework's environment and agents were in constant flux: new producers entered the market and procedures were expanded to include other biologicals as well. The article describes the dynamics involved in the sustained efforts to maintain a stable framework in the face of constant alterations between 1895 and the 1920s.

In 1899, Wilhelm Dönitz, a member of the German Institute for Serum Research and Serum Control, concluded that serum therapy was in danger of running aground if the principles of *Wertbestimmung* could not be stabilized (Dönitz 1900, 361). For the implementation of serum therapy, the procedure for determining the value of the serum's potency, i.e. *Wertbestimmung* (hereafter also translated as evaluation), played a vital role in transforming a highly complex biological remedy that was developed experimentally, into a standardized, mass-produced pharmaceutical.

In Germany from about 1894 onward, a legal framework was established to deal with new biological remedies. That legal framework tightly integrated industry, the state, and medical science. The evaluation of diphtheria serum became a blueprint for the evaluation of other sera that were developed after the turn of the century. This article will reconstruct the multiple and ongoing efforts to standardize *Wertbestimmung* and the effects of those efforts on the actors involved. It describes the dynamics of these efforts between 1895 and the 1920s, when the framework shifted from the standardization of biological remedies to mass-produced biological pharmaceuticals.

https://doi.org/10.1017/S0269889708001701 Published online by Cambridge University Press

The article highlights eight junctures at which significant adjustments to the procedure were negotiated amongst multiple actors. The first section describes the initial context of *Wertbestimmung* and the institutionalization of the procedure during the autumn and winter of 1894–1895. The second section focuses on the serum producers, especially two new producers that entered the market in 1895. The third section concentrates on refinements in the evaluation procedure in 1897; and the fourth section highlights the enlargement of *Wertbestimmung* to include the diagnostic use of tuberculin in 1899. In the first years after 1900, several other sera were certified and the procedure of *Wertbestimmung* became more and more standardized. The fifth section draws on a compendium published in 1906 outlining state control of sera to analyze standardization practices. The sixth section considers Paul Ehrlich's efforts to establish a department for veterinary medicine and highlights the importance of veterinary sera and the function of animals in the context of *Wertbestimmung*. The difficulties arising during World War I are described in the seventh section. The final section of the article assesses efforts to re-stabilize the framework of *Wertbestimmung* in an international context in the 1920s.

1. The Context of *Wertbestimmung* and the Institutionalization of Evaluation around 1894

In fin-de-siècle Germany, *Wertbestimmung* was situated at the nexus of the following developments: the nation's rapid industrialization in the 1890s, the emergence of a pharmaceutical industry, the institutionalization of a public health policy, and the growing regulation of different social spheres (Vec 2006). Large-scale producers of biologicals faced challenges very similar to the challenges faced by producers of other technologically complex products. Manufacturers had to deal with highly sensitive products that reacted immediately to environmental variations. In confronting these difficulties, the production process had to be rearranged to guarantee standards of quality. In addition, national standards had to be set to ensure the uniformity of materials and units of measure.[1]

The prospering chemical and pharmaceutical industries were confronted with similar problems of standardization. Just as fabricating standardized chemicals demanded rigorous specifications (Hickel 1973; Holsten 1977; Wimmer 1994), so too did producing standardized serums require strict adherence to generally accepted norms. It was difficult to standardize the quality of diphtheria serum. Since it was a remedy of biological origin, the procedures used to establish the value of the serum's potency were very complex. The essential components involved in evaluating procedures, such as the serum hosts, bacteria cultures, or test animals, were themselves biologicals. Evaluation

[1] In the area of high precision instruments, these problems led to the creation of the *Physikalisch-Technische Reichsanstalt* in the 1880s (cf. Cahan 1989).

https://doi.org/10.1017/S0269889708001701 Published online by Cambridge University Press

was designed to measure the potency of a serum and fix its therapeutic value – the amount of antitoxin determined the therapeutic value of an antitoxic serum and was called an antitoxin unit, or an immunization unit (Cavalli-Sforza 1969).

Evaluation was part of a regime of prophylactic state regulations. After August 1894, diphtheria serum became available in German pharmacies and was shortly thereafter introduced to the scientific community and celebrated as a great success in the treatment of infectious diseases. Economically, serum therapy promised to become a major and very profitable market. Detailed research information was freely available in medical publications. Since there was no patent on diphtheria serum, health professionals trained in bacteriology were free to reconstruct the experiments and produce serum without fear of litigation. While this situation favored the interests of a free market, it risked allowing low-quality or even dangerous sera to enter the market. Given this situation and the lack of information about the biological components and the long-term effects of the serum, the new serum therapy attracted the attention of state officials concerned about public health risks. Subsequently, a system of state control was implemented and institutionalized (Hüntelmann 2006b; Throm 1995).

In Germany, the regulation of biologicals and public health matters fell within the jurisdiction of the Empire and the federal states. Hence, establishing national standards involved the cooperation of various imperial and federal entities. Between November 1894 and February 1895, several meetings brought together high ranking medical officers of the German Empire and the federal states, scientific experts, and representatives of the pharmaceutical industry. As a result of these meetings, in February 1895 the Controlstation for Diphtheria Serum (hereafter Controlstation) was created as part of a larger regime of administrative mechanisms, including fixed pricing, data collection on the effectiveness of the serum, rules governing the distribution of the serum in pharmacies, and prescription requirements. Prussian medical authorities were charged with overseeing these mechanisms. Locally, the process of serum production was monitored by a medical officer; at a national level, oversight was the responsibility of the Controlstation (Hüntelmann 2006b).[2]

Inside the state-run institute, serum was tested for purity and potency. According to official guidelines, two medical officers evaluated the serum samples simultaneously and independently. Based on a standard toxin kept at the institute, a solution of diphtheria toxin was added to diphtheria serum and injected into a guinea pig. If successful, the mixture of serum and toxin would neutralize each other and the test animal would show no severe reactions or any infiltrate at the injection site over a period of four days

[2] The implementation of state regulation is documented in the correspondence between state authorities, scientists and industry from October 1894 to February 1895 in the Federal Archive (Bundesarchiv Berlin, BAB), R 86/1646, and in the Prussian Secret Archive (Geheimes Staatsarchiv Preußischer Kulturbesitz in Berlin, GStA PK), HA 1, Rep. 76 VIII B, No. 3747 and 3748.

https://doi.org/10.1017/S0269889708001701 Published online by Cambridge University Press

(minimum dosis L0). If the test animal remained healthy (*glatt*), the serum sample was considered potent, and it was approved.[3]

For state officials, evaluation was an objective and quantifiable criterion for regulating the quality and potency of the serum. It allowed them to compare different sera in a centralized, imperial institute, unconstrained by regional or local considerations.

2. Expanding the Framework of *Wertbestimmung* – New Producers Enter the Market

No sooner had the administrative regime for evaluating serum been set up, than changes became necessary. In the spring of 1895, the chemist Carl Enoch directed a query to the local health authorities, the Medical Bureau, in Hamburg. Together with the physician Adolph Ruete, he had produced diphtheria serum and now sought permission to distribute it.[4] Ruete and Enoch were the first of many to submit similar requests, including the chemical and pharmaceutical company E. Merck in Darmstadt in 1895 and the Swiss company Haeflinger & Cie. in Bern in 1896. The original instructions for serum control and evaluation had been worked out in close cooperation between state authorities, scientists, the Farbwerke Hoechst, and the pharmaceutical company Schering. Both companies were based in Prussia and well known to the medical authorities. By contrast, Enoch, Merck, and Haeflinger were located in Hamburg, Hesse, and Switzerland. The example of Ruete and Enoch can serve to illustrate how every new producer who wanted to sell "state certified" serum had to undergo a comprehensive audit designed to guarantee the quality of serum production. What would later become routine inspection (Otto 1906, 13–14), initially, in 1895, took more than a year to complete.

To market a state-approved serum in Germany, the serum manufacturer had to receive permission from state medical authorities. In the case of Carl Enoch, the request was transmitted via the local authority in Hamburg and the Imperial Health Office to the responsible Prussian Ministry of Cultural Affairs (hereafter PMCA). During the summer of 1895, members of the Imperial Health Office analyzed the purity and potency of the serum produced by Enoch's laboratory. In addition, the Imperial Health Office informed the medical authorities in Hamburg about the legal requirements pertaining to serum production. The city of Hamburg had to enact legislation specifying that a prescription was necessary and that only state-approved serum could be sold in pharmacies. The producer had to agree to a number of measures, including continuous livestock testing by a licensed veterinary, recordkeeping

[3] Cf. the official instructions for the *Wertbestimmung* in the Archive of the Paul Ehrlich Institute in Langen (APEI), Dept. Va, No. 1, Vol. 1.

[4] For the correspondence and notes concerning the audit of Ruete and Enoch, see BAB, R 86/1646.

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for every step in the production process, and state inspection of every batch of serum. Furthermore, state authorities conducted inquiries as to the company's reputation before they would order the district veterinary and medical officer to inspect all aspects of the production process.

With initial inspection, procedures for the standardization of serum production were established. The district veterinary officer in Hamburg had been instructed to visit Enoch's institute. He inspected the stables and checked whether the horses were healthy. In general, the production plant, the reporting system, employee qualifications, and the laboratory equipment were inspected.[5] The producer's ability to produce serum was checked and, obviously, Enoch was trained in the proper procedures of *Wertbestimmung* at the Controlstation.[6] After the initial inspection, the laboratory of Carl Enoch should have been re-audited monthly or at least at regular intervals.

But after the first audit new problems emerged. At the end of January 1896, Enoch tried to resolve numerous open questions about the control and distribution of serum: what amount of serum had to be sent to the Controlstation? What were the minimum immunization units? How much time was needed to test the batch? Should the phials be filled in the Controlstation or in the production plant?[7] And other questions concerning the nomination of the medical officer in the production plant had also arisen. It took months of correspondence between Enoch, the Medical Bureau in Hamburg, the Controlstation, and the PMCA before all of these questions could be answered; ultimately however, Enoch was allowed to produce and distribute state-approved diphtheria serum.

Elsewhere, similar hurdles also stood in the way of serum production. Nearly two years passed between the time that E. Merck established its bacteriological department in Darmstadt in early 1895 and the start of regular distribution (Throm 1995, 172–174). In the case of Haeflinger, the initial inspection was complicated by the fact that the Foreign Office and Swiss embassy had been consulted.[8] After serum producers had been granted approval, problems continued to arise. After Merck began advertising their state-approved diphtheria serum in 1896, the institute complained to ministerial officials that the company had submitted only a single batch of serum.[9] But Merck was not the only company plagued by difficulties.

[5] For the correspondence between April and July 1895, cf. BAB, R 86/1646. The initial inspection was taken seriously and in several later cases, changes had to be made by the producer before they were registered for state control, cf. APEI, Dept. IV, No. 1, Vol. 1.

[6] This emanates from a letter sent by the Controlstation, Wilhelm Dönitz to Carl Enoch, 25.8.1896, APEI, Dept. Vd, No. 4, Vol. 1. In other cases, the instruction was institutionalized as voluntary training in the laboratory of the state-run institute, APEI, Dept. III, No. 6, Vol 1.

[7] Carl Enoch to the Controlstation, 31.1.1896, APEI, Dept. Vd, No. 4, Vol. 1.

[8] On Merck, cf. APEI, Dept. Vd, No. 3, Vol. 1 and the files in the Merck Archive, Darmstadt, K 1/179. For the Swiss company Haeflinger & Cie., cf. BAB, R 86/1646 and APEI, Dept. Vd, No. 5, Vol. 1.

[9] Institute for Serum Research and Serum Survey to PMCA, 9.9.1896, APEI, Dept. Vd, No. 3, Vol. 1.

https://doi.org/10.1017/S0269889708001701 Published online by Cambridge University Press

3. Stabilizing the *Wertbestimmung*

As long as there had been only two serum producers, emerging conflicts could be resolved directly through negotiations between medical officers at the Controlstation and producers. At times, these negotiations took place at Emil Behring's research laboratory in Marburg, which had been financed by Hoechst.[10] Behring's assistant at the laboratory, Angelo Knorr, as well as Arnold Libbertz from the Farbwerke Hoechst, often met with Paul Ehrlich or his assistant Wilhelm Dönitz at the institute in Berlin or on location at the production facilities to discuss matters concerning state control.[11] But as the number of manufacturers grew, such negotiations became more difficult.

After 1895, three problems came to the fore. Early on, research was done to improve the value of sera. By 1895 the Farbwerke Hoechst were already able to produce sera with 300 or even 500 immunization units. In relation to less potent sera, now lower quantites of serum could be administered to patients. One advantage of high-value serum was that, as the quantity of serum was reduced, the probability of side effects caused by the natural elements of the serum also fell. For the producer, high-value serum led to a reduction in test fees, because these were assessed on the quantity of serum. Unfortunately however, initially the effect of high-value sera was unreliable and the value of immunization units declined rapidly (Dönitz 1900; Hardy 2006).[12]

Secondly, it emerged that the reference unit "test toxin" was not as fixed and stable as originally assumed by Paul Ehrlich and Emil Behring. This led to conflicting results in the determination of immunization units by the serum producer and the Controlstation. Production at Merck, for example, had not yet fully begun when the company was informed at the end of 1895 that the test toxin, which was used as a reference unit for the *Wertbestimmung* and which had been received only a few months earlier, had already weakened. In April 1896, difficulties with the test toxin cropped up again. Gustav Landmann, head of the bacteriological department at Merck, complained that the divergent results obtained by the Controlstation and his own department were due to the fact that the test toxin had not been as potent as declared by the state-run institute.[13] Likewise in England, serum therapy was discredited because of conflicting results derived from measuring immunization units and the potency of sera. In London, a fact-finding committee, comprised of members of the Royal Institute for Preventive

[10] The close working relationship between Knorr, Ehrlich, Dönitz, and Libbertz is reflected in their correspondence in APEI, Dept. Va, No. 1, Vol. 1. More generally on the cooperation between Ehrlich and the chemical and pharmaceutical industry, see Travis 1989, Liebenau 1990, and Lenoir 1997. On the establishment of the Institute for Experimental Therapy in Marburg, see Throm 1995, and Linton 2005.

[11] The close relationship between the state-run institute and Farbwerke Hoechst led to complaints. Carl Enoch protested that a meeting on state control of dried serum powder had been held without him, but with the Farbwerke Hoechst and Schering (cf. the correspondence in September 1898 and March 1899 in APEI, Dept. Va, No. 1, Vol. 1).

[12] See the complaints about the decline of high-value sera in APEI, Dept. Va, No. 1, Vol. 1.

[13] Hermann Kossel, Controlstation, to Merck, November 1895; and Gustav Landmann, Merck, to the Controlstation, 9.4.1896, both APEI, Dept. Vd, No. 3, Vol. 1.

https://doi.org/10.1017/S0269889708001701 Published online by Cambridge University Press

Medicine and the Royal Society of Physicians and Surgeons, had been established to ensure proper determination of the value and effect of sera produced in Britain (Ehrlich 1898a, 299; Dönitz 1900, 361).[14]

The third problem involved determining the immunization units and the method of evaluation. The value of antitoxin units was based on clinical signs displayed by the test animals. Thus, for example, guinea pigs were not expected to show any reaction following subcutaneous injection of a mixture of serum and toxin. From the outset, the clinical definition of "no reaction" was a matter of dispute between the Controlstation and producers. Occasionally, discussions about the value of tested serum samples also preoccupied serum producers and the state-run institute, because "changes in behaviour" or an "absence of swelling" often depended on the individuality of the test animal and the acuity of laboratory staff. Furthermore, given the ongoing research on the stability of so-called high-value serum, no definitive criteria were available to distinguish between different grades of immunity (Dönitz 1900; Hardy 2006). To solve these problems and to improve the method of evaluation, the PMCA issued an order on reduced toxin potency and the instability of high-value sera. The new scientific orientation was reflected in the transformation of the Controlstation for Diphtheria Serum into an Institute for Serum Research and Serum Survey (hereafter ISS) in the spring of 1896. The new name emphasized not only the shift to theoretical questions, but also the growing importance of serum therapy.

At the end of February 1897, the director of the ISS, Paul Ehrlich, informed the PMCA about the new method of evaluation, which was officially implemented at the end of April 1897.[15] A more precise method of evaluation had been worked out to obtain an absolute standard. Ehrlich's discovery that the toxins compartmentalized in single elements, each with different reactions to the antitoxin, provided an explanation for the decline of the toxin's toxicity (Ehrlich 1898a and 1898b). The reference point in the "newly" generated framework was no longer the test toxin, but a standard serum. Based upon Emil Behring's research on the dehydration of serum, the standard serum was completely dried and hermetically sealed. According to Ehrlich, if preserved in a vacuum tube and stocked in a dark, cool environment, this standard serum would remain stable (Ehrlich 1898a), just like comparable prototypes of the metre or kilogram (Otto 1906, 28). The standard serum was stocked in large quantities in vacuum tubes. Every two months, a glass tube was opened and the powder dissolved. The standard serum was then compared with the standard toxin that defined the immunization-units

[14] The committee cooperated with the Controlstation: for example, Allan MacFadyen and German S. Woodhead visited the state-run institute in Germany to learn about the procedure of *Wertbestimmung* (see the correspondence in APEI, Dept. Vc, No. 5, Vol. 1). The committee's results had been published in *The Lancet,* and a report about the article was given to the PMCA, APEI, Dept. Va, No. 1, Vol. 1.

[15] Paul Ehrlich to Rudolf Bosse, Minister of Cultural Affairs, 28.2.1897, Rockefeller Archive Center, Paul Ehrlich Collection 650 Eh 89 (RAC, PEC), Box 59, Folder 11. At the end of April 1897, Ehrlich informed the serum producers about the new method of evaluation within the ISS, APEI, Dept. Va, No. 1, Vol. 1.

https://doi.org/10.1017/S0269889708001701 Published online by Cambridge University Press

or antitoxin-units. At the same time, all registered serum producers and related state institutes obtained a tube with standard serum.[16]

Another important innovation involved basing evaluations not on the minimum dosis (symptom free reaction), but rather on the *dosis letalis* (lethal reaction). A lethal dose was defined as a quantity sufficient to kill a guinea pig of 250 to 280 grams within just four days (*doses letalis* L†). A normal toxin was defined as a hundredfold deadly dose dissolved in one centilitre saline-glycerine solution; and 0.1 centilitre of normal serum was required to neutralize one centilitre of normal toxin. One immunization unit was defined as one centilitre of this normal serum (Otto 1906, 27). Comparative values were obtained by diluting or concentrating the mixtures, or by scaling up and down.

The standard toxin was produced in large quantities at the state institute. Because Ehrlich believed that toxic reactions would cease after about one year, the toxin units were adjusted in relation to the standard serum on a yearly basis. Normally, the serum samples were mixed with a corresponding dilution of toxin and injected into the test animal. Using a *dosis letalis* L† had resolved problems that had arisen in using the minimum dosis L0, such as measuring laboratory animal reactions. The mixture of toxin and antitoxin was adjusted so that the laboratory animal simply died within four days. The death or the survival of an animal was a rigid, binary criterion and demonstrated automatically the minimum value of the serum (Ehrlich 1898a; Dönitz 1900; Otto 1906, 40). Defining the standard serum in relation to an arbitrary fixed *dosis letalis* became the guiding principle behind all other official methods of *Wertbestimmung*. Moreover, the complex measuring procedure,[17] the interplay between standard serum, standard toxin, laboratory staff, and test animal, was an artificial in vitro model for the interplay of infection, remedy, physician, and patient.

Drawing on his practical work on the *Wertbestimmung* of diphtheria serum, Ehrlich developed his side-chain theory as a model to explain immunity. The chemical nature of the different physiological toxin-antitoxin reactions was a prerequisite of Ehrlich's theoretical model. Based on his earlier work on the cellular oxygen supply and the composition of toxins, Ehrlich postulated the existence of organic counterparts that were able to bind the toxins. According to Ehrlich, cells consisted of a kernel and associated side-chains with different supply functions. Due to their similar molecular structure, the toxins joined the side-chains, neutralized them, and disrupted the unity of kernel and side-chain, thus causing the clinical symptoms of poisoning. The organism's efforts to regenerate the side-chains led to an overproduction. The surplus side-chains entered the circulatory system, retaining the specific ability to bind toxins – what we call antitoxins (Ehrlich 1898a; Aschoff 1902; Ehrlich and Morgenroth 1904;

[16] On the global distribution of standard serum beginning in 1897 and the standardization of a subscription service after the turn of the century (see APEI, Dept. Vc, No. 5, Vol. 1).

[17] Drawing on Baird 2004, one can characterize "measuring instruments" as encapsulated knowledge composed of working knowledge and model knowledge.

https://doi.org/10.1017/S0269889708001701 Published online by Cambridge University Press

Wassermann 1914; Silverstein 1989; Silverstein 2002; Prüll 2003). Paul Ehrlich regarded the organic antitoxins as "magic bullets" that correlated exactly with the toxins and neutralized them, ideally without any side-effects.[18] Ehrlich's concept was founded on the principles of chemotherapy and prompted him to search for chemical substances that would neutralize and disable the disease-causing agents (Bäumler 1971; Lenoir 1997).

4. Expanding the Framework of *Wertbestimmung* to Diagnosis (tuberculin)

The evaluation of diphtheria serum became a model for the evaluation of other sera like tetanus (Hardy forthcoming). Soon the system of state control and the evaluation of biologicals was again enlarged to encompass organic diagnostics. Robert Koch's announcement that tuberculin was a remedy against tuberculosis was celebrated enthusiastically in the summer of 1890. But far from living up to therapeutic expectations, tuberculin caused several deaths and triggered a public health scandal (Elkeles 1990; Gradmann 2005). Subsequently, very few physicians used tuberculin as a remedy against tuberculosis. After its decline as a remedy, tuberculin embarked on a second career in the diagnosis of human and bovine tuberculosis. Despite its marginal importance as a remedy, tuberculin became state certified in 1899.

Developments leading up to state certification of tuberculin again illustrate the official motives behind *Wertbestimmung*. Stimulated by successes in the treatment of diphtheria, several new attempts to develop a remedy for tuberculosis began after 1895, especially by Emil Behring (Zeiss and Bieling 1941; Linton 2005) and Robert Koch, who had developed a new preparation called Tuberculin TR (Beck 1898). In addition, in January 1897 the head of the Imperial Health Office, Carl Köhler, called for a standardized method of evaluation for tuberculin. Köhler complained that using tuberculin to diagnose bovine tuberculosis produced unreliable results. Köhler proposed that the ISS should develop a standard method for the evaluation of tuberculin.[19]

The production and evaluation of tuberculin remained more or less unchanged after 1891,[20] but was completely different from the production of diphtheria serum.[21] In short, tuberculin was based on cultures of tuberculin bacteria. The culture medium and the bacteria were evaporated and concentrated to one-tenth of their original volume, before the bacterial body was finally filtrated out (Koch 1891; Prüfungsverfahren

[18] This concept assumed the existence of a specific substance that corresponded to a specific disease-causing agent or species of bacteria. On the connection between species and specificity, see Mazumdar 1995.

[19] Carl Köhler to Imperial Chancellor, 11.1.1897; Imperial Chancellor to PMCA, 20.1.1897, both GStA PK, 1. HA, Rep. 76 VIII B, No. 4162; PMCA to Paul Ehrlich, 4.2.1897, APEI, Dept. VII, No. 1, Vol. 1.

[20] Ehrlich claimed that the production of tuberculin (*tuberculinim kochi*) had remained unchanged from 1891 to 1910 (see Ehrlich to PMCA, 20.8.1910, APEI, Dept. VII, No. 1, Vol. 1).

[21] On the production of serum, see Simon's contribution to this volume, and Simon and Hüntelmann forthcoming.

https://doi.org/10.1017/S0269889708001701 Published online by Cambridge University Press

1908; Möllers 1950, 581–583). In refining the method, Wilhelm Dönitz pointed out the hurdles he had to overcome in obtaining a standard value. Before he could create a coherent frame of reference, Dönitz first had to define a "standard tuberculin." To adjust variations in the quality of tuberculin, he mixed different varieties of tuberculin preparations. Modeled on procedures used for the evaluation of diphtheria serum, Dönitz was working on a *dosis letalis* that would kill a guinea pig within 24 hours.

For the regular procedure of *Wertbestimmung*, between forty and fifty guinea pigs were infected with tuberculosis. After three or four weeks, a dose of tuberculin sufficient to kill the guinea pig within 24 hours was injected (Dönitz 1898; Otto 1905; Prüfungsverfahren 1908). In his report on the new evaluation method, Ehrlich concluded that it was possible to determine a reliable standard value and thus compare different tuberculin preparations. Ehrlich also recommended publishing the principles of *Wertbestimmung* for tuberculin, because other companies besides the Farbwerke Hoechst had started producing tuberculin.[22]

The development of a standard method for the evaluation of tuberculin set off a dynamic series of events. The State Secretary of the Interior concluded that uniform instructions should be issued governing the use and certification of tuberculin. In addition, Ehrlich's report on the contamination of new tuberculin preparations with microorganisms reinforced calls for state control.[23] Consultations between imperial and federal medical officers resulted in a decision to enact state control of tuberculin in mid-1899. Thereafter, Ehrlich and the medical officer in the Imperial Health Office, Paul Musehold, continued to suggest ways of verifying and improving the evaluation method.[24]

In many respects, the case of tuberculin reflects broader efforts to stablilize the method of *Wertbestimmung*: The existence of a stable evaluation method was the premise on which official state control of biologicals was based. As more and more actors joined the fray, a stable method of *Wertbestimmung* became increasingly important. As new producers entered the market, it became necessary to set objective standards, not only to allow comparison of different preparations, but also to provide practitioners and patients with reliable diagnoses and therapies. *Wertbestimmung* also reinforced the rationality and scientific basis of serum therapy – especially in the wake of the public health scandal that had been triggered by tuberculin (see Gradmann in this issue). Moreover, the mysteries of mixing and diluting serum – second only to homeopathic remedies – made it necessary to establish an objective value. Richard Otto, a military surgeon who was posted to the IET, stressed that evaluation and state control of the

[22] Report by Paul Ehrlich to the PMCA, 29.1.1898, and the request for publication, 4.3.1898, both in GStA PK, 1. HA, Rep. 76 VIII B, No. 4163.
[23] State Secretary of the Interior to the PMCA, 24.4.1898; and report by Paul Ehrlich to the PMCA, 5.5.1898, ibid.
[24] Reports of the ISS and the Imperial Health Office, 30.1.1899, 5.5.1899, 31.8.1899, APEI, Dept. VII, No. 1, Vol. 1.

https://doi.org/10.1017/S0269889708001701 Published online by Cambridge University Press

serum would strengthen confidence in the new serum therapy (Otto 1906, 40). In effect, the *Wertbestimmung* became a technology of trust (Porter 1995).

In comparison with other sera, only very small quantities of tuberculin were certified annually. Nevertheless, diagnostically, tuberculin paved the way for other agents such as mallein (for glanders) or the serological preparations used in the "Wassermann-Test" for syphilis. And tuberculin was the starting point for the expansion of the ISS. After moving to Frankfurt in the autumn of 1899, the institute was renamed Institute for Experimental Therapy (hereafter IET). Aside from the experimental work that was done in the biological department, the chief tasks of testing serum samples for purity and improving existing evaluation techniques was still done in the *Prüfungstechnische Abteilung*.

5. Stabilizing the Environment of *Wertbestimmung*

In 1906, Richard Otto published a compendium on the State Control of Sera (*Die staatliche Prüfung der Heilsera*). The compendium was updated in 1921, 1927, and 1935, giving us snapshots of the framework of *Wertbestimmung* after 1900 as it expanded to include other biologicals, like sera for dysentery, streptococcus, or epizootic diseases such as swine pest. Over time, the evaluation procedures required greater standardization as several other producers entered the market.[25] For example, the procedure for evaluating tetanus serum was altered so that vacuum drying could be used to preserve the toxin, which would otherwise rapidly lose its potency (Otto 1906).

The case of tuberculin also illustrates the stabilization of the *Wertbestimmung*. Like diphtheria serum, the evaluation method was considered valid and stable, but had to be adjusted in later years. As would be the case for many other biologicals later, state control of tuberculin was at first "provisional," i.e. producers could decide whether they wanted it tested or not. Only after this provisional phase in which the method was improved, did state control become an obligatory passage point (Callon 1986) for all producers (Otto 1906). Obligatory testing of Tuberculin (*tuberculinum kochi*) began in 1902.

The case of tuberculin also demonstrates the important role of bacteria in the different processes of standardization, for the test animal was injected with both tuberculin and bacteria. Efforts to improve the tuberculin standard continued after it had been created in 1899. Richard Otto tried to bring two important elements of

[25] Most of the producers were concentrated regionally around Frankfurt, like the dominant producers of serum, the Farbwerke Hoechst and Ludwig Wilhelm Gans (Hoechst), the Behringwerke in Marburg, and Merck in Darmstadt. Moreover there was Schering in Berlin, the Rheinische Serumwerke in Cologne, the Sächsische Serumwerke in Dresden, Ruete and Enoch in Hamburg, and some regional producers of veterinary sera in Eastern Prussia.

https://doi.org/10.1017/S0269889708001701 Published online by Cambridge University Press

uncertainty under control: the tubercle bacillus and the guinea pig. The potency of the bacteria depended on the working knowledge of scientists and laboratory staff, as well as on breeding practices, including the culture medium, the temperature and time of breeding, the number and method of animal passages, and the means of killing bacteria cultures.[26] The tubercle bacillus and the culture medium were bred and injected using the same method. Otto pointed out, for example, that the injection of bacteria had to be made subcutaneously and not intraperitoneally. The guinea pigs also posed a problem, because the disease's course depended on the individual constitution of the test animal, meaning that they had to be standardized individually. Three or four weeks after a large number of guinea pigs had been infected with tuberculosis, an experienced laboratory assistant handpicked a selection of those showing severe signs of tuberculosis for use in the test arrays (Otto 1905; Otto 1906, 75–78).

The main improvements in the procedure and the technical arrangements of *Wertbestimmung* had been made shortly after 1900 and did not change significantly after 1906. This is reflected in the different editions of the compendium of Richard Otto: editions from the 1920s still picture the arrangement of tubes and flasks built by Ehrlich and the Allgemeine Elektricitätsgesellschaft[27] in 1897 to remove oxygen or humidity from the serum, as well as the special pipettes that he had developed together with the company F. & M. Lautenschläger to mix the different dilutions and measure minute quantities of toxin or serum (Otto 1906, 37; Otto and Hetsch, 1921 and 1927; in all editions see figs. 2, 3, 4 and 5).

Unlike the repetitive, technical work in the survey department, the other departments of the IET worked experimentally on the development of pharmaceuticals and the composition of blood. As the framework of *Wertbestimmung* was stabilized, less manpower had to be deployed in the survey department and more resources could be devoted to experimental work. This shift in emphasis also had financial ramifications. In the first years of its existence, the state-run institute was regularly financed by test fees.[28] Ehrlich was unhappy about this and complained frequently to Friedrich Althoff that it hampered his research.[29] As Ehrlich was finishing his work on the constitution of toxins and the method of evaluation in November 1898 (Ehrlich 1898a), he wrote the chemical company BASF, thanking them for the dyestuffs and soliciting future support. Having worked so long on serotherapy, Ehrlich now wished to return to his old interest in the theory of histological and biological coloration.[30] Henceforth, his

[26] On the significance of working knowledge, see Baird 2004.

[27] The Allgemeine Elektricitätsgesellschaft produced large-scale electric bulbs in Berlin and the engineers were specialists in glasswork (cf. Ehrlich 1898a). On mass production of electric bulbs and their initial role for standardization, see Luxbacher 2003.

[28] Funding for the IET came chiefly from fees charged for serum certification (see GStA PK, 1. HA, Rep. 76 Vc, Sekt. I, Tit. XI, Part II, No. 18, Vol. 1).

[29] Cf. the letters from Ehrlich to Althoff around 1900 in the RAC PEC, Box 1, File 1. Althoff was assistant state secretary in the PMCA and a promoter of Paul Ehrlich within the Ministry. On Althoff, see Brocke 1991.

[30] Paul Ehrlich to BASF, 15.11.1898, RAC PEC, Box 80, File 1.

https://doi.org/10.1017/S0269889708001701 Published online by Cambridge University Press

interests turned to experimental research on chemo-therapeutics, such as Salvarsan, and cancer. That research was put on a sound financial basis in September 1906 with the establishment of the Georg-Speyer-Haus, a private foundation of Georg and Franzisca Speyer, dedicated to biomedical and chemo-therapeutic research and working alongside the state-run institute, both of which were now headed by Ehrlich (Kolle 1926).

The long-term objective of the IET was to stabilize the framework of *Wertbestimmung* and, by implication, serum production. This objective involved the practical application of Ehrlich's side-chain theory and chemo-therapeutic concepts. Toxic agents had to be found for the bactericidal sera and antibacterial sera replaced with antitoxic sera. Furthermore, as far as the antitioxic sera was concerned, the scientific objective was to extract the toxin chemically in the purest form (Ehrlich 1898a, 300). In the case of veterinary sera, the problems with bactericidal sera were especially acute.

6. The Institutionalized Role of the Animal in the Framework of *Wertbestimmung*

In 1906 Paul Ehrlich began recommending to the PMCA that an independent department of veterinary medicine be created to accommodate the large rise in the number of veterinary sera tests conducted at the IET. Ehrlich explained that testing veterinary sera was especially difficult and expensive.[31] Ehrlich's repeated requests were denied for financial reasons in 1907 and 1908, but supported by the Ministry of Agriculture once the establishment of a veterinary department appeared imminent in 1909 and funding was appropriated in 1910.[32]

For a number of reasons, the veterinary department was indicative of the growing importance of veterinary medicine for the *Wertbestimmung*. Undoubtedly, veterinary medicine was crucial to the national economy and as a result the evaluation of veterinary sera was of vital importance to the IET and the producer. The veterinary department also reflected the key role of animals in the process of *Wertbestimmung* not only as serum hosts and test animals, but in the case of veterinary sera, also as patients themeselves.

State approval of red murrain serum began in 1899 and was soon followed by sera against swine pest and chicken cholera. The test fees for red murrain sera increased steadily, beginning at around 2,000 Marks in 1899, doubling by 1904–1905, before rising to over 10,000 Marks in 1907.[33] In addition, the evaluation of veterinary sera was very complex because the sera were actively bactericidal. While the antitoxic serum was effective against the toxin, antibacterial serum was effective against the

[31] Ehrlich to the PMCA, 21.3.1906, GStA PK, 1 HA, Rep. 76 VIII B, No. 3523.
[32] On Ehrlich's requests to the PMCA and the rejections of the treasury department, see GStA PK, 1. HA, Rep. 76 Vc, Sekt. I, Tit. IX, Part II, No. 27.
[33] The figures are listed in Ehrlich to the PMCA, 22.8.1907, ibid., and in the financial reports in APEI, Dept. II, No. 7, Vol. 1.

https://doi.org/10.1017/S0269889708001701 Published online by Cambridge University Press

bacteria itself and could weaken, destroy, or eradicate it. The production of bactericidal sera differed from that of antitoxic sera, because the toxins could not be separated from the body of the bacteria and thus substances from the bacteria's corpus were used for the immunization process. The success of the immunization procedure depended on the relationship between the injected bacteria cultures and the afflicted organism, the compatibility of the animal host's blood, and the antibodies' reaction to the test animals (Otto 1906; Wassermann 1904; Friedberger 1904).

These complex processes and the unpredictable reaction of the bactericidal serum to the recipient made it more difficult to find a valid method of *Wertbestimmung*. For sera to be state approved, the existence of a stable method of evaluation was a sine qua non. Conversely, this meant that a veterinary serum could only receive state approval if a valid method of evaluation had been found. Despite the fact that anthrax serum had a demonstrable immunizing or curative effect, scientists failed to develop an effective method of evaluation. The scientists, Merck, and the IET had undertaken serious efforts using all kinds of test animals in countless test arrays, but all to no avail. A member of the IET concluded in 1903 that the "impact of the serum is abnormal, irregular, unstable, and without any validity."[34]

In the case of red murrain serum, Gustav Lorenz had first developed a stable method of *Wertbestimmung* that was later reworked by members of the IET (Lorenz 1895; Marx 1901). Based on previous experience with the evaluation of diphtheria serum or tuberculin in different arrays (serum sample, standard serum, control array), diminishing doses of serum (ranging from a minimum dose L0 to a maximum dose L†) were injected into mice and, an hour later, the bacteria culture added. To account for the effects of individuality or coincidence, each dose was injected into two mice. The test results between standard serum and serum sample had to correspond (Otto 1906, 66–69). Although more than one hundred test animals were involved in analogous test arrays, producers and medical officers at the IET arrived at different results. Numerous letters expounded upon the emerging problems of using different species of mice (grey or white) or time intervals.[35] The evaluation of swine pest serum became even more complex because it was unclear whether the immunization with one strain of bacteria was active against the disease in general or only against a specific strain. For example, the Farbwerke Hoechst developed a monovalent swine pest serum *Suisepsin* that was effective only against one strain of bacteria and the company Ludwig Wilhelm

[34] Sobernheim 1897, as quoted in Schubert 1903, 5. Test animals that had been given low doses of serum survived, while animals that had been given high doses died. And the test arrays were irregular: arrays repeated under the same conditions came up with different results (see also the files concerning anthrax serum in the archive of Merck in Darmstadt, K 1/128; and APEI, Dept. XII, No. 1, Vol. 1). Otto and Hetsch concluded in 1927 that a consistent and valid method had not been found (Otto and Hetsch 1927, 120–124).

[35] Cf. the correspondence between Carl Enoch and the IET in April 1904 and October 1911, APEI, Dept. IX, No. 1, Vol. 1; further notes about problems are in Otto 1906, 67.

https://doi.org/10.1017/S0269889708001701 Published online by Cambridge University Press

Gans marketed a polyvalent serum based on numerous strains of different origin (ibid., 69–72).[36]

The fragile framework of the *Wertbestimmung* of veterinary sera was also reflected in the importance of animals as serum hosts and biological indicators. The creation of antitoxins or bactericidal sera depended on the serum hosts, their health, and principles of animal husbandry. For this reason, a journal was used to meticulously track every individual characteristic and behavioral change of the serum host. Adjusting the immunization procedure to fit the host's specific immune system demanded considerable working knowledge and expertise.

As biological agents, the test animals demonstrated the potency of the serum injected with bacterial cultures or toxins. In turn, the test animals had to be susceptible to the bacteria or toxins. While it was desirable for serum hosts to be as large as possible in order to harvest greater quantities of the blood needed to produce serum, test animals had to be as small and manageable as possible – like mice, rats, or guinea pigs. And whereas a degree of individuality was acceptable in serum hosts, test animals had to be standardized. Each test animal had to react in the same way in order to achieve valid test results unaffected by local circumstances.[37]

The evaluation of veterinary sera illuminates the motives of the serum producers. Unlike human sera, where obligatory state control was implemented as soon as possible, several serum producers applied for state control of veterinary sera voluntarily, despite high testing fees. Following M. Norton Wise, the value of precision is expressed in precision of measurement and connotes certainty, objectivity, and rationality – "it shows quality" (Wise 1995, 3). Hence, voluntary adherence to control measurements of the IET also served as a marketing tool for producers. In the case of red murrain and swine pest serum, state approval was seen as a guarantee of quality and used as a marketing instrument.[38]

For serum producers, state approval also had important legal implications. Maximizing profits had to be balanced against minimizing the risks posed by impure or ineffective serum. In legal disputes about the effects of the serum, manufacturers could prove that the serum was produced in accordance with official guidelines (Eiermann 1894; Hüntelmann 2006a). For red murrain serum, issues of quality took on greater significance. In order to strengthen confidence in red murrain serum and its use, the

[36] Similar problems concerning monovalent or polyvalent sera had also arisen for dysentery sera. Monovalent serum was very effective once the special strain had been identified, but for unknown strains of bacteria, less effective polyvalent serum was used. The production and state control of polyvalent sera was more difficult because the serum's potency was tested on different strains (cf. the files for swine pest serum in APEI, Dept. IX, No. 3, Vol. 1; Dept. IX, No. 6, Vol. 1 and Dept. IX, No. 7, Vol. 1).

[37] On animal logistics (acquisition and disposal), see APEI, Dept. IV, No. 2, Vol. 1. In the early years, test animals were purchased on demand, bought from different dealers, or raised in stables near the institute. In the 1920s, the uniformity of test animals became more important in heredity and biomedical research. On the standardization of test animals, see Schwerin 2004; Logan 2002; Rader 2004.

[38] Cf. the advertisements for state-approved red murrain serum in APEI, Dept. IX, No. 1, Vol. 1.

https://doi.org/10.1017/S0269889708001701 Published online by Cambridge University Press

Farbwerke Hoechst offered compensation for any pig that died after or in spite of a prophylactic immunization. This compensation was cancelled after 1909, when the method of immunization against red murrain and the evaluation of serum had been deemed "undoubtedly safe" and of "impeccable quality."[39]

7. Decreasing Stability in the Framework of *Wertbestimmung* during World War I and the Postwar Period

After the outbreak of World War I, the objectives of the IET changed dramatically. Contrary to past efforts aimed at enlarging and stabilizing the framework of the *Wertbestimmung* and improving techniques of evaluation, attention now turned to simply defending the standards in the face of a wartime economy. Between 1914 and the early 1920s, the institute struggled to cope with fewer staff, the sinking quality of serum hosts and test animals, the abandonment of high quality standards, and the special demands imposed by the war.

Before the outbreak of war, serum hosts were kept under excellent hygienic conditions. But after 1914, as the cost rose for maintaining horses and more horses were drafted into the military, producers began exploring alternatives. During World War I and in the postwar period, serum horses were lent to farmers for fieldwork and vice-versa draft animals served as serum hosts.[40] In place of horses, cattle and sheep became substitute hosts for the production of diphtheria serum, even though they produced less effective serum.[41]

While on the supply side fewer serum hosts were producing lower quality serum, on the demand side greater quantities of serum were needed. Moreover, the serum produced had to be tested rapidly. Although tetanus serum had been tested only in small quantities before the war, during the war its importance grew markedly. The quantities tested grew from 315 litres in 1913–1914, to 2,124 litres the following year, and 16,471 litres by 1918. The large quantities of serum were used for prophylactic immunization of all soldiers who had suffered serious injury. In addition, demand rose constantly during the war for other sera, such as diphtheria serum, red murrain serum, and for tests of amboceptors for the Wassermann-Syphilis-Test. Moreover, the institute also had to produce vaccines for the army. Between 1914 and 1916, nearly

[39] Cf. the announcement of the Farbwerke Hoechst in December 1908 (ibid.).

[40] The cofounder of the Behringwerke, Carl Siebert, asked in May 1923 if the company could use horses of farmers as serum dispensers (see Carl Siebert to the Prussian Ministry for Public Health, May 1923, and the answer from the Imperial Health Office, 2.7.1923, BAB, R 86/2710).

[41] Farbwerke Hoechst was granted permission to produce and distribute cattle serum in 1912. Ruete and Enoch requested state approval for cattle serum in July 1914. The serum's strength was only one-hundred-fold, APEI, Dept. Vd, No. 4, Vol. 1 and Dept. Va, No. 1, Vol. 2. Cf. the Annual Report of 1915 in the APEI, Dept. IV, No. 1, Vol. 2.

https://doi.org/10.1017/S0269889708001701 Published online by Cambridge University Press

two thousand litres of vaccine against typhoid fever and cholera were produced for the Medical Department of the War Ministry.[42]

So it is no surprise that during wartime the potency of most sera decreased. Before World War I, state approved serum was subject to strict quality control. For instance, tetanus serum was approved and certified as a remedy only if the serum met the minimum quality standard of a four-fold dose of immunization units. To cover the high demand of serum during the war, serum with two-fold and three-fold immunization units had already been approved and certified for preventive immunization. In addition, the regular revision of tetanus serum after two years was interrupted because of the work involved, the lack of test animals, and the high demand for serum.[43] The quality-standards for red murrain serum also declined. This serum was needed in large quantities during the war to cover the high demand for pork. Hence, state-control of red murrain serum was suspended in the autumn of 1914 by the Prussian Ministry of Agriculture. As a result, red murrain serum circulated on the market without being state approved and the complaints of veterinarians about ineffective serum bear witness to the fact that serum with fewer immunization units was being sold.[44] During the war, the IET could neither reliably guarantee the serum's quality, nor did it have the power to act on grievances.

The situation was aggravated by the fact that more routine work had to be done with fewer staff working in poorer conditions. The head of the survey and the veterinary department were military surgeons posted to the IET. After 1914 the military surgeons and members of the institute were sent to war as hygienists. After other members of the institute had departed or died, the head of the biological research department, Hans Sachs, was charged with managing day-to-day affairs.[45] As a consequence, during the war the institute conducted only war-related research on sera for dysentery and gas gangrene or on the sero-diagnosis of typhoid fever.[46]

Things became even worse when Paul Ehrlich died in August 1915 and Sachs became interim director of the institute until 1917. Ehrlich had supervised all the affairs of the institute and he was the final arbiter of unclear test results and procedural difficulties with the *Wertbestimmung*. Ehrlich had controlled nearly all daily activities of the institute's members: He advised scientists, supervised routine work, and briefed

[42] For the figures, see the Annual Reports between 1913 and 1919 in APEI, Dept. IV, No. 1, Vol. 2.
[43] IET to Prussian Ministry of Interior, 8.7.1916, APEI, Dept. 6, No. 2, Vol. 1 (cf. the Annual Reports for 1914–1918 in APEI, Dept. IV, No. 1, Vol. 2).
[44] Cf. the request of the company Ludwig Wilhelm Gans for permission to sell less effective serum in June 1916, the complaints about impure and less effective serum at an army slaughterhouse in December 1916, the remarks of the district veterinary of Lindau in December 1916, and the correspondence between the veterinary Eugen Dietz, Ludwig Wilhelm Gans, and the IET in October 1916, all in APEI, Dept. IX, No. 1, Vol. 2.
[45] For the correspondence concerning the status of Hans Sachs as indispensable, see GStA PK, 1. HA, Rep. 76 Vc, Sekt. I, Tit. IX, Part II, No. 22, Vol. 4. On the correspondence concerning the application for the suspension of Kurt Bierbaum due to the high workload in January 1917, and requests for more laboratory staff, see APEI, Dept. III, No. 1, Vol. 2.
[46] Kolle 1926; Annual Report for 1917 in APEI, Dept. IV, No. 1, Vol. 2.

https://doi.org/10.1017/S0269889708001701 Published online by Cambridge University Press

his co-workers on the different methods of *Wertbestimmung*, improvements to existing methods, or about the daily work routine (Marquardt 1951; Bäumler 1979). Moreover, with Ehrlich's death, the IET's international reputation as a leading authority in the evaluation of serum declined. Its former authority had been assured by several arrangements: The standard serum used for evaluation was preserved in the German institute and sent to serum producers and research institutes throughout the world. The institute's annual report of 1913 proudly announced that 56 producers and regulatory agencies had subscribed to the German standard, making the IET the biometrical "master of measurement."[47] After the outbreak of war, the number of institutes subscribing to the standard serum dropped to 24 and then to five in 1918.[48] Increasingly, the German institute lost its internationally pre-eminent status and – given its concentration on vaccines for the army, survey duties, and depleted staff – also its leadership role in the realm of immunology.

8. The International Standardization of Biological Products in the Early 1920s

After the war and the chaotic postwar period, the new director Wilhelm Kolle substantially restructured the institute. The IET struggled to regain its pre-eminence in the realm of biometrology and serum-evaluation in the German Empire. During the war, both the Imperial Health Office and the Institute for Infectious Diseases had demonstrated their ability not only to produce serum, but also to enhance the methods used in the *Wertbestimmung*. The Imperial Health Office, for example, evaluated and certified foreign swine pest serum and conducted research on the evaluation of sera for scarlet fever[49] and gas gangrene (Menk 1931; Schlossberger and Menk 1931).

The precarious position of the IET in the postwar period was made worse by other circumstances as well. In the 1920s, the German serum producers had to compete with numerous other foreign serum producers. In addition, several countries had built up semi-public institutes to produce sera and vaccines to satisfy their own demand. In the face of growing international competition, German serum producers complained more and more about the test fees they were required to pay to the IET. The serum producers argued that the higher prices for German serum were caused by the test fees that put German manufacturers at a disadvantage in international markets. After the collapse of the German postwar economy, serum producers were more interested in lowering costs than in technical improvements to the *Wertbestimmung*. The request of the Sächsische Serumwerke to distribute unapproved serum abroad was denied by the state on grounds of principle, but in the mid-1920s public health authorities and

[47] According to Cahan 1989 on the Physikalisch-Technische Reichsanstalt.
[48] Cf. Annual reports between 1913–1918 in APEI, Dept. IV, No. 1, Vol. 2; Dept. Vc, No. 5, Vol. 1.
[49] Cf. Annual reports of the Imperial Health Office after 1925, BAB, R 86/4274; Zeller and Beller 1930.

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the serum producers agreed to cut test fees and relax price controls on the German market.[50]

The international competition and standards for vaccines and sera were debated in the Health Organisation of the League of Nations. At the very first meetings of the Provisional Health Committee in 1921, the standardization of sera and a schedule for further investigations were discussed as important issues of collective security. Thorvald Madsen, director of the Danish serum institute and president of the Health Committee, outlined the prospective measures. While the German method of *Wertbestimmung* of diphtheria serum was internationally well established and the system of subscriptions had only to be re-established, the evaluation of tetanus serum was more problematic, because different methods of evaluation and scale units existed in Germany, France, Italy, and the United States. Madsen described the situation for dysentery and other bacterial sera as wholly unsatisfactory because neither the principles for sera testing, nor the methods of evaluation had been developed.[51]

Madsen suggested apportioning the scientific work to the various national institutes, e.g. the Medical Research Council in Great Britain, the Pasteur Institutes in Paris and Brussels, the Rockefeller Institute in the United States, his own institute in Denmark, as well as the IET and other German research institutions. The relationship between German and Allied scientists and the German Empire and the League of Nations was ambiguous (Borowy 2005; Mazumdar forthcoming). The German scientists were indispensable experts in the realm of immunology and serology, but they were also discredited after the war and the political aim in the postwar period was to keep Germany down (Macmillan 2003, 166–180). On the German side, many scientists were reluctant to cooperate internationally with "hostile" colleagues (Mazumdar forthcoming). Given his good relationships with both German and Allied scientists, the Dane Madsen was the ideal mediator and initiator of the "new" cooperation. Despite early scepticism, Wilhelm Kolle became more and more engaged in the Health Organization and began re-establishing contacts with the international scientific community of immunologists.[52]

Although the scientists of the IET gradually reentered the community of international experts and public health technocrats, the Germans were no longer dominant players. The work on the evaluation of tetanus, tuberculin, or dysentery serum was now coordinated in the international Permanent Standardization Committee. This committee came to set the agenda of international conferences and to delegate

[50] For the discussions about test fees around 1923, see BAB, R 86/2710 and 2712; APEI, Dept. A, No. IVa, Vol. 2.

[51] Memorandum by Thorvald Madsen on the standardization of antitoxic sera, September 1921, APEI, Dept. B, No. 6, Vol. 1; and Archive of the League of Nations, Genève (ALN), 12 B, Doss. 11346.

[52] Kolle's reservation about international cooperation can be found in the correspondence to the responsible Ministry in November 1921 in APEI, Dept. B, No. 6, Vol. 1. On his considerations that otherwise the German scale units would have been overruled, cf. ibid. The need for international cooperation justified to the Ministry of the Interior, 13.2.1935, APEI, Dept. B, No. 6, Vol. 5.

https://doi.org/10.1017/S0269889708001701 Published online by Cambridge University Press

research projects to national institutes (Goodman 1971; Weindling 1995; Dubin 1995). One example of this international cooperation was the definition of a new international reference unit for tetanus serum: the international immunization unit was based upon the American unit, but the procedure was based on the German method of evaluation and the respective standard serum had been prepared at the IET, with the the Danish Institute for Serotherapy serving as a mediator between the different serum institutes.[53]

Although the evaluation of sera was still important in the early 1920s, by 1923 the international standardization of other remedies like salvarsan, vitamins, insulin, or digitalis grew in significance (Knaffl-Lenz 1928).[54] Thus, the framework of *Wertbestimmung* was again enlarged. For example, in the case of salvarsan, both chemical and biological evaluation were deemed essential. In 1925 Wilhelm Kolle proposed principles for evaluating salvarsan that were analogous to those used for serum: initial audits of the producer, permanent control of the production process, recordkeeping, and biological tests. Kolle favored development of a standardized salvarsan that would serve as a reference unit for salvarsan samples.[55] Henry H. Dale criticized Kolle's efforts as being unnecessary and expensive, and he warned against mixing biological standards and the serum question.[56] With the evaluation of salvarsan and other preparations like digitalis, the framework for the *Wertbestimmung* had again been shifted. Dale himself recognized: "I have always maintained that the term 'biological products' is an absurdity. [. . . It] is the standardization which is biological, not the remedies."[57] With that, Dale was describing a fundamental shift from the "standardization of biological remedies" to "biological standardization of certain remedies."

9. Conclusion – the Dynamics of *Wertbestimmung*

In the 1920s, the means of standardizing the mass production of complex remedies continued to occupy the attention of the Permanent Standardization Committee. Evaluation served to transform an undefined, imponderable serum into an objective,

[53] Resolution of the Permanent Standardization Committee on anti-tetanus-serum, July 1923, ALN, 12B, Doss. 27693, No. 29624.

[54] In the files concerning the "Standardization of Biological Products" and "Biological Standardization," the standardization of sera played only a marginal role after 1923. Cf. LNA, 12B, Doss. 26142, and the Conference Proceedings of the Permanent Standardization Committee, LNA, 8E, Doss. 3551.

[55] Wilhelm Kolle, Memorandum on the standardization of salvarsan, 1925, APEI, Dept. B, No. 6, Vol 1.

[56] Dale as cited in a memo concerning the conference plan in 1925, LNA, 12B, Doss. 26142, No. 42616; and Dale to Ludwik Rajchman, 4.10.1927, ibid., No. 31593; for the international standardization of the serological syphilis test, see Mazumdar 2003.

[57] Henry H. Dale to Raymond Gautier, 19.10.1925, ALN, 12B, Doss. 26142, Nr. 46867. In this context, it is noteworthy that until the mid-1920s, conferences were held on the standardization of biological products and after 1925 conferences were held on "Biological Standardization of Certain Remedies" or "Biological Standards." The remedies that were standardized (such as digitalis, insulin, or vitamins) differed in their composition, production, and use.

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measureable, comparable remedy with an exactly quantifiable effect. It required that every factor, including bacteria cultures, producers, serum hosts, test animals, as well as the technical arrangements and measuring procedures, be regulated and standardized. Both the production process and the final product were standardized and the link between evaluation and standardization was ultimately embodied in the IET and the Permanent Standardization Committee of the League of Nations.

The original aim of these efforts had been to protect the public from impure or ineffective serum. But patients played only a marginal role in the subesquent development, practical work, and testing procedures of the IET. Efforts to improve the *Wertbestimmung* and accommodate changes unleashed complex institutional dynamics. Once a new serum had been developed, state medical authorities sought reliable evaluation methods, which in turn led the IET to seek official state control of the serum. The members of the institute focused on technical refinement of the *Wertbestimmung*, ultimately becoming the "Masters of measurement."

But from the outset, efforts undertaken to stabilize the *Wertbestimmung* had consequences that neither medical officers, scientists, nor the serum producers foresaw. After a uniform method for evaluating diphtheria serum had been established in 1895, the framework of the *Wertbestimmung* suddenly shifted: New producers entered the market, the toxin became an unstable unit of reference, and although the serum's potency had been improved, the stability of its value was compromised. Moreover, the framework of *Wertbestimmung* was enlarged to encompass other sera as well. In other words, the framework of *Wertbestimmung* itself elicited powerfully dynamic and countervailing forces: no sooner had the framework been fixed, than the environment changed and the framework was again destabilized; and this in turn unleashed renewed and ongoing attempts to integrate, stabilize, and adjust the *Wertbestimmung*.

Acknowledgments

This article has been written in the context of two projects financed by the German Research Foundation – DFG HE 2220 and DFG GR 2116. For helpful suggestions I would like to thank Eric J. Engstrom, Christoph Gradmann, Volker Hess, Ulrike Klöppel, Alexandre Métraux, and the anonymous reviewers.

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