Medical History, 1990, **34**: 65-78.

PAUL EHRLICH AS A COMMERCIAL SCIENTIST AND RESEARCH ADMINISTRATOR

by

JONATHAN LIEBENAU *

Historians and biographers have studied Paul Ehrlich as a biochemist, a medical messiah, and an eccentric.[1] The links with industry of this Nobel Prize-winning pioneer of experimental therapeutics and immunology have, however, been largely neglected. Perhaps this was because commercial involvement was regarded as unseemly by historians, or because those ties were thought to be insignificant in relation to the major contributions Ehrlich made to therapeutic practice and theory. More recently, attitudes have changed: Ehrlich's resurrection as a company scientist is almost complete after a large commemorative exhibition mounted by Hoechst AG and that company's sponsorship of a major new biography,[2] facilitating further analysis of Ehrlich's commercial work. This paper goes beyond biography to provide an analysis of an early example of medical science as a corporate activity.

INSTITUTIONAL STRUCTURE

Ehrlich's corporate ties became strongest when he directed the Königliches Anstalt für experimentelle Therapie (1896–1915), which became the Paul Ehrlich Institute in Frankfurt-on-Main. This Institute was a centre of four overlapping groups: academic medical scientists, practitioners, government officials, and producers of new therapeutics. Within it, several new medicines were developed or improved, and the quality and influence of its work quickly elevated it to the stature of the Pasteur Institute. But its links with industry differentiated Ehrlich's institute from the Pasteur, as it became a centre of theoretical medical science, the official regulator of sera and vaccine, and the most exciting product-development laboratory well into the inter-war years.

*Jonathan Liebenau, Ph.D., Lecturer in Information Systems, London School of Economics, Houghton Street, London WC2A 2AE.

I am indebted to the archivists and librarians of Hoechst AG, the Paul Ehrlich Institute, and the Wellcome Institute for the History of Medicine. I would also like to thank the anonymous reviewers for many constructive suggestions. This work was carried out while I was supported by the generous help of the Leverhulme Trust in addition to a travel grant from the UK Economic and Social Research Council.

[1] See, for example, Claude E. Dolman, 'Paul Ehrlich', *Dictionary of scientific biography*, New York, Charles Scribner's Sons, 1971, vol. 4, pp. 295–305; Martha Marquardt, *Paul Ehrlich*, London, W. Heinemann, 1949.

[2] Ernst Bäumler, *Paul Ehrlich: scientist for life*, New York, Holmes B. Meyer, 1984.

https://doi.org/10.1017/S0025727300050274 Published online by Cambridge University Press

The genesis of this institutional development dates from the development of diphtheria antitoxin, in the 1890s. Antitoxins were produced using a radically new conceptualization of the character of disease-causing agents and the ability of the body to cope with them. Injecting a medicine made from the blood of a diseased animal required a totally new attitude to therapy. Although animal extracts of various sorts had been used as injectables, and vaccines seemed conceptually similar, the processes involved in the extraction of antitoxins were based on a novel and unexpected theoretical structure. Furthermore, there was an element of mystery in the process of antitoxin production, uncomfortably reminiscent of homeopathic theory.

After three years of chemical tests on the formulation of diphtheria antitoxins, developed by Emil von Behring and Shibasaburo Kitasato in 1890, a number of producers worldwide were anxious to manufacture it and the medicines which would evidently follow.[3] Antitoxins were produced in a straightforward manner. The disease-causing bacillus was grown in cultures and the toxin extracted. The toxin was then injected in increasing quantities over a few weeks into the host animal: first guinea pigs and sheep were used, later horses. The animals displayed some symptoms of the disease but remained essentially healthy while their immune systems produced a rising titre of antitoxins. Some blood was extracted, allowed to clot, and the serum separated out. After being carefully handled and packaged it was injected into the afflicted person to counteract disease.

The simplicity and promise of this procedure created considerable optimism. Many diseases were apparently curable in this way. All that was needed was to isolate the causative agent, extract the toxin, and prepare the therapeutic antitoxin. This procedure was tried by some experimenters, especially in company laboratories, for nearly all diseases, leading to the marketing of products. But from an early stage problems plagued the makers of antitoxins. It seemed impossible to control the strength of the antitoxin. This could be roughly measured by its volume and by the amount it took to kill an experimental animal, but such standards were inadequate to say the least. By developing a satisfactory testing procedure, Paul Ehrlich began the process of formalizing not only a research programme for his group, but also the foundation of technical standards for drug regulation.[4]

Once it was clear that Behring's antitoxin was a marketing success, the *Reichsgesundheitsamt* (Ministry of Health) seized the opportunity to impose regulations. Many physicians were, of course, concerned that this new class of therapeutic products was being put on the market, and wanted some assurances about safety, purity, and consistency. Already by November 1894 legislation limited their use except with a physician's prescription, through apothecaries. The criteria for approval

[3] E. Behring and S. Kitasato, 'Ueber das Zustandekommen der Diphtherie-Immunität und der Tetanus-Immunität bei Thieren', *Dt. med. Wschr.*, 1890, no. 49: 1113–14; E. Behring, 'Untersuchungen über das Zustandekommen der Diphtherie-Immunität bei Thieren', ibid., no. 50: 1145–8.

[4] Aside from Bäumler's biography (op. cit., note 2 above), a number of detailed studies have added much to our appreciation of Ehrlich. They include: I. Galdston, 'Some notes on the early history of chemotherapy', *Bull. Hist. Med.*, 1940, **8**: 956–64; J. Parascandola and R. Jasensky, 'Origins of the receptor theory of drug action', ibid., 1974, **48**: 199–220; J. Parascandola, 'Carl Voegtlin and the "arsenic receptor" in chemotherapy', *J. Hist. Med.*, 1977, **32**: 151–71; L. P. Rubin, 'Styles in scientific explanation: Paul Ehrlich and Svante Arrhenius on immunochemistry', ibid., 1980, **35**: 397–425.

https://doi.org/10.1017/S0025727300050274 Published online by Cambridge University Press

of antitoxin included an assessment of its potency, using a method of assay analysing the amount necessary to neutralize a given volume of toxin.[5] To facilitate this laboratory work, the Control Station for Diphtheria Antitoxin was established in 1895. Given its task, the appropriate location was alongside Robert Koch's Institute for Infectious Diseases, in the Charité Hospital in Berlin. Koch assumed the nominal directorship, but testing was conducted by Drs Hermann Kossel and August von Wassermann.[6]

As interest in antitoxin grew worldwide and production increased, the functions of the testing laboratory at the Control Station also expanded. By 1895 there were already three major commercial producers of antitoxin in Germany: Hoechst, Merck, and Schering. Hoechst and Schering co-operated and allowed all their antitoxin to be tested at the Control Station.[7] Soon the logistics of maintaining a smooth flow of product samples through the laboratory created pressures on space. Furthermore, the complex testing procedures needed constant reassessment. It was clear that new products were on their way, particularly tetanus antitoxin, which had been developed along with diphtheria antitoxin. Moreover the function of the laboratory was illimitable: with the academic orientation of Kossel and Wassermann, the laboratory was from the start working towards a theoretical understanding of immunity.[8]

Because of the large-scale testing functions, as well as the increasing volume of experimental and theoretical work, and through the sympathetic offices of the director of the Prussian Ministry of Educational and Medical Affairs, Friedrich Althoff, a larger facility was provided in the Berlin suburb of Steglitz in 1896 and Paul Ehrlich was made director.[9] Work at the Steglitz laboratory, which was called the Institute for

[5] P. Ehrlich, 'Die staatliche Kontrolle des Diphtherieserums', *Berl. klin. Wschr.*, 1896, no. **20**: 441–3. See also M. J. Rosenau, *The immunity unit for standardizing diphtheria antitoxin (based on Ehrlich's normal serum)*, Hygienic Laboratory Bulletin 21, Washington, USGPO, 1905.

[6] G. Siefert, 'Bundesamt für Sera und Impfstoffe, Paul-Ehrlich-Institute—its structure and scope', *Drugs Made in Germany*, 1982, **25**: 28–36. See also E. Hickel, 'Das Kaiserliche Gesundheitsamt und die chemische Industrie im Zweiten Kaiserreich (1871–1918): Partner oder Kontrahenten?', in G. Mann and R. Winau (eds.) *Medizin, Naturwissenschaft, Technik und das Zweite Kaiserreich*, Göttingen, Vandenhoeck and Ruprecht, 1977.

[7] See W. Vershofen, *Wirtschafts-geschichte der chemisch-pharmazeutischen Industrie*, vol. 3, *1870–1914*, Aulendorf, Cantor, 1958, pp. 29ff. W. Bernsmann, 'Arzneimittelforschung und Entwicklung in Deutschland in der zweiten Hälfte des 19. Jahrhunderts', *Pharm. Ind.*, 1967, **29**; 1968, **30**; Hoechst AG, *Die Zusammenarbeit Behring—Hoechst 1892–1904*, vol. 37, Dokumente aus Hoechster Archiven, 1968; Hoechst AG, *Farbwerke vorm. Meister Lucius & Brüning 1863–1913*, 1913, p. 29; A. Fiermann, 'Die Einrichtungen zur Darstellung des Diphtherie-Heil-Serus in den . . . Hoechster Farbwerke', *Münchener med. Wschr.*, 1894, **51**: 1038–40, P. Korn, 'Geschichte der bakteriologische Abteilung der Schering AG 1893–1942', MS, Schering AG Archive, Berlin; H. Hollander, *Geschichte der Schering Aktiengesellschaft*, Berlin, Schering, 1955, pp. 29ff., 96. File "xc 1.2" Schering Archive: I. Possehl, 'Impfstoffe, Sera, Diagnostika-Resultate bakteriologischer und immunologischer Forschung', MS, 1983, pp. 6ff. See also H. Loewe, 'Paul Ehrlich und Emil van Behring in ihren Beziehungen zu den Farbwerke Hoechst', *Arzneimittelforsch.*, 1954, **4**: 1–15.

[8] P. Ehrlich, H. Kossel and A. von Wassermann, 'Ueber Gewinnung und Verwendung des Diphtherieheilserums', *Dt. med. Wschr.*, 1894, **16**: 155, 237, 293. W. 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 1896–1924 veröffentlichen Arbeiten', *Arbeiten aus dem Staatsinstitut für Experimentelle Therapie und dem Georg Speyer-Hause zu Frankfurt a/M*, 1924, **13**: 7ff.; Bäumler, op. cit., note 2 above, p. 57.

[9] Ibid., p. 59; Siefert, op. cit., note 6 above.

https://doi.org/10.1017/S0025727300050274 Published online by Cambridge University Press

Serum Research and Serum Testing, focused increasingly on theoretical problems of the nature of immunity, as well as the technicalities of standardizing and testing, and the logistics of certifying commercial preparations. During this period, 1896–9, Ehrlich concentrated his work on the establishment of an international unit of antitoxin using assay techniques which could be easily adopted.[10]

The laboratory's concern to establish an international unit was reinforced in 1896 by the report of the *Lancet*'s commission on the "Relative Strengths of Diphtheria Anti-Toxic Serums".[11] The *Lancet* tested antitoxin from the three main German suppliers and three British suppliers, as well as a French, a Belgian and a Swiss product. They found large discrepancies between the brands, and levels of potency diverged widely from those claimed on labels. Of the samples tested, those from Schering and Hoechst were evidently superior. Ehrlich cited these results as proving the need for an international standard which was easy to follow and unambiguously enforceable.[12]

The same article advanced several related arguments. Beginning with the understanding that "one of the main tasks of the Institute is to measure the potency of the antidiphtheria sera produced in Germany", he analysed the factors causing the loss of potency: water, by hydration; oxygen, by oxidation; light; and heat. The first two were controllable at production, and any loss of potency resulting from them could be assessed in the commercial serum, along with standards of purity. These assessments could then be used as a criterion for certification. As a standard he used a desiccated serum which Behring had produced for him at Hoechst. Further industrial co-operation was secured for procedures to evacuate tubes from the electric lamp works of the Allgemeine Elektricitätsgesellschaft, which "in the most cooperative manner", wrote Ehrlich, "placed apparatus at our disposal".[13]

COMMERCIAL SCIENCE

From the late 1890s, Ehrlich already had partisan feelings towards certain companies. Some, he believed, were incapable of following the necessary procedures with sufficient care and "inconsistencies have repeatedly been observed in the course of dealings" with them.[14] The procedures which he outlined were officially confirmed by an order from Althoff in 1897 and the methods, developed in co-operation with Hoechst and Schering, were applicable to the rest of the industry.[15] In order to meet the standards, moreover, manufacturers were to obtain fresh supplies of standard toxins from Ehrlich's laboratory about every three weeks. Such dependence worked distinctly in favour of those firms who had produced antitoxins early, and in particular for Hoechst.

The Hoechst Company had begun modestly, in 1863. A centralized company laboratory was established in 1883 in a building peripheral to the main plant. The

[10] Bäumler, op. cit., note 2 above, p. 47; see also note 3 above.
[11] 'Relative strengths of diphtheria anti-toxic serums', *Lancet*, 1896, ii: 182–96.
[12] Paul Ehrlich, 'Die Wertbemessung des Diphtherieheilserums und deren theoretischen Grundlagen', *Klin. J.*, 1897–8, 6: 135, 155, 167, 234, 292.
[13] Ibid.
[14] Ibid. Translation from *The collected papers of Paul Ehrlich*, ed. P. Himmelweit et al., 3 vols., London, Pergamon, 1956–60, vol. 3, p. 53.
[15] Bäumler, op. cit., note 2 above, pp. 68–9.

https://doi.org/10.1017/S0025727300050274 Published online by Cambridge University Press

laboratory director, Dr E. von Gerichten, who held a doctorate in chemistry, was charged with a variety of tasks arising from the dyestuffs manufacturing process, including producing new colours and testing for constant quality. He had a small staff of chemists but maintained frequent contact with academic scientists. This staff, in collaboration with academic workers, exploited opportunities to patent, without restriction, in Germany and the United States. By the late 1880s Hoechst already held many patents on intermediate products and spin-offs from their development programmes.[16]

As the academic pharmacology community directed its attention to synthetic quinine, the main interest at Hoechst turned to the fever-reducing effects of alkaloids. Friedrich Stolz, the first full-time pharmacologist in the company laboratory, developed various alkaloid solutions, finally settling on one preparation which he called "Pyramidon". In the late 1880s, Pyramidon became a major money-maker for Hoechst, judging both by its prominence in company discussions, and by the royalties, routinely paid to inventors at the firm, which Stolz earned. It provided a strong incentive to invest in the possibilities of further developments.[17]

The second major influence on the decision to commit resources to research on pharmaceuticals was the emphasis on finding a treatment for tuberculosis. Robert Koch had contacted Hoechst around 1890 about producing Tuberkulin, his anti-TB agent, and this was seen as a marvellous opportunity to break into a huge new area of the drug business. He suggested that Emil Behring be contacted about a possible role in the development of Tuberkulin and other bacteriologically-based medicines. Behring had to continue to work in Berlin until 1892, when he was permitted to leave the armed forces into which he had been conscripted as a medical officer. When he moved to Frankfurt to establish Hoechst's antitoxin production programme he found a staff of some dozen chemists and pharmacists testing drugs and monitoring the production of Tuberkulin and Pyramidon.

By the mid-1890s physicians in Germany especially were excited about the promise of medical science, and were searching for new products. For the pharmaceutical firms, the production of new products was essential for competitive advantage. The industry was growing quickly, and the markets were constantly being challenged. The best way for these firms to distinguish themselves and open new markets was for them to introduce new medicines. This they did with great competitive zeal, and every potential new product was immediately patented. Although relatively few of these patents were developed into the manufacture of new drugs, they did delineate areas of enquiry in which the company was specializing. The number of products which each firm then offered for sale increased dramatically. Despite a good deal of overlap among standard medicines on offer, many branded or speciality products were more or less unique to each firm.[18]

[16] Jonathan Liebenau, 'Industrial R&D in pharmaceutical firms in the early twentieth century', *Business Hist.*, 1984, **26**: 329–46.

[17] Ibid. Hoechst AG, *Dr. Friedrich Stolz, der Erfinder des Pyramidons*, vol. 12, Dokumente aus Hoechster Archiven, 1966; "Friedrich Stolz" file, Hoechst Archive.

[18] Hoechst trade catalogues, Hoechst Archive; see also Jonathan Liebenau, 'Patents in the chemical industry, tools of business strategy', in *idem* (ed.), *The challenge of new technology*, Aldershot, Gower, 1988.

https://doi.org/10.1017/S0025727300050274 Published online by Cambridge University Press

Even while in Berlin, Ehrlich agreed a contract with Hoechst, in March 1894, to supply diphtheria antitoxin and to be exclusively available to Hoechst for a period of fifteen years.

The first years of production were highly successful and in 1903 the Hoechst Company took stock of its record of diphtheria antitoxin production. Close to 20,000 litres had been produced and sold for over 4 million marks, far more than any competitor.[19] In publicizing this record, the company stressed the close collaboration it had had with Koch, Behring, and Ehrlich.[20] In ten years, the production facilities had grown from being a small offshoot of the company research laboratory under the personal direction of Behring, to a complex of buildings including separate ones for the production of Tuberkulin, one for most sera and separate stables for the isolation and treatment of horses used in production. By 1898 the bacteriological laboratory had also been split off from the pharmaceutical research building, and was the new centre co-ordinating the production of a wide range of biologicals.[21]

Behring stayed with the company during the period when he was looking for a professorship. He held one for a short time at Halle, but was offered the position (over the faculty's objection) as Director of the Hygiene Institute and Professor of Hygiene at Marburg in 1895.[22] He had been with Hoechst for three years, during which time he set up their antitoxin production. He left acrimoniously, suspicious that he was being cheated out of some of the profits arising from his efforts, and would later establish his own company, the Behringwerke in Marburg, to compete with Hoechst.[23]

With Koch's Institute for Infectious Diseases and other clinical research monopolizing hospital space in Berlin, Ehrlich and his team had little opportunity to conduct controlled bedside trials. As it became clear that facilities at the Steglitz laboratory were inadequate and a move would be necessary, criteria of a preferred location were drawn up.[24] A large provincial town with ample hospital facilities to investigate the new experimental therapeutics would be preferable. The general scientific milieu was also important. Many places might have satisfied these requirements, but a number of characteristics made Frankfurt-on-Main stand out. There were a number of small medical research groups there, and particular expertise in pathology (Carl Weigert), laryngology (Moritz Schmidt-Metzler), and neurology (Ludwig Edinger)—three areas of special significance for studies of diphtheria and immunity. Futhermore, there was support from local interests, mobilized by Frankfurt's Mayor, Franz Adickes. Adickes made funds available for the construction of the new institute and used his influence among leading philanthropists to make them favourably disposed towards Ehrlich and his new venture.[25] But the most significant, if less stressed, factor was the proximity of two

[19] Annual Report for 1903, Hoechst Archive.
[20] Hoechst publicity material, Hoechst Archive.
[21] *Farbwerke vorm. Meister Lucius & Brüning*, op. cit., note 7 above, p. 29; Hoechst Archive.
[22] H. Schadewaldt, 'Emil von Behring', *Dictionary of Scientific Biography*, New York, Charles Scribner's Sons, 1971, vol. 1, pp. 574–8.
[23] *Die Zusammenarbeit*, op. cit., note 7 above, pp. 101 ff.
[24] Bäumler, op. cit., note 2 above, pp. 68 ff.
[25] Ibid.

https://doi.org/10.1017/S0025727300050274 Published online by Cambridge University Press

chemical companies with which Ehrlich was already on good terms, Hoechst, just outside Frankfurt, and Leopold Casella & Co. nearby.

Even before the establishment of the Frankfurt Institute in 1899, Ehrlich had had extensive professional and commercial contacts with Hoechst. In correspondence with August Laubenheimer, the company's influential advisor and research director, Ehrlich described much of his work, always sensitive to the possiblity of new products.26 One clear example of this was his research in 1891 on methylene blue. In experiments with the nervous system of animals, he noticed that the dye distributed itself selectively within the body. He, and his collaborator, Paul Guttmann, also found that the dye could be effective against malarial symptoms in instances where the patient seemed resistant to quinine treatment.[27]

Ehrlich was always thereafter aware of the widest implications of this phenomenon of selective staining. In 1891 he stated his interest in developing methylene blue into a major therapeutic agent. "I know", he wrote, "that bacteria work at various sites to produce different diseases" and that it required much experimentation to make correlations between location and pathogen, and then further experimentation to find substances which transmit antibacterial agents to those sites.[28] This early work with methylene blue was one of a number of projects which led to the elaboration of Ehrlich's side chain theory of immunity. It also resulted in a patented antipyretic which Hoechst successfully developed and marketed in 1893.[29]

GOVERNMENT-INDUSTRY LINKS

In 1899 the re-constituted Royal Institute for Experimental Therapy, formed out of the old Institute for Serum Research and Serum Testing in Steglitz, was established on a site provided by the city of Frankfurt, adjacent to what later became the university and the main hospital complex. It was opened by ministerial and local goverment dignitaries, along with others from nearby universities, hospitals, and, of course, from the Hoechst company.[30] The Hoechst presence was somewhat de-emphasized by the expedient of listing non-company affiliations for some of its representatives at the ceremony, perhaps in response to expressed fears that, with such obvious close ties, the government laboratory would become in effect "das Institut der Hoechster Farbwerke".[31]

The newly-stated functions of the Frankfurt Institute were clearly expressed and differentiated. Its purposes were, to test all the government-controlled sera; to serve as a hygiene and bacteriological laboratory to the city, including local hospitals and

[26] Hoechst AG, *Vorarbeiten zum Salvarsan*, vol. 14, Dokumente aus Hoechster Archiven, 1966; Hoechst AG, *Um die Zubereitung des Salvarsan, 30 Briefe Paul Ehrlichs an Hoechst—Ein Beitrag zur modernen Galenik*, vol. 19, Dokumente aus Hoechster Archiven, 1966.

[27] P. Ehrlich and P. Guttmann, 'Ueber die Wirkung des Methylenblaus bei Malaria', *Berl. klin. Wschr.*, 1891, **39**: 420, 483, 506, 551.

[28] Ehrlich to Laubenheimer, 1891, Hoechst Archive.

[29] Parascandola and Jasensky, op. cit., note 4 above; Antipyrene papers, Hoechst Archive.

[30] Walter Greiling, *In Banne der Medizin. Paul Ehrlich, Leben und werk*, Düsseldorf, Econ, 1954, p. 113.

[31] Ibid.

https://doi.org/10.1017/S0025727300050274 Published online by Cambridge University Press

individual physicians; and to explore the basis of immunology, and in particular serology, from a theoretical standpoint.[32]

To be able to integrate these functions, the organization of the Institute had to be complex. The major official function—to test sera and vaccines—was put aside in a minor department, while whole research groups were devoted to those areas deemed to be of the greatest theoretical interest. By 1905 there were four main departments. The product-testing department was responsible for setting standards and certifying products sent to it. The experimental biology department was nominally also concerned with testing diphtheria antitoxin, but from 1904 was more deeply involved with general haematology. This again combined two broad functions. On the one hand, the staff was meant to conduct tests on behalf of the public health and medical authorities in Hesse-Nassau, Rhineland, and Westphalia; on the other, they pursued their own research along lines directed by Ehrlich into the theory of complement fixation and into the theory of proteins in combination and their production into antibodies. Hans Sachs became head of this department. He structured his work around the side chain theory and most of the experiments there were set up as assessments of the interactions between toxins and antitoxins, or the specific affinities associated with polyvalent sera.[33]

The third, so-called "bacteriology and hygiene" department, headed by Albert Neisser, was conceived as a service sector for Frankfurt hospitals and private physicians. Most of its work came in through apothecaries who were provided with sterile kits for physicians to collect sputum suspected of containing diphtheria bacilli (Klebs-Loeffler). In its early years, the scale of this operation was small compared with similar services provided by city health departments in New York and Philadelphia.[34] In Frankfurt only one or two samples were tested daily until 1903, when there was a serious diphtheria epidemic. The number of tests then approached five daily. More importantly, the department was to organize notification procedures for the public-health and hospital authorities. Again, in contrast to comparable operations in the United States, the Institute did not distribute antitoxin directly, but rather advised the medical profession about which commercial products to use.[35] Standard testing for typhus also was introduced in 1903, possibly because in the period of increased testing during the diphtheria epidemic a large number of typhus cases were identified. In the same year, 1903, the number of miscellaneous samples tested began to increase greatly, so that within a couple of years ten culture analyses were being performed each day, about a third of which were conducted on behalf of the city hospitals. In addition, 145 Frankfurt physicians were served, and a smaller number from surrounding areas. The relationship between the laboratory's functions

[32] Kolle, op. cit., note 8 above, p. 10.

[33] Siefert, op. cit., note 6 above, G. Eissner and G. Heymann, '50 Jahre Chemotherapeutisches Forschungsinstitut Georg-Speyer-Haus', *Arzneimittelforsch.* 1956, **9**: 501–8; Paul Ehrlich, 'Das Königliche Institut für experimentelle Therapie zu Frankfurt a/M', in *Festschrift z. XIV. Internationaler Kongress für Hygiene und Demographie, Berlin, 1907, Medizinische Anstalten auf dem Gebiete der Volksgesundheitspflege in Preussen*, Jena, Fischer, 1907; Kolle, op. cit., note 8 above, pp. 1–60.

[34] J. M. Liebenau, 'Public health and the production and use of diphtheria antitoxin in Philadelphia', *Bull. Hist. Med.*, 1987, **61**: 216–36.

[35] Kolle, op. cit., note 8 above.

https://doi.org/10.1017/S0025727300050274 Published online by Cambridge University Press

as a testing facility and as a promoter of antitoxins was close indeed. In a sense, the government laboratory was simply unofficially endorsing Hoechst biologicals.[36]

An additional function became associated with the third department when Neisser was appointed head of a training school for public health workers in Wiesbaden. This led to its further involvement with general public health work, including experiments and tests on water and milk, and aid to the work of disinfectors. Even this activity was not limited to the public sector, and the laboratory freely certified products and facilities for private concerns. This busy and outward-looking department also functioned as a specialized public-health training facility, teaching bacteriology to government disinfectors, water workers, and others, while co-ordinating with courses offered elsewhere.[37]

Moreover, the bacteriology and hygiene department was not divorced from the theoretical work at the heart of the Institute—elucidating the side chain theory. In this role it served primarily as a source of material for the rest of the Institute, but Neisser also collaborated on the more theoretical investigations. In addition to his publications on bacteriological technique and public health, Neisser published (with Ehrlich's senior assistant Kiyoshi Shiga) on free receptors in typhus and dysentery—a central issue for the side chain theory—and defended Ehrlich against Svante Arrhenius, whose competing agglutination theory had significantly different implications for research programmes.[38]

In 1902, along with the general expansion of the Institute's range of activity, a cancer research section was established. Growing out of general work on histology, a large-scale investigation of carcinomas in mice was begun. It too was organized under the general direction of Ehrlich. Its primary technique was to alter the conditions of tumour transplants to investigate the serial virulence of cancer cells in recipients and the response of the immune system to foreign bodies. This was a very large-scale and long-term investigation, involving analytical techniques which were later to be central for chemotherapeutic experiments.[39]

A further function of the Institute was to train Frankfurt physicians in new theories and laboratory techniques. Ehrlich gave weekly lectures on either immunology or haematology, while Neisser offered a series on either bacteriological techniques or hygiene and epidemiology. From 1902, when two military surgeons were assigned to the institute, regular courses on "*Kriegshygiene*" (military hygiene) were added to the curriculum.[40] Teaching military hygiene was not unique among medical institutions. The link between medical research and the growing military state was explicitly expressed in 1907 by the motto embellishing the new wing of the Kaiser Wilhelm military surgeons' training academy:[41]

[36] Ibid.

[37] Ibid., p. 13; Ehrlich, op. cit., note 33 above, pp. 98–101.

[38] M. Neisser and K. Shiga, 'Ueber freie Rezeptoren von Typhus- und Dysenteriebazillen und ueber das Dysenterietoxin', *Dt. Med. Wschr.*, 1903, **29**: 61. See also Rubin, op. cit., note 4 above.

[39] Kolle, op. cit., note 8 above, pp. 20–2; Janina Hurwitz, *Paul Ehrlich als Krebsforscher*, Zurich, Juris, 1962; Ehrlich, op. cit., note 33 above, pp. 101–4. Bäumler (op. cit., note 2 above, p. 83) gives 1901 as the date of establishment, but it was not in operation until the next year.

[40] Ehrlich, op. cit., note 33 above, p. 102.

[41] "Pure science/True humanity/Self-sacrificing patriotism". *Stabsarzt* Dr Ridder, 'Der Neubau der Kaiser Wilhems-Akademie für das militärärztliche Bildungswesen' in *Festschrift*, op. cit., note 33 above.

https://doi.org/10.1017/S0025727300050274 Published online by Cambridge University Press

For all its differing tasks, the Institute's uniting function was to supervise the production of sera. In 1906, the first year of the publication of its *Arbeiten*, the Institute presented its report to the industry and the medical community on 'The government tests of antitoxins'.[42] At that time, four products were routinely tested: diphtheria antitoxins, tetanus antitoxin, tuberculin, and an erysipelas serum of recent origin. In addition, a variety of products falling into intermediate categories were analysed for purity. All producers were liable to inspection, and any firm which wished to introduce a new product into the market had to have it certified by the Ministry of Health. In order to satisfy the certification requirements, the firms needed to have a specified number of trained personnel who were required to maintain strict records of manufacture and sale, and had to submit to other government controls via the laboratory.[43]

Ehrlich's work at the Institute was productive and fulfilling. Its three functions of testing, servicing, and researching operated well, and his staff helped to administer an efficient laboratory. Ehrlich was, however, concerned about the indiscriminate impact of the Institute and in 1904 he wrote a strong polemic against what he saw as a great threat to the future of medicine. His organization and techniques had led to a proliferation of products and a loss of the control which he had maintained over biological medicines. The research front, Ehrlich believed, was moving away from the unfinished task of producing curative drugs, while manufacturers continued to offer even longer lists of products.

> To the initiate, the lack of sufficient positive knowledge is revealed by the inactivity which now characterizes a field once entered upon with so much promise. The innumerable drugs which have overwhelmed medicine in the past few years, of which only a few are of any value and thus denote any real progress, have sufficed speedily to allay the original enthusiasm. A feeling of indifference has thus been engendered, which is constantly being increased by the advertisements which are daily becoming more and more evident. Apart from these evils, however, this line of study is at present suffering especially from two other evils:
>
> 1) the habit, when a drug has been partly accepted, of immediately following it with a dozen rivals of similar composition, and
> 2) the exclusive preference given to drugs acting purely symptomatically, which are not true curative agents.[44]

He was not inclined to blame the producers and advertisers of such rivals and false cures, but rather the dominance of a chemical, as opposed to the biological and medical, way of thinking. "A change for the better will occur only when purely

[42] *Arbeiten aus dem Staatsinstitut für experimentelle Therapie*, 1906.
[43] Ehrlich, op. cit., note 33 above, pp. 92–6.
[44] *Collected papers*, op. cit., note 14 above.

https://doi.org/10.1017/S0025727300050274 Published online by Cambridge University Press

biological points of view are adopted, i.e. if the initiative is transferred from the chemical to the biological laboratory." This required positive action to recover control of treatment, and to make theoretical therapeutics a part of practical medicine. Only thus could physicians be sure that medicine did not become subordinated to chemistry.

> As physicians we must cease to be content with the auxiliary role of advisers in these important questions. In this subject, our very own since time immemorial, we must insist on taking first place. Now is the time that we must turn to more general, biological conceptions, and it is therefore the duty of everyone to contribute his brick to the construction of this new therapy.[45]

Ehrlich's bricks soon took the form of walls as he worked toward the establishment of a new institute, devoted solely to this programme of research based on biological conceptions.

One of the philanthropists closest to Mayor Adickes was the prominent Frankfurt Jew, Georg Speyer. Speyer's family had been city financiers for many generations and their wealth and seniority within the Jewish community placed them in the central position among local benefactors.[46] Their Foundation was the mainstay for such institutions as the Jewish orphanage, old-age home, hospital, and cemetery. In 1902, upon the death of Georg Speyer, Franziska Speyer began plans to establish another medical institution in the city, this one to facilitate research in general medicine[47] perhaps along lines similar to the Rockefeller Institute for Medical Research, founded that year in the United States. Frau Speyer was sister-in-law to the leading Berlin chemist, Ludwig Darmstaedter, who in the past had given advice about medical and scientific philanthropic activities to the Foundation, and sat on its board.[48] The connection with Paul Ehrlich was easily established when Darmstaedter sought him out.

When Ehrlich, the most prominent medical scientist in the city, made known his views about the need for a biologically-oriented research programme, Darmstaedter was receptive and conceived a plan for the Foundation.[49] Rather than create a general research institute, Ehrlich wanted to perform a large number of specific tasks. For him, the most challenging and rewarding medical problems were to be found in toxicology, pharmacology, and therapeutics. These he conveniently split into the study and use of such biologically-devised agents as the antitoxins, and such synthetically-produced drugs as the methylene blue compounds being used as antipyretics.[50]

The research methods appropriate to these two kinds of agent were significantly different, and a separate institution for the sole purpose of chemotherapeutic research would also be useful. Ehrlich's wishes were used as a guide in the planning for the

[45] Ibid.
[46] Speyer papers, Frankfurt Stadtsarchiv; see also Eissner and Heymann, op. cit., note 33 above.
[47] Ibid.
[48] Ibid.; Bäumler, op. cit., note 2 above, chapters 5, 8, 9.
[49] Darstaedter's report to Speyer Stiftung, Speyer papers, Frankfurt Stadtsarchiv.
[50] Ibid.

https://doi.org/10.1017/S0025727300050274 Published online by Cambridge University Press

Georg Speyer Haus, which opened in 1906. He explained its purpose in the following way:

> Here we shall still be concerned with the problem of curing organisms infected by certain parasites in such a way that the parasites are exterminated within the living organism, so that the organism is disinfected, but in this case, not by the use of protective substances produced by the organism itself through a process of immunization, but by the use of substances which have had their origin in the chemists retort. Thus, the task of the new institute will be a *specific chemotherapy of infectious diseases*. It is easy to see that this line of approach, by its very nature, must be a much more difficult one than that of serum-therapy. Magic substances like the antibodies, which affect exclusively the harmful agent, will not be so easily found in the series of the artificially produced substances.[51]

The model for even this specific form of programme was already available. Earlier research on various arsenical-dye anti-trypanosome substances had been supported by the Bayer Farbwerke, which prepared several hundred specified compounds for testing.[52]

In further describing his ambitions for the new laboratory, Ehrlich reconstructed the intellectual process which had led him to conceive his new programme. Central was the notion that the distribution of a substance within the body was an issue different from the specific activity of that drug. The empirical task could be split into the "construction of organotropic medicaments", and the process of attaching them to the appropriate pharmaceuticals. "We intend", he explained, "to use certain chemical complexes as vehicles to carry appropriate pharmacophore groups to the desired types of cells".[53] Through this process, new products could be conceived which would contribute to the primary purpose of such a programme: the discovery of new, rational, curative remedies. And this task, Ehrlich believed, could best be performed in partnership with the chemical industry "which", Ehrlich stated, "has devoted its best resources to the service of medicine".[54]

Contacts with Hoechst grew even closer. The new line of research generated a larger number of substances on which the company could take out patents on Ehrlich's behalf. During this period before the patenting of Salvarsan, in 1909, Ehrlich had an average of 8–10 substances patented a year.[55] These did not include every tested chemical produced in the series, but most of those of any significant therapeutic effect, whether as a germicide of low toxicity or as a febrifuge, were patented. Salvarsan was developed at the Speyer Haus, controlled by and with the backing of the government institute, and patented, produced, and marketed worldwide by Hoechst.[56] Salvarsan remained a *cause célèbre* in medicine through the

[51] P. Ehrlich, 'Address delivered at the dedication of the Georg-Speyer-Haus' (1906); *Collected papers*, op. cit., note 14 above, vol. 3, pp. 53–63, on p. 60.

[52] Bäumler, op. cit., note 2 above, see also P. Ehrlich and K. Shiga, 'Farbentherapeutische Versuche bei Trypanasomener krenkungen', *Berl. klin. Wschr.*, 1904, **13**, **14**: 421, 546, 584.

[53] Ibid., repr. in *Collected papers*, op. cit., note 4 above, vol. 3, pp. 24–9.

[54] Ibid. See also Bäumler, op. cit., note 2 above, pp. 107–30.

[55] Drawn from counts of patents in the *U.S. Patent Register*, 1906–9.

[56] See Hoechst AG, *Die Salvarsan-Prozesse*, vol. 7, Dokumente aus Hoechster Archiven, 1965.

https://doi.org/10.1017/S0025727300050274 Published online by Cambridge University Press

First World War. Up to the time when the overseas patents were revoked, it earned a tremendous amount of money, not to mention the boost it gave the company's reputation.[57]

Salvarsan seemed to be the culmination of Ehrlich's programme. It caused him a great deal of trouble since he was constantly called into court to defend himself against all kinds of affronts, but even so, to him it justified the Speyer Haus:

> for the first time a new type of therapeutic institution was formed, in which my dearest thought was realised, by chemical syntheses being applied to the service of medicine in the most direct way. Whereas, formerly, the substances were offered to the medical men by the chemist for testing purpose, the conditions could now be reversed, and the chemotherapist could give the chemist points which led to the desired recovery of genuine curative substances.[58]

It is certain that the Hoechst Company saw the Georg Speyer Haus as an extension of their own laboratory. This is clear from their archives and internal memoranda. Each change in the research programme or in the staffing of the Speyer Haus laboratory was noted and commented upon. From the company's point of view, the Institute was a close ally. Far from there being any distrust between regulating authority and those being regulated, the staff in Frankfurt were seen almost as part of the firm. Informal contact was frequent, and samples and test runs were often provided by one for the other.[59] When Neisser went on an expedition in 1905 to study the spread of syphilis in a monkey colony, he reported back to the company, which had provided him with chemicals and special preparations, just as he gathered material for the Institute's syphilis experiments.[60] Similarly, when Wilhelm Kolle, later to head the Institute and the laboratory, was offered the directorship of a large new pharmaceutical department at Casella, it was considered as much a part of Hoechst's business as if he were their employee.[61]

Casella also contributed to research at the Georg Speyer Haus, although Ehrlich's ties with Hoechst precluded the possibility of his rewarding that firm with patents. Instead he allowed them to use his name in association with some products, and provided them the valuable publicity of acknowledging their aid and support. The Institute also received a percentage of the profits as a fee for testing services.[62]

For the pharmaceutical industry, Ehrlich and his institute were a legitimate part of the nation's commercial development. Just before the outbreak of the First World War, Carl Duisburg, then director of Bayer, summed up his feelings about trends in the industry by extolling the advantages of applied science:

> First, we need a fully equipped chemical laboratory, then a pharmacological institute with a staff of men trained in medicine and chemistry, an abundance of

[57] Ibid.
[58] *Collected papers*, op. cit., note 14 above.
[59] Bäumler, op. cit., note 2 above, pp. 124–5.
[60] File on Neisser expedition 1905, Hoechst Archive.
[61] Speyer Stiftung Papers, Cassella File, Frankfurt Stadtsarchiv.
[62] Ibid. See also T. S. Work, 'The work of Paul Ehrlich and his position in the history of medical research', *Int. Archs allergy appl. Immun.*, 1954, **5**: 98–114.

https://doi.org/10.1017/S0025727300050274 Published online by Cambridge University Press

> animals to experiment upon, and finally—the latest development in this field—a chemotherapeutic and bacteriological department, equipped according to the ideas of Paul Ehrlich; all these must be in close connection with one another.[63]

When William Kolle took over the Institute for Experimental Therapy he maintained the relationship between Hoechst and the combined laboratories of the Institute and the Georg Speyer Haus in the post-war period. Their collaborative functions centered on Salvarsan, where the three bodies saw their interests as being identical. Much of the correspondence concerns the defence of their patents both in Germany, where they were being copied illegally, and overseas, where numerous producers had taken advantage of the expropriation of German-held patents to make their own branded Salvarsan.[64]

This particular array of institutions, intellectual goals, governmental functions, political necessities and profit-seeking motives—expertly balanced by Ehrlich—had wide influence. Within that context the most exciting therapeutics of the age were developed, by monopolizing the new antitoxins of the mid- to late 1890s, and then by developing and controlling the first widely used chemotherapeutic agents.

Ehrlich's goal, exemplified in the Georg Speyer Haus, was to free physicians from the threatened grip of chemists and produce specific synthetic agents which could be targeted at particular pathogens. This project necessarily, and probably preferentially, had the co-operation of the pharmaceutical industry. With Hoechst, this co-operation reached its height. Hoechst had already seen the benefits of a concerted research effort—its lead in diphtheria antitoxin, for which Behring was responsible, had assured the company that it could best set the standards which it had a hand in producing. Its success with Pyramidon had indicated early on how control over a new synthetic product could benefit its business. Long before the programme to produce an arsenic-based anti-trypanosome, Hoechst had mastered the uses of patents. It used their powers not only to capitalize on medicines it had developed and produced, but also to control the flow of information about developments elsewhere.

From the points of view of the Speyer Haus and the government Institute there were no problems associated with Hoechst's use of their developments. The partnership had been built on an understanding that the regulator should work in close co-operation with the major producer of antitoxins. To support a research programme of the ambitiousness of Ehrlich's, the backing of the companies was required. They were needed to finance the work in the first place and to control the production in a trustworthy way. The patents also had to be owned and defended by a powerful organization. Ehrlich also needed that power, to be able to control the vast productivity of his research team. Furthermore, the products of the research itself could not be made available until after the work was finished to the standards of the laboratory. A strong commercial force was an essential partner for Ehrlich.

[63] C. Duisberg, 'German chemical industry', *Chem. News*, May 1913, **23**: 246–7.
[64] *Salvarsan-Prozesse*, op. cit., note 56 above.

https://doi.org/10.1017/S0025727300050274 Published online by Cambridge University Press