TIMELINE

Paul Ehrlich: Magister Mundi

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Abstract | Paul Ehrlich, a founding father in fields across a wide range of medical sciences, was born 150 years ago. To mark this anniversary, this article gives an overview of his life, highlighting his major scientific contributions and paying tribute to Paul Ehrlich the man.

"You had a sensitive soul. Forgive us if, at times, we hurt you." Emil von Behring, the creator of serum therapy, said only these few words at the funeral of his long-time colleague, friend and, at times, opponent Paul Ehrlich. He had prepared a much longer speech for this occasion, but his own failing health and the emotional strain of the situation did not allow him to deliver a lengthy funereal oration. Later, in a published obituary, von Behring wrote: "With you, Paul Ehrlich, someone from the heroic period of experimental and therapeutic science has gone. You have become the 'Magister Mundi', the teacher of the world in the medical sciences. Rest now from a laborious but fruitful life's work. You have fulfilled an important mission for the progress of human knowledge and accomplishment. Farewell, dear soul."

Paul Ehrlich (FIG. 1), born on 14 March 1854, belonged to the first generation of German Jews who were free to make their own professional choices and who subsequently contributed so successfully to German society. Ehrlich's ancestors had been distillers, traders and inn keepers. His father was a lottery collector and chairman of the Jewish community in the small town of Strehlen in Lower Silesia, where Ehrlich was born. Their professional orientations had still been constrained by rules that had been imposed on Jews in earlier centuries.

Among his great contemporaries, such as Robert Koch and Emil von Behring, Ehrlich stood out in several ways. First, he was both a great conceptualizer and a highly talented experimentalist. At his command was a remarkable gift of abstraction, as well as the ability to translate complex scientific findings into medical practice. Second, among the biologists of his days, Ehrlich was uniquely far-sighted in recognizing the role of chemistry for bringing accuracy to, and unifying concepts in, medicine. Last, and perhaps most importantly, Ehrlich had a singular talent for asking deceptively simple but powerful and far-reaching questions. Perhaps it was this combination of qualities that made Paul Ehrlich the most universal medical scientist of his time.

Ehrlich became best known as the founder of chemotherapy (TIMELINE; BOX 1), and as a major force in theoretical and practical immunology. However, he also made important contributions to histology, provided the morphological and functional basis for clinical haematology, and greatly enriched medical diagnostics through clinical chemistry. His almost single-handed creation of chemotherapy provided important clues to the burgeoning fields of pharmacology and to drug research in general. The very concept of chemotherapy, and his classification of cancer cells as 'feindliche Brüder' (hostile brothers), would suggest that Ehrlich's contributions to experimental cancer research were largely motivated by therapeutic intentions. However, his famous monograph *On Carcinogenesis*, written with H. Apolant in 1908, makes it very clear that Ehrlich's approach to this field was largely cell-biological and immunological in nature. Ehrlich introduced into experimental oncology the study of transplantable tumours; some of the animal models that he and his co-workers first created lasted well into the second half of the twentieth century and are even used today, if only occasionally.

Finally, we should not forget that Ehrlich worked as a staff physician for many years. Several publications give testimony to his superb ability to observe, describe and interpret clinical phenomena, and he retained an intense interest in pathophysiology until the end of his life.

In this article, I will provide an overview of each stage of Ehrlich's career, highlighting his major scientific achievements across a range of fields, including histology, haematology, bacteriology, immunology and chemotherapy. Further information on Paul Ehrlich can be found in REFS 1–6.

Histology

It all started with histology. During a histology course in the laboratory of the famous anatomist Wilhelm Waldeyer (1836–1921) in Strasbourg, Ehrlich became deeply involved with new staining techniques, especially using aniline dyes, which had just been discovered and were still at the centre of the attention of many chemists. It is possible that Ehrlich's initial fascination was largely aesthetic in character; now, under Waldeyer's guidance in Strasbourg, dyes became a scientific passion. In 1877, he published his first paper on the use of aniline dyes in microscopic technology; one year later he acquired his medical Doctor's degree with a thesis on "the theory and practice of histological staining", which he submitted to the University of Leipzig.

These early contributions to histology were only the beginning. There was much more to be learned from the interactions of dyes and biological structures. Why do certain structures take up eosin or malachite green whereas other tissues stain with these dyes only weakly or nor at all? There must be strong affinities between biological structures and certain dyes, Ehrlich concluded. Soon, he generalized this statement to include other

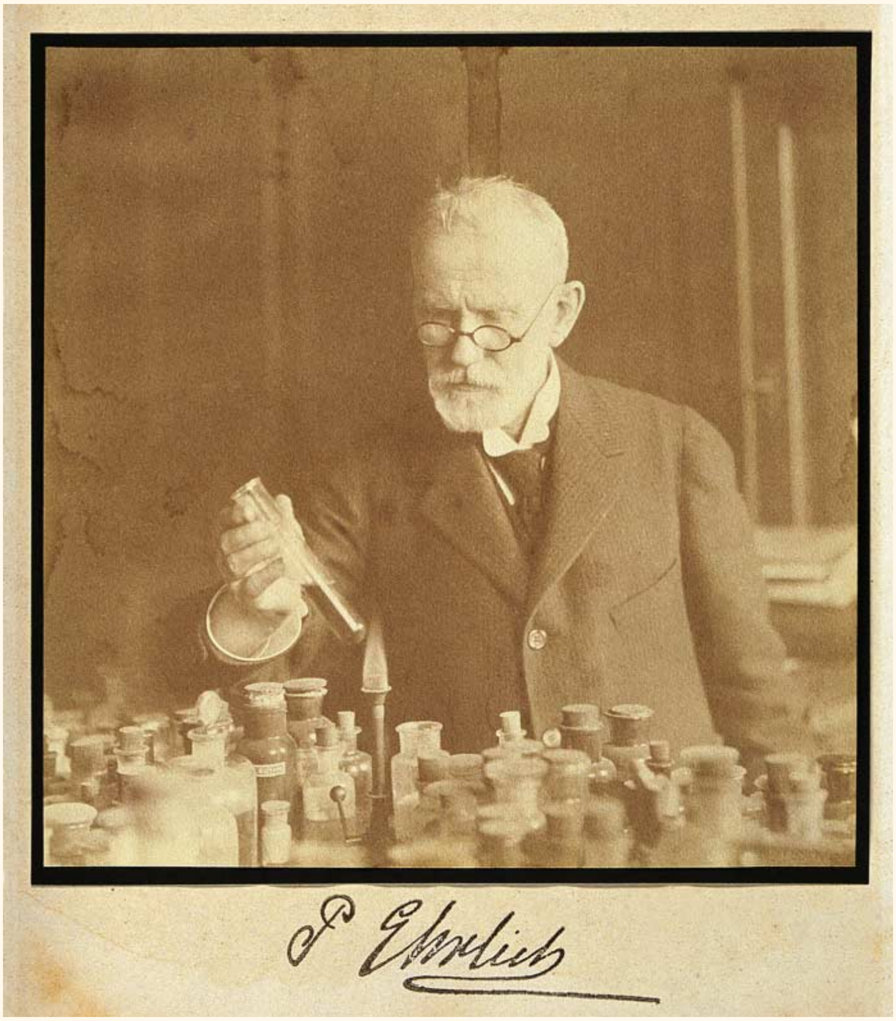

Figure 1 | **Paul Ehrlich.** Photograph, 1915. Courtesy of the Wellcome Library, London.

chemicals that were not dyes, but he also recognized that dyes offered the special opportunity of visualizing and eventually quantifying the affinities of dyes with biological structures. By also applying his staining techniques to living animals, he noticed that methylene blue stained nerve axons not only in dead tissues, but also in the living animal. A decade later, these experiments led to pharmacological studies on the analgesic effects of methylene blue and even later to the finding that this dye could be used to treat malaria tropica. *Corpora non agunt nisi fixate* — a drug will not work unless it is bound — became an axiomatic statement that guided Ehrlich through many scientific disciplines.

Haematology

Ehrlich's staining techniques enabled him to distinguish between the different types of white blood cell. He became the first scientist to characterize mast cells by their basophilic granules and to identify these cells as a structurally and functionally distinct type of cell. In 1879, he described eosinophil cells as yet another type of white blood cell. It was largely on account of these studies that Friedrich Theodor Frerichs, one of the leading physicians of his time and director of the medical clinic at the Charité in Berlin, offered Ehrlich the position of an assistant. During his stay at the Charité, Ehrlich invented many novel methods of staining that allowed the characterization and quantification of blood cells; this was seminal work that provided haematology with a firm cytological basis. Ehrlich stayed at the Charité as a senior house physician until 1899, but his publications on haematological topics continued until 1902. By that time, his contributions to the morphology and function of various leukocytes, as well as his seminal studies on anaemias, had earned him a solid reputation — so solid indeed, that another famous haematologist, Maxwell Wintrobe, later called Ehrlich "the father of haematology".

Bacteriology and immunology

On 24 March 1882, Ehrlich attended Robert Koch's historic lecture on the aetiology and pathogenesis of tuberculosis. Koch presented irrefutable evidence for the bacterial causation of this disease. His method of staining, however, was not yet ideal. It needed improvement, which Ehrlich was able to provide within a few months; Ehrlich in turn received Koch's recognition and attention, and in 1887 Ehrlich became a Privatdozent (lecturer at the medical faculty).

During the years at the Charité, Ehrlich's career seemed to be focused on a single topic: the use of various dyes and related chemicals for the study of biological systems and, consequently, the development of new diagnostic and therapeutic procedures. Two events, however, interrupted the continuation of this course. In 1888, Ehrlich was diagnosed with tuberculosis and was advised to travel to milder climates, and to take a break from work. Together with Hedwig Pinkus, whom he had married in 1883, he left Berlin and embarked on what might have been the only extended journey that Ehrlich undertook for pleasure and personal reasons. The couple visited Italy, spent the winter in Egypt and returned to Germany during the next spring via Malta and Sicily. Back in Berlin, Ehrlich felt fully restored. Koch now invited him to join him at his new Institute for Infectious Diseases, which, during the coming years, was to become a hotbed of international bacteriology and immunology.

This professional move led to another event that would influence Ehrlich's further development. A year earlier, Emil von Behring had joined Koch. von Behring and his Japanese colleague Shibasaburo Kitasato had just published a landmark paper on bacterial toxins and antitoxins, inspired by Pasteur's groundbreaking studies on immunity against rabies. Aided by the fact that they were now united under one roof, Ehrlich and von Behring started to cooperate. Ehrlich utilized his results from earlier work on the plant toxins abrin and ricin to develop new immunization schemes for diphtheria toxin. It was through Ehrlich's contributions that the breakthrough made by von Behring and Kitasato gained medical applicability. Ehrlich designed immunization schemes that resulted in high antibody titres. Moreover, he pointed the way to using large animals, particularly horses, for the commercial production of antidiphtheria serum. In parallel to this work, he showed that antibody immunity was transferred from mother to foetus through the placenta, and later through the milk. Most importantly, however, he developed methods to standardize sera with respect to

Timeline | The emergence of chemotherapy

- **1873** Paul Ehrlich, then a medical student at the University of Strasbourg, experiments with histological staining. An 1871 paper by Emil Heubel on lead poisoning, which showed that lead is taken up by human organs in a highly selective fashion, was an important starting point.
- **1890** Ehrlich and Leppman show that methylene blue interacts preferentially with nerve tissue and has analgesic effects.
- **1891** Ehrlich and Guttmann use methylene blue in the treatment of malaria; two patients experience clinical remissions.
- **1902** Laveran and Mesnil show Na-arsenate to be effective in experimental trypanosomiasis in mice.
- **1902/1903** Ehrlich and colleagues experiment with benzo dyes in experimental trypanosomiasis. Ehrlich, together with Sachs, discovers triphenyl-methane, which also works in experimental trypanosomiasis.
- **1907** Ehrlich finds atoxyl (*p*-aminophenyl-arsenic acid).
- **1909** Ehrlich and Bertheim synthesize Salvarsan.
- **1909–1914** Final formulation of the principles of chemotherapy.
- **1920** Effectiveness of suramin for sleeping sickness is shown — a direct consequence of work on the trypanocidal effect of dyestuffs by Ehrlich, Mesnil, Laveran and colleagues. Other antiparasitics follow, such as pentamidine (1939), primaquine (1946) and melarsoprol (1949).
- **1929** Fleming discovers the antibiotic penicillin.
- **1935** Domagk discovers the antibacterial action of prontosil, the first drug in the sulphonamide class. Fuller later shows that sulphanilamide is the active principle of prontosil.
- **1942** Diversification into anticancer agents; alkylating agents are discovered by Goodman and Gilman. Many others follow, such as aminopterin (1948) and 5-fluorouracil (1957).
- **1946** Discovery of thiosemicarbazones as active agents against tuberculosis. Several other novel chemotherapeutic agents are also discovered, such as trimethoprim, methotrexate and ciprofloxacin.
- **1946** Diversification into antifungal chemotherapy — the isolation of griseofulvin from *Penicillium griseofulvum* — inspired by antibacterial work with penicillin and thyrotricin. The discovery of other antifungals follows: amphotericin B (1955) and imidazolyl antifungals (1969).
- **1959** Diversification into antivirals; iododeoxyuridine, an antiherpetic for eye infections, discovered by Prusoff. Followed by many others, such as amantadine (1960), methisazone (1963), adenine arabinoside (1978) and acyclovir (1980).

antibody concentration. Immunity in Ehrlich's definition was quantified as "the multiple" of the lethal dose of a toxin that is tolerated by the immunized animal. This work provided the basis for producing antidiphtheria toxin on an industrial scale. In 1908, this achievement was rewarded with the Nobel prize for Physiology or Medicine. Ehrlich shared the prize with the Russian immunologist Eli Metschnikoff, who had discovered phagocytosis.

Antibodies against toxins also fascinated Ehrlich in a fundamental way. Because of their ability to precisely address certain chemical groups on target molecules, Ehrlich called them 'magic bullets'. This term was borrowed from the romantic opera *Der Freischütz* by Carl Maria von Weber, in which a man sells his soul to the devil for a number of magic bullets, which will enable him to win a marksmanship contest and with it the hand of the lady he loves. In Ehrlich's language, magic bullets were molecules that bound to parasites or their toxins with the highest possible affinity and displayed very low affinity, if any, for the 'haptophoric' groups (binding groups) of the host. The term was born out of his immunological work, but was later also used in connection with synthetic molecules, which were aimed at specific biological targets.

In an attempt to explain the generation of these enigmatic antibody molecules, Ehrlich postulated that the cells of a mammalian organism carry a great number of side chains (receptors) on their surface. If a toxin such as diphtheria toxin is released into the organism, it binds to one of the side chains to which it has high affinity. The side chain that carries the toxin is now useless for the cell and is therefore shed into the circulation. Consequently, the cells express more receptors of the same kind on their surface. This response of the organism tends to be redundant: more side chains of a particular type are synthesized and shed into the bloodstream than are actually needed.

This 'side-chain theory' contained three ideas that became central to the modern view of antibody generation: first, the existence of specific receptors to bind antigens; second, the identification of these receptors as antibodies, which are formed in large numbers as a response to receptor occupation; and third, the redundancy of the response. Ehrlich's side chains are analogous to B-cell receptors; side chains were also envisaged to be antibodies — again, analogous to present-day knowledge of B-cell receptors. On binding the respective antigen, a B lymphocyte multiplies through clonal expansion. The receptor (antibody) is then produced at high rates in a population of expanded B cells that differentiate into plasma cells.

Chemotherapy

In 1899, Ehrlich and his family moved to Frankfurt, where he became the director of the newly established Royal Institute for Experimental Therapy. This institute took the place of the smaller Institute for Serum Research in Berlin-Steglitz, which had served as the hub for serum standardization in Germany under Ehrlich's directorship since 1896. The new institute continued this service function on a broader and greatly modernized basis. In addition, it had a department dedicated to the study of basic immunology. Ehrlich now had an institute that would in time become a suitable instrument for his immunological and immunotherapeutic studies. He and his wife took residence in a modest but beautiful home in Frankfurt's noble Westend.

A few years later, Ehrlich also found his ultimate place of activity for further developing chemotherapy. The new institute, called the 'Speyer House', was founded by Franziska Speyer in memory of her husband who had died of cancer. It was intended to be an important first step to establishing a university in Frankfurt. Ludwig Darmstädter — a friend of the Speyers, an accomplished chemist, entrepreneur, man of letters and also a friend of Ehrlich — persuaded Franziska Speyer to place the institute under Ehrlich's directorship and to let him determine its scientific course. As a stroke of good fortune, the new institute could be erected on land immediately adjacent to the Royal Institute of Experimental Therapeutics at Sandhofstrasse no. 44. Ehrlich had found his 'empire'.

He had to hire new staff: two chemists and a physiologist, Wilhelm Roehl, who later became known for developing the first agent

Box 1 | Paul Ehrlich and the emergence of chemotherapy

Ehrlich's chemotherapy led directly into antibacterial chemotherapy. Prontosil, discovered in 1935 (TIMELINE), is the sulphonamide of chrysoidin, a dyestuff that had been used as a urinary disinfectant. It turned out that the dyestuff was not essential for the *in vivo* activity; rather, the sulphanilamide moiety was responsible for the antibacterial efficacy. And in the antiparasitic field, the discovery of the effectiveness of suramin for sleeping sickness, and of primaquine for malaria, represent achievements that can be traced back directly to Ehrlich's work on dyestuffs (suramin) and arsenicals.

Other lines of chemotherapy developed more indirectly: antibiotics have a tradition of their own, which started with a discovery by Pasteur and Joubert in 1877, and continued with many attempts to utilize what was then called 'microbial interference' therapeutically. However, this line of research did not gain much clinical significance until the development of penicillin. Antifungal chemotherapy started as a derivative of antibacterials research. Griseofulvin (TIMELINE) marks the 'branching point' at which a separate tradition of antifungal research was established. Oncological chemotherapy started with alkylating agents (TIMELINE) and included antibiotics and antimetabolites, and, more recently, monoclonal antibodies. Conceptually, this line of investigation owes much to Ehrlich. It has, however, no direct experimental (chemical) precedent in Ehrlich's work. Finally, antiviral chemotherapy emerged from antitumor chemotherapy, notably out of work with antimetabolites by Prusoff (TIMELINE).

against sleeping sickness at the Bayer laboratories. Most importantly, Sahachiro Hata, a student of Shibasaburo Kitasato, joined him in 1909. In setting the institute's course, Ehrlich went back to trypanosomes, but rapidly expanded the spectrum of pathogenic organisms to include spirillae and spirochaetae. A member of the latter group had just been identified by Fritz Schaudinn at the Charité as the causative agent of syphilis in man. At the beginning of the twentieth century, syphilis and its many clinical manifestations had become a scourge of mankind, comparable in its longtime threat to human immunodeficiency virus in our time.

As a chemical starting point, Ehrlich chose organo-arsenical compounds that he had used earlier in experimental trypanosomiasis. One of his collaborators, A. Bertheim, synthesized dioxydiaminoarsenobenzol, which later became compound 606. A single dose of this compound cured rabbits with syphilitic keratitis. In comparison with other arsenical drugs, 606 looked sensational. The strictly organized, deductive way in which Ehrlich and Hata exploited this class of compounds — checking chemical structure against biological activity, toxicity and distribution — preempted much of the methodology of finding drugs in the burgeoning pharmaceutical industry. Again, he was abiding by his own postulate "chemisch zielen lernen" (learn how to aim chemically), setting historical precedent once more.

Clinicians tried the new substance, cautiously at first, and then with greater assurance, as it seemed rather well tolerated. Compared with conventional therapy with mercury salts, the results were overwhelming. Hoechst became involved and produced the compound on an industrial scale, with Ehrlich and his team guiding the production and the standardization of their substance. Salvarsan, as the new drug was called, became what today's moguls of the pharmaceutical industry would call a 'blockbuster'. The effectiveness of a man-made drug raised expectations that went further than the elimination of the causative agent of syphilis could deliver.

Shortcomings became known: the chronic forms of syphilis (paralysis, aortic aneurysms and tabes dorsalis) did not respond so well. Moreover, the drug had to be dissolved in sterilized water before being injected intravenously. Many so-called side effects of Salvarsan turned out to be due to improper handling of the drug. In some cases, the rapid lysis of bacteria led to local reactions that could be attributed to endotoxin. Large sectors of the medical profession were not prepared to use a highly effective drug that had to be applied under sterile conditions. During 1912 and 1913, Ehrlich devoted most of his time and energy to guiding Salvarsan through its first phase of clinical use and towards developing a new version of the drug (Neosalvarsan) that avoided some of the shortcomings of its predecessor. Neosalvarsan was more effective than Salvarsan and caused almost no irritation when applied to mucous membranes.

Closing perspectives

Ehrlich was now at the pinnacle of his professional career. A street in Frankfurt was named after him, and he received the highest title that the German government could bestow on a scientist: 'Wirklicher Geheimrat', 'Real Privy Council' with the title 'Excellency'. Ehrlich's sixtieth birthday in March 1914 was celebrated as a great event. He was greeted and praised by many friends all over the world in numerous letters, telegrams and newspaper articles. His collaborators published a 'Festschrift' to which many of his famous teachers and students contributed.

However, there was also dissonance. Radical and anti-Semitic journalists launched a campaign against Salvarsan and its creator. These people argued that chastity and adherence to a frugal lifestyle were more adequate and morally acceptable means of defeating syphilis than Salvarsan. The cure of a disease, especially a sexually transmitted disease, should not become the source of a lucrative business. Some went so far as to suspect a Jewish conspiracy behind Salvarsan, but Ehrlich remained very calm in the middle of this turbulence. One of the protagonists of the smear campaign against him was tried and convicted to a year in prison.

In 1914, the First World War broke out. Ehrlich hated the idea of it. To a man of his international standing, the idea of civilized nations going to war with each other seemed like a regression into mediaeval patterns. "If a politician is not by nature a decent person, he should at least become one for the sake of reason." However, in a letter to a colleague in Spain he expressed the feeling that his country had a "clean conscience."

Ehrlich tried to continue his life of thinking, experimenting, exchanging views with his peers, smoking up to 25 cigars a day and eating very little. Journalists described his style of talking as mercurial: he touched on many subjects as they entered his broad scope of attention and showed his ability to connect seemingly unrelated topics. And yet if something really caught his interest, his mind could hold onto it like a steel trap. Ehrlich must have been charming in one-on-one conversations with people he liked. In such situations, he could display the richness of his imagination, his ability to think laterally while still keeping focused, and he could hold his friend or partner with probing looks from his blue eyes over the dark rim of his spectacles.

So many facets in one man, some of them appearing like contradictions: a brilliant conceptualizer but also a highly effective medical practitioner. A loyal German who nevertheless held strong cosmopolitan views. A director of two institutes who personally defined their overall goals and yet left his collaborators much latitude to find their own solutions to problems. A Jew who never practiced his religion but quietly held the beliefs of his ancestors in high esteem.

Ehrlich was convinced he had no artistic talents. Although he liked music, it did not speak to him very deeply; concerts to which he went with his wife Hedwig were times for reflection rather than artistic pleasure. "Two unforgettable hours," he once said to her after a symphony concert. "I haven't thought that deeply about arsenophenylglycin in a long time." He read the new French authors — André Gide, Guy de Maupassant, Anatole France — but his favourite books were crime stories, preferably by Conan Doyle, which, as he claimed, stimulated his detective abilities. Poetry? A verse here and there. One that he particularly liked is by Friedrich Nietzsche:

> The least of things only, the gentlest
> A lizard's rustle, a breath
> The whisk of a moment —
> Little it takes for moments of bliss.

Why was Ehrlich so successful? He himself attributed scientific success to the four great 'G's: Geduld (patience), Geschick (skill), Glück (good fortune) and Geld (money). Others later added Gesundheit (good health), a proposal to which he would have consented. The pace at which he had worked to achieve so much carried a price. Ehrlich's health was failing to the extent that he had to rest, give up his cigars and maintain a diet. During Christmas of 1914, he had suffered a light stroke, which slowed him down somewhat but did not seriously incapacitate him. Ehrlich meant to restore himself at a sanatorium in Bad Homburg, which was under the direction of a Dr Pariser, a distant relative. He had come there to recover, regain his appetite and strength, and then go back to work. But on 20 August 1915, he suffered a second stroke. This time, it was a more serious one. Death came to him suddenly and unexpectedly. "Until the last minute my husband was cheerful, entertaining and intellectually fresh," said Hedwig.

Europe was in the middle of the First World War; waves of nationalism ran high, and the press of the countries at war with Germany did not honour Ehrlich, the man and the scientist, appropriately. There was one notable exception, however; crossing the barriers of war came words of respect, reason and gratefulness from the *London Times*: "He has opened doors into the unknown and at this hour all the world is in his debt."

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1. Bäumler, E. *Paul Ehrlich: Scientist for Life.* (New York, Holmes and Maier, 1984).
2. Ehrlich, P. in *Gesammelte Arbeiten* (ed. Himmelweit, F.) Vols 1 & 2 (Springer Berlin–Göttingen– Heidelberg, 1957).
3. Jokl, E. Paul Ehrlich: man and scientist. *Bull. NY Acad. Med.* **30**, 968 (1954).
4. Herken, H. Paul Ehrlich; Pioneer of Chemotherapy. Address at the dedication of the Paul Ehrlich Wing, Weizmann Institute for the Sciences, Rehovoth, Israel, 25 March (1976).
5. Loewe, H. *Paul Ehrlich: Schöpfer der Chemotherapie.* (Wissenschaftliche Verlagsanstalt Stuttgart, 1950).
6. Silverstein, A. M. *Paul Ehrlich's Receptor Immunology.* (San Diego, Academic, 2002).

Competing interests statement
The author declares no competing financial interests.

Online links

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1908 Nobel Prize for Physiology or Medicine: http://www.nobel.se/medicine/laureates/1908/
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