

Paul Ehrlich (1854-1915): founder of chemotherapy and pioneer of haematology, immunology and oncology

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Summary

The Jewish-German histologist, microbiologist, biochemist, immunologist and pharmacologist Paul Ehrlich, by his research founded chemotherapy and pioneered immunology, haematology and oncology. For his contribu-

tion in immunology he was awarded the Nobel Prize of Medicine and Physiology in 1908.

Key words: chemotherapy, Ehrlich, haematology, immunology, “magic bullet”, oncology

Ehrlich’ first years

Paul Ehrlich was born on 14 March 1854 in the little town of Strehlen, not far from Breslau. His Jewish family had lived there since the 18th century. Paul grew up in economically favourable conditions with a kind-hearted father, Ismar and an energetic, business-minded mother, Rosa, who dominated the family. Paul was a bookish child who preferred to spend his time reading rather than participating in the wild games of his schoolmates. He was a diligent schoolboy who was particularly good in mathematics and the natural sciences. His grandfather’s distillery with all its chemical apparatus had obviously made an indelible impression on the boy and this experience probably laid the foundation of his lifelong interest in chemistry. On the other hand, both at school and later on as an adult, he had difficulties expressing himself in German both orally and in writing. The same was true of English and French. This would cause some complications in the years to come, when as a world-famous scientist he had to present his results before an international audience [1].

First experiments with colours and their chemotherapeutic action

Ehrlich’s student years coincided with the almost explosive development of organic chemistry during the latter half of the 19th century and the synthesis of a great number of dyes that laid the foundation of the

German chemical industry. These synthetic dyes would prove useful for staining cells and tissues, and this is where Ehrlich made his first important scientific contribution. Ever since his schooldays, he had been fascinated by dyes and the possibility of using them in medical research, and he was encouraged by his mother Rosa’s cousin Carl Weigert (1845-1904) an outstanding pathologist. During the holidays, Paul conducted experiments in Strehlen with anilin dyes that he mixed into the food of his mother’s domestic white pigeons. The idea was that they should assume a nice blue colour, but the most obvious result of the experiment was that the pigeons died. The intended result, in this case the change of colour, had an undesired side effect. This early experience made a deep impression on the young Ehrlich and illustrated a central problem in chemotherapy, the medical field that he would devote a great part of his life to develop.

After graduating from the Gymnasium (secondary school), he studied natural sciences somehow unsystematically for a term at the University of Breslau. Ehrlich had a strong inclination towards medical research, but the actual practice of medicine had no appeal to him. With his sensitive, not to say timid disposition, he was reluctant to witness the suffering of his patients, and perhaps also not willing to inflict pain on them during their treatment. In the end, coupled with the strong support of Weigert, his family managed to persuade him. During his medical studies, first in Strasbourg where he passed a preparatory examination (“Physikum”) and after that in Breslau, he became

more and more fascinated with dyes and their medical uses. Weigert had already established himself in this field, where he became a pioneer in the staining of tissue sections for microscopic examination in pathology. Through him, Ehrlich came in contact with the botanist Ferdinand Cohn and the pioneer of experimental pathology Julius-Friedrich Cohnheim (1839-1884). In Cohn's laboratory, Ehrlich met Robert Koch (1843-1910) for the first time [2].

He reasoned that the biological effect of a substance, for instance a dye, is dependent on a chemical affinity between the substance and different structures which occur in cells and tissues. This chemical affinity is specific and it must consequently be possible, by systematic testing, to select substances suitable as drugs, i.e. with well-defined biological effects and no undesired side effects. For instance, among the seemingly endless number of new compounds produced in organic chemical laboratories, there must be some that kill or inhibit certain bacteria, but are harmless to the human organism.

A pioneer of histological staining and haematology

Ehrlich passed the examinations for his MD in 1877 and the next year he completed a thesis in Breslau entitled "Some Contributions to the Theory and Praxis of Histological Staining" [3]. In his thesis, he reported the discovery of an, until then, unknown kind of cell, which he called "mast cell", that surrounded the blood vessels and contained granules that could be stained with basic dyes. The discovery of the mast cells is of course of considerable interest as such, but it also illustrates a line of thought which would become central in Ehrlich's research. His demonstration of the staining characteristics of the white blood cells with aniline dyes allowed others to understand better the abnormalities of blood cells, thus contributing to the foundation of haematology.

While still a student, Ehrlich began investigations on the aniline dyes. With their aid he discovered (1877-1881) all the different types of white blood corpuscles; he distinguished leukaemia according to the prevalent type of cell; and he introduced his tri-acid stain for blood. The staining of bacteria was very difficult, and in 1881 Ehrlich introduced the highly satisfactory methylene blue stain. Much of Koch's work was done with stain, and by laborious staining over a prolonged period, he discovered the tubercle bacillus. On the day following Koch's announcement of his discovery, Ehrlich evolved a rapid method for staining the microorganism. This method is now known as the Ziehl-Neelsen

method - after Franz Ziehl (1857-1926) and Friedrich Neelsen (1854-1894). In 1882 Ehrlich introduced his diazo-reaction for the diagnosis of typhoid fever, and in 1885 his work on the oxygen affinities of the tissues led to vital staining [4].

Ehrlich's discovery of the mast cells and his new methods for the staining of cells and tissues had gained him international recognition. The head of the Medical Clinic II at the well-known Charit Hospital in Berlin, professor Friedrich-Theodor von Frerichs (1819-1885), offered the young physician a position at the clinic with excellent opportunities for research. Frerichs gave to his new chief assistant ("Oberarzt") complete freedom to choose his own line of research, in accordance with one of the professor's leading principles: "Science is a bird that only sings in freedom." Here, Ehrlich spent seven happy years while he worked on improving his staining methods and made fundamental contributions to haematology. During this time, he married Hedwig Pinkus, the daughter of a wealthy textile mill owner [5].

In 1885, Ehrlich published the results of an investigation of the uptake of oxygen in the animal organism. By staining living organs and tissues, he could show that they had a markedly variable ability to take up oxygen. These results were received with great interest, and two years later he got a prestigious prize for his discoveries. Nevertheless, the year 1885 was an unlucky one for Ehrlich. His professor and enthusiastic patron, von Frerichs, died suddenly and the new head of department, Karl Gerhardt, was a clinician of a more conventional type. He was not at all prepared to give Ehrlich the rather privileged position that he had enjoyed under Frerichs which had been a prerequisite for his successful research. Ehrlich found his position at the clinic as well as his research opportunities unsatisfactory, and this contributed to the deterioration of his health. He had a persistent cough. In 1888 he detected tubercle bacilli in his expectorations. Ehrlich suddenly left his position at the Charit and he set out for the dry desert climate of Egypt in an attempt to cure his supposed tuberculosis. A year later he returned to Berlin, apparently cured of tuberculosis but without a position that would allow him to continue his research.

A pioneer of immunology

The only remaining solution was to establish himself as a private researcher. Fortunately, Ehrlich's father-in-law generously provided the means for this. Not far from his private residence, he established his laboratory. This was a new beginning for him as he

also embarked on a completely new line of research. It was now that he started his investigations of the plant poisons, ricin and abrin, and their ability to cause the formation of antibodies in mice. This research naturally led to a collaboration with Emil von Behring (1854-1917). A close friendship, that would last their whole lives.

In 1891 Ehrlich discovered that the injection of poisons, such as ricin, induced the production of antibodies in the blood, and in the same year he discovered the latent period in the development of active immunity [6]. In 1892 he illuminated the distinction between active and passive immunity. About this time many unsuccessful attempts had been made to provide standards for the dosage of the diphtheria antitoxin. In 1897 Ehrlich published his classic paper on this subject. The method that he recommended was long employed in practice, and the scientific principles laid down in this paper are still fundamental. In 1897 he evolved also his well-known “side-chain” theory of immunity. He assumed that cells with the capacity to form antibodies, have receptors on their surfaces in the form of side-chains, which can bind substances that are alien to the organism (antigens), should such substances come in contact with the cell surface. This binding presupposes that there is a chemical affinity between antigen and receptor, in other words it is an example of Ehrlich’s fundamental idea about chemical specificity as the basis for all biological functions. When the receptor has bound the antigen, the cell is stimulated to form a great number of new receptors that are shed to the blood and appear as free, circulating antibodies specific for the antigen in question. In 1899-1900 Ehrlich (Figure 1), with Julius Morgenroth (1871-1924), made fundamental advances in the study of haemolysis, and introduced the terms “complement” and “amboceptor” [7]. His “side-chain theory”, abandoned for many years, nevertheless led others to investigations of importance to immunology. Moreover, in recent decades this theory had been revived by contemporary immunologists, albeit in a more sophisticated form [8].

The methods that Ehrlich devised for the determination of the antibody level in serum, and for the production of highly active diphtheria antitoxin, were integral for the success of Behring’s serum therapy against diphtheria.

There was great interest in Ehrlich’s side-chain theory, but it was also criticized as being too “chemical” and fanciful. This criticism was aimed at Ehrlich’s preference for advancing oversimplified chemical models where he, for instance, assumed that the interaction between toxin and antitoxin leads to the



Figure 1. Ehrlich photographed around 1900, probably shortly after he became Director of a new state research institute in Frankfurt am Main.

formation of stable chemical bonds. Undeniably, Ehrlich introduced a number of new concepts in immunology that might appear rather hypothetical. Despite this criticism, there is no doubt that his entirely speculative side-chain theory portends in many ways the fundamental concepts of our modern views of how antibodies are formed.

Ehrlich had been in contact with Koch ever since the former had helped improve the method for staining the tubercle bacillus in 1882. It is also likely that he tested Koch’s tuberculin on himself when he believed that he had been infected with tubercle bacillus. Undoubtedly, he had been convinced of the effectiveness of treatment, and during a period in 1890-91, he worked himself in the Moabit Hospital where tuberculin was being tested clinically. At this time, when severe criticism against the therapeutic use of tuberculin was being voiced, Ehrlich was one of its strongest defenders. In later years, he was more guarded and thought that Koch had been premature in his attempts to use tuberculin to treat the disease. Generally speaking, the early 1890s was a period of naive optimism and enthusiasm for both prophylactic and therapeutic progress in medicine.

When Koch established his Institute for Infectious Diseases in 1891, Ehrlich was given a laboratory

at the institute, where he worked for three years. The excellent results obtained with diphtheria antitoxin induced Althoff, the Prussian Minister of State, to found at Steglitz (Berlin) an institute for serology and serum-testing, and Ehrlich was appointed its Director (1896).

Ehrlich was very satisfied with his new institute and much of his fundamental work on the determination of antibody activity as well as the elaboration of his theory about the principles of immunization was carried out here. In 1897, Ehrlich was appointed "Geheimer Medizinalrat", and after negotiations with the mayor of Frankfurt am Main, the Royal Prussian Institute for Experimental Therapy was established in 1899 with Ehrlich as its director, a position that he held until his death.

Ehrlich and the foundation of chemotherapy

During the first decade of the 20th century it became increasingly obvious that both active immunization (vaccination) and Behring's serum therapy was far from being the "magic bullet" that had originally been believed. On the contrary, there were reports of anaphylactic reactions when the serum treatment had to be repeated.

The idea of a chemical explanation of both the normal functions of the human organism and its diseases, can be traced all the way back to Paracelsus (1493-1541). The idea of examining the chemist's arsenal of different compounds in order to find suitable drugs is nothing new. What distinguishes Ehrlich from his predecessors and makes him so successful is the systematic and critical way he goes about his task.

Ehrlich's thoughts on defence against bacteria had turned to chemical aspects, and he was investigating what he called "chemotherapy"- the cure of bacterial infections with substances of known chemical identity.

The choice of Frankfurt am Main as the place for the new institute was certainly not a random one. Here, the laboratory was close to a flourishing chemical industry that would become an important foundation for Ehrlich's research – which the industry also supported economically. Franziska Speyer, the widow of a wealthy banker, donated in 1906 a large sum of money to set up an institute for chemotherapy in memory of her late husband, Georg Speyer, with Ehrlich as its director. At the opening ceremony, Ehrlich gave a speech in which he promised that now the chemists could synthesize compounds that would have effect only on the parasites which attack the body. These synthetic remedies would work as "magic bullets" that

automatically found their target without causing any harmful side effects. A promise that may seem rather typical of the scientific optimism of the period. Nevertheless, his words would prove to be prophetic [9].

From the 1880s Ehrlich had been exploring the physiological and pharmacological properties of various dyes, demonstrating, for example, the affinity of the newly discovered malaria parasite for methylene blue. In 1904, Ehrlich and his Japanese collaborator Kiyoshi Shiga had found that mice infected with trypanosomes could successfully be treated with the dye trypan red. In cases where the trypanosomes became resistant to trypan red, they proved to be sensitive to atoxyl, an arsenic-containing compound that Koch used to treat sleeping sickness. The problem was that atoxyl sometimes caused blindness. When Ehrlich and his collaborator Alfred Bertheim had succeeded in determining the correct structure of the compound, they started to systematically synthesize hundreds of derivatives of atoxyl in the hope of increasing its effectiveness against trypanosomes and reducing its toxicity. Eventually these efforts, so typical of Ehrlich's methodological way of looking for therapeutically useful substances, resulted in the first great breakthrough in the treatment of the dreaded venereal disease syphilis [10].

A prerequisite for a systematic investigation of a great number of compounds as possible remedies for a disease is to have a suitable animal model that can be used for the testing. It was therefore a great step forward in the attempt to find a cure for syphilis when Imile Roux (1853-1933) and Ilie-Ilitch Metchnikoff (1845-1916) at the Pasteur Institute in 1903 were able to infect monkeys with syphilis. Ehrlich also started to work with monkeys in his search for atoxyl derivatives that were effective not only against trypanosome illnesses, but also hopefully could be used in the treatment of human syphilis. However, the cost of using monkeys in such tests was prohibitive, and when Sabachiro Hata (1873-1938) arrived from Japan in 1909 in order to work with Ehrlich on spirochete-induced diseases, he began to use syphilis in rabbits as animal models.

Hata now tested the numerous arsenic compounds that had accumulated in the laboratory during many years of trypanosome research and that had been well tolerated by the laboratory animals. When Hata arrived at the preparation number 606, a distant relative of atoxyl, and tested this compound, he found that it was well tolerated and effectively cured not only relapsing fever but also syphilis [11].

In the beginning, Ehrlich was somewhat guarded in his attitude to 606. He had seen too many compounds that had seemed promising enough but in the

end had to be rejected because the therapeutic effect was not certain enough or because of unpleasant side effects. However, preparation 606 seemed really promising, and he became more and more optimistic when he saw the results of the therapeutic experiments on animals and the extensive toxicity tests. The demand for 606 was such that Hoechst Company had to work long hours to provide Ehrlich with the product of the final but one step in the synthesis of 606. The very last step in the synthesis was done in Ehrlich's own laboratory. The science of chemotherapy - Ehrlich's term - was born.

For the clinical testing of 606, a total of 65000 doses were manufactured in the Georg-Speyer-Haus and provided *gratis* to a selected number of physicians, whom Ehrlich had confidence in. He constantly worried about how the sensitive compound would be stored and whether it might be administered to the patients in an incorrect way if it were made freely available. At least on one occasion his worries proved to be well founded. The reports of the doctors, who participated in the clinical testing, were on the whole positive. However, there was one exception; the dermatological clinic in Prague reported severe complications, involving the kidneys and the nervous system after injections of 606. Ehrlich was not satisfied until he had been able to show that the ampoules used on these occasions had been opened and then resealed several days before the content had been injected to the patients. This was, in Ehrlich's opinion, the obvious explanation of the complications. The results were very good for newly diagnosed syphilis, while the effect on long-standing syphilis, for instance paralytic cases, was not encouraging [12]. Thus, it seemed well justified when Ehrlich decided to rename preparation 606 as salvarsan (arsenic that cures).

While the ovations of the press knew no boundaries, some of his medical colleagues were instead considerably more restrained. They pointed to the side effects of the salvarsan treatment. Others complained of not having participated in the clinical testing of salvarsan.

The fanaticism of his salvarsan adversaries and their spiteful and irrelevant arguments must not disguise the fact that there were real problems with salvarsan, which cannot be explained by incorrect storing or administration. To begin with, the usefulness of the drug was limited, it was effective only on newly diagnosed syphilis. Furthermore, subcutaneous or intra-muscular injections of salvarsan caused severe pain in some patients, while others experienced no serious discomforts. However, the greatest problem was that salvarsan sometimes caused inexplicable deaths, perhaps due to some

hypersensitivity of the patients. The mortality was 1/1000, a reasonably low figure considering that it was a question of treating a very serious illness for which there was no other cure. Even so, Ehrlich was worried about the mortality and he tried to produce a less toxic derivative of salvarsan. In 1912 "neosalvarsan" was synthesized, a derivative that was easily soluble and seemed to have less complications on injection.

About three decades later, the advent of the sulfonamides for the treatment of bacterial infections was a direct, though delayed, outgrowth of Ehrlich's demonstration that dyes could be antibacterial agents. When penicillin was introduced, Ehrlich's drugs against syphilis were abandoned, but he had set in motion the activities of the 20th century that were to revolutionize the therapy of microbial diseases.

Ehrlich and cancer

Some investigators had thought that they could be able to create experimental malignant tumors, however what they succeeded was the creation of infectious or inflammatory tumors. Ehrlich proved that in a limited number of cases it is possible to transmit a malignancy from one organism to another. But even so, it is about inoculation of cancerous infiltrates rather than transplantation of tumor tissue fragments.

In the USA and Germany the fight against cancer started amidst the fear for microbes. Ehrlich was among those who supported theories that cancer originated from infectious causes. In 1911, he demonstrated the possibility of vaccination of rats by injecting subcutaneously fragments of tumors of moderate aggressiveness. He also proved the predisposition of some animals to develop malignant tumors while in some others only benign growths developed. With his works Ehrlich demonstrated the existence of a "natural non-susceptibility" of some individuals to develop cancer, comparable to the antiinfectious immunity. In this concept one can find again strong analogies with the Pasteur's theory of antimicrobial immunity.

At the beginning of the 20th century Ehrlich suspected that different reactions of immunological nature might happen to humans, in an attempt to explain why some individuals seemed predisposed to cancer development while others did not.

Ehrlich's "magic bullets"

Since the work of Pasteur on the bacterial basis of wound infection and of Joseph Lister on the anti-

septic treatment of wounds, in which chemical agents were used to kill the contaminating bacteria, medical scientists dreamed of the possibility of an agent that would destroy invading microbes without damage to the patient's healthy tissues. So vaccines and antitoxins were devised. They were crude and impure materials, containing complex substances far beyond the chemical knowledge of the time, and not clear thought about how they acted. However, Ehrlich conceived the idea that much simpler substances might act powerfully against microbes without harming the patient.

It was Ehrlich who coined the term "magic bullet" to mean a chemical bullet that would kill the microorganism but not the patient. Salvarsan was hardly the perfect bullet since it was a toxic drug with unpleasant side effects.

Applying the stereochemical ideas of Emil Fischer and other organic chemists, Ehrlich devised a "side-chain" notion to explain how antigens and antibodies interacted. His formulation was essentially a chemical interpretation of immunity, part of a molecular vision of reality that included the possibility of pharmacological "magic bullets", the ultimate aim of chemotherapy.

Why do dyestuffs combine with particular cells, on particular parts of cells, and not with others? Does not this question arise about any substance, coloured or not, that act as drug? Dyestuffs are convenient because they can be seen to be fixed by particular cells. But the chemical problem is the same whether the reagent is a visible dye or an invisible drug. It is the problem originally raised by Claude Bernard's studies. Ehrlich was particularly enthusiastic about the word "receptor" for the submicroscopic structures that "received" a dye or a drug.

Ehrlich looked for substances - dyes at first, other germicides later - that were fixed by microbes but not by the human or animal host of the microbe. Disinfectants and the like were effective killers but destructive also to host tissues, and he thought of modifying them chemically so that they were bound to receptors in the microbe but not by those in the host.

Salvarsan was the first drug with practically "chemotherapeutic" activity. Ehrlich's hope that salvarsan would kill the spirochete that causes syphilis was too optimistic, but the power of the drug was undoubted and attracted the name "magic bullet".

Improvements on salvarsan were therefore looked for, and several related compounds in due course replaced it. Salvarsan and its successors attacked few other microbes, and no more "magic bullets" were discovered until the sulphonamides and penicillin.

Ehrlich's search for a "magic bullet" which would

seek out and kill germs in the body without destroying host cells was rewarded by the synthesis of arsenical compounds effective in the treatment of syphilis, but the principles he enunciated did not lead to an effective battle against microorganisms until about thirty years later.

Ehrlich called the discovery of 606 a "magic bullet", a new therapeutic weapon which could specifically locate and destroy those organisms causing disease. This notion of specificity - "magic bullets" drawn to specific targets - while obviously most applicable to the treatment of certain bacterial infections, had a powerful impact on the organization and practice of biomedicine overall. Ehrlich's powerful metaphor became a central organizing feature of the 20th century medicine and the widespread image of the "golden age". The "magic bullet" imagery depicted the institution of medicine and its practitioners as able to control and vanquish disease. The new biomedical paradigm of specific cause and cure, with its strong ties to laboratory science and new technological apparatus, also was central to the rising status of medicine, so characteristic of the "golden age".

Although Ehrlich's discovery of a chemotherapy for syphilis was not followed quickly by other antimicrobials, by the 1930s the development of sulphonamides marked the continued promise of "magic bullet" medicine.

With antitoxin manufacture successfully underway, chemical companies, especially Hoechst and Bayer, turned their attention to diseases as targets of industrial innovation. In this they were particularly motivated by Ehrlich's development of the side-chain theory, receptors and the promise of experimental chemotherapy.

Today, scientists worldwide certainly look for molecular explanations for all sorts of biomedical problems, and undoubtedly, Ehrlich was the man who really opened our eyes to this new line of thought.

Honours and last years of Ehrlich

Ehrlich had always shunned publicity and preferred a quiet fame among his scientific colleagues, where he undoubtedly had become a great name. Even so, he had received a number of honours, among them the Nobel Prize in Physiology of 1908 (Figure 2). In 1911, the official Prussia showed its esteem by appointing him "Wirklicher Geheimrat" with the title "Excellenz" the highest distinction that the Prussian government could bestow on any scientist. He had also received countless medals, not to mention a number of



Figure 2. Ehrlich photographed around 1907, World Health Organization, Geneva.

honorary doctor's degrees and an assortment of different decorations. To celebrate his 60th birthday, a so-called "Festschrift" was published, where his great achievements were celebrated in 37 chapters. His last years (Figure 3) were darkened by the outbreak of the first World War, which drastically curtailed his international scientific contacts. The enormous workload that salvarsan had entailed was of course also a strain on his health, which was hardly improved by his constant cigar smoking, a habit that he had acquired in his youth.



Figure 3. Ehrlich in his office in 1910.

In 1914, his health deteriorated significantly and he showed increasing signs of circulatory discomfort. At Christmas time, he suffered a minor stroke, but his condition seemed to improve, even if he missed his beloved, albeit forbidden cigars. In August 1915, Ehrlich entered a nursing home to recuperate, and there he suffered another stroke. He died peacefully on 20 August at Bad Homburg, Hessen. At his funeral in the Jewish cemetery in Frankfurt am Main, his friend von Behring said in a moving eulogy, that the deceased had become a "Magister Mundi" (a teacher of medical science all over the world). Perhaps, this was Ehrlich's greatest role, as an intellectual leader and inspirer who directed the medical thinking on new and fruitful paths.

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