Paul Ehrlich: From magic bullets to chemotherapy

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Paul Ehrlich 1854-1915

SUMMARY

Paul Ehrlich is one of the most notable figures in the world of science. Considered by many as the father of chemotherapy, he was awarded the Nobel Prize in Physiology and Medicine in 1908 for his contributions to immunology. This document outlines some of his most important findings, including those who led him to create his famous*«magic bullets»*, precursors of current chemotherapeutic agents.

Keywords: *Nobel Prize; Chemotherapy; Medical history.*

Paul Ehrlich: de las balas mágicas a la quimioterapia

RESUMEN

Paul Ehrlich es una de las figuras más notables en el mundo de la ciencia. Considerado por muchos como el padre de la quimioterapia, sus aportes al campo de la inmunología lo hicieron acreedor al premio Nobel en Fisiología y Medicina en el año 1908. El presente escrito reseña algunos de sus hallazgos más importantes, incluyendo aquellos que lo llevaron a idear sus famosas «balas mágicas», inspiradoras de la concepción de los agentes quimioterapéuticos actuales.

Palabras clave: *Premio Nobel; Quimioterapia; Historia de la medicina.*

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A century after being awarded the Nobel Prize for Physiology and Medicine, theories proposed by Paul Ehrlich, far from being contested, have been refined and consolidated so that under this influx, fields of medical science as chemotherapy and serum therapy have achieved immeasurable progress.

It is not free for Paul Ehrlich to be considered as a central figure in the birth of chemotherapy and immunology, apart from being a genius and messiah of medicine, among many of the attributes that he has been entitled to.

Son of Rosa Weigert and Ismar Ehrlich, who worked for a lottery company as an office manager, Paul Ehrlich was born in 1854 in Strehlen, territory of today Poland, before East Prussia[1-3].

During his stay through the universities of Wroclaw, Strasbourg, Freiburg and Leipzig, the young medical student developed a growing interest in using dyeing chemicals, in order to stain animal cells and tissues. He was particularly concerned by the fact that some types of cells captured certain colors and excluded other[1], the «specific affinity» concept was probably being born in his mind, foundation of the theories that he would post later on the immune response and the experimental therapeutics.

His doctoral thesis, conducted at the University of Leipzig (1878), titled «Contributions to the theory and practice of histological staining. Part I, the chemical coloring concept. Part II, Chemical, technological and histological concepts of aniline colors»[4], as well as his work on chemical dyes developed in the Medical Clinic of Berlin, as Professor Frerichs'[2] assistant, took him later to discover salvarsan, the first known curative medicine for syphilis.

In this same line, his first investigations on therapy obtained special importance since Ehrlich showed interest in elucidating the relationship between pharmacological activity and the chemical structure of certain medicines[5].

In addition, he wanted to identify changes in the therapeutic activity as a result of changes in the chemical structure of certain compounds such as chemical dyes that had been used so far only as diagnostic elements. Then he applied the methylene blue for pain treatment, due to its affinity for nervous tissue, as for that of malaria in human beings, thanks to the affinity for *plasmodium*, its causative agent.

Together with his assistant Shiga, studied the effect of the red trypan dye on animals rather than on humans, with the objective to treat some infections caused by protozoa, such as trypanosomiasis. Certain experimental types of this disease were approached by Ehrlich through the use of atoxyl, derivative of arsenic, whose structural formula was established in the right way thanks to their joint work with his colleague A. Bertheim[2].

Likewise, Ehrlich investigated on the anesthetic effects and the body distribution of cocaine, which he attributed first to the presence of a particular functional group, and second to the structure itself[5].

By 1890, Ehrlich decided to focus its attention on the nascent field of immunology, thanks to the invitation that Robert Koch made to him to work in the newly created Institute of Infectious Diseases in Berlin, where Emil von Behring recently had discovered the antitoxins against tetanus and diphtheria. However, antitoxins had very low power, thus preventing their use in clinical trials. Ehrlich was then in charge of developing a precise method to measure the neutralizing power of each antitoxin related to the standard and then he monitored the power of the antitoxin produced by experimental animals after by after injection of the toxin or toxoid[5,6].

The final result consisted of standardized preparations, very powerful and effective, which attracted great interest in the serum therapy[7]. It is at this point of his career where anyone can find the origin of Ehrlich's theory about lateral chains (side-chains), which actually correspond to the immunoglobulins produced by B cells and to the receptors of T cells.

Thus, It was proposed the existence of chemical and non-biological interactions between toxin and antitoxin, at the same time mediated the first by the presence of two groups that he named toxophore and haptophore, one of those had no toxic effect. According to his theory, the toxophore bodies joined the cells through toxophil bodies or «lateral chains». He argued that each cell had a supply of lateral chains acting as well as cellular receptors for toxins, or as antitoxins, as well, once they were released into the blood[6,8].

It is evident the correspondence existing between Ehrlich's theory on lateral chains and the interaction between surface molecules present on B or T cells with a specific antigen generating a clonal expansion that leads to the release of immunoglobulins into the blood stream.

Despite the remarkable work done by Ehrlich towards standardizing and conferring power to the antitoxins discovered by Emil von Behring, the first Nobel Prize in Physiology and Medicine in 1901 was awarded to the last one[2].

However, Professor Theodor Langhans of Berne considered until the end that Paul Ehrlich was a potential creditor for the award as written in a letter sent to the Nobel Foundation[9]:

«As far as Paul Ehrlich is concerned, we need to select his most important contributions, his investigations on ricin (the «toxalbumin» or Lectin of the castor bean), and on abrin (a powerful phytotoxin of the precatory bean) going back to 1891 and following directly those of Behring's. Both of these toxins are related to the toxalbumoses of bacterial origin and can be prepared in large quantities and sufficient purity, which made it possible for Ehrlich to investigate the problem of the immune response with almost mathematical precision. He arrived at the most interesting result that the peak of immunity is reached after repeated doses on the sixth day, comparable to the crises in pneumonia or measles, and Ehrlich drew attention to the analogy of the two situations. Better known are his experiments in which he studied the transfer of immunity from mother to child through lactation or inheritance, investigations that he extended to tetanus and swine erysipelas (Schweine-Rotlauf). But even more important and most original are Ehrlich's views on the origin of antitoxins (antibodies), his determination of the strength of the serum against diphtheria in 1897 which he expanded to tetanus.

He considers antitoxin (antibody) a normal component of the cell with special «sidechains» (Receptors) as part of the operational cellular apparatus. The toxin of tetanus combines with such a side chain with a profound effect on the entire cell including the nucleus. As soon as the «sidechain» is occupied by the toxin, a compensatory formation of many new sidechains results, in Ehrlich's views, in an incredible abundance in which the excess sidechains are ejected from the cells, enter the blood stream and thus form the antiserum which neutralizes the invading toxin...

This explanation is vastly different and much more innovative than anything that has been thought or written on the origin of antibodies so far. Ehrlich's ideas on toxoids (attenuated toxins) and epitoxoids prove him to be an ingenious and highly original thinker. His earlier hematological work, the discovery of the mast cells, the histochemical staining of living nerve fibers with methylene blue, his vital staining, have by now been fully accepted and clinically applied.

In short, I would like to nominate Behring in Marburg and Paul Ehrlich in Frankfurt as prime candidates for the first Nobel Prize.

I consider the two candidates as the most original and felicitous investigators in the field of medicine»[9].

Ehrlich had to wait seven years to get his deserved award. In 1908, in recognition to his contributions to immunology, he received the Nobel Prize in Physiology and Medicine, in the company of the Russian immunologist and bacteriologist Ilya Ilyich Mechnikov from the Pasteur Institute of Paris, France[2] and during the following years he obtained several nominations for the same award.

By that time Paul Ehrlich maintained a close long-standing relationship with the Farbwerke-Hoechst[7] company (now Aventis), dedicated to the manufacture of coloring substances.

Although he always counted with available laboratories and economic funds, this relationship was key in achieving the 606 tests carried out on mice, guinea pigs and rabbits, which culminated with the finding that the derivative from arsenic which he called salvarsan (that saves through arsenic) was effective against the fearsome spirochete that causes syphilis or *Treponema pallidum*[5], discovered a long time ago by Schaudinn and Hoffmann in Berlin.

Although the first tests carried out by Ehrlich discarded the compound used in the 606 trial because of its apparent ineffectiveness, he decided to try it again. This decision was influenced by Kitasato, his former colleague and also by his disciple Hata, who had developed a method to infect rabbits with the spirochete, which called the attention of Ehrlich and led him to evaluate it in infected rabbits[2].

While the #606 compound showed high effectiveness against *Treponema pallidum*, Ehrlich, cautious with his discovery, tried in an unsuccessful way, even against his partner Farbwerke-Hoechst, to restrict access to the

new medicine, since he considered that before allowing its general use, it was necessary to conduct a larger number of clinical trials.

Despite the effectiveness of salvarsan or #606 and that of the subsequent neosalvarsan or #914, the new discoveries only were able to face a growing opposition, which even put him in jail, when the demonstration of its benefits silenced the voices of his contradictors.

By that time, Ehrlich had already used the term *«magic bullets»* to refer to the compounds that specifically acted against microorganisms that cause disease. He used to compare these chemical substances with real bullets that, because of their special affinity for pathogens, had destructive power over them.

According to Ehrlich, the *«magic bullets»* should show a maximum toxicity against parasite and a minimum against the host, properties that he was in charge of explaining, in terms of differences related to the chemical affinity with the cellular protoplasm. This led him to classify such substances into «parasitotropic» and «organotropic»[5,10]. In addition, he coined the term «chemotherapy» to separate it from the traditional field of pharmacology to the experimental therapeutic one that according to him, the intention was to discover chemicals with specific action on pathogenic infections, unlike pharmacology, which would address only the symptoms produced by toxic doses of effective medicines against infectious diseases, once these were tested in superior healthy animals[10].

Ehrlich thought that this apparent bias made that the pharmacology contribution to the search for truly curative medicines was very poor, without considering that thanks to research in this field, medicines such as antipyretics, analgesics and hypnotics, important in the symptomatic treatment, have been discovered.

On the other hand, he argued that the benefits of chemotherapy resided in the experimental induction of the disease and in the study on the effect of medicines used against it in animals used for this purpose.

His affirmations received much criticism, not only because it was felt that the implementation of specific medicines against particular diseases, as old as the man himself, e.g, ipecacuana against dysentery and mercury against syphilis, was not only inseparably linked to the traditional pharmacology, but also to pharmacological methods rather than chemotherapy, since medicines that were used against most common diseases in that age[5], have been more precisely known.

Therefore the birth of the new science of chemotherapy was not free of controversy. However, this was not an obstacle for his followers to continue ahead with the developing of their own *«magic bullets»* in tacit agreement with the decision taken time ago by Paul Ehrlich, in the sense of bringing dyes from the field of histology to the chemotherapy´s[11], as he had done it with the methylene blue, red trypan and salvarsan[5,10] (although it was not actually a dye, had a characteristic yellow hue[11]).

Some of the most recognized Ehrlich's followers were Edgar Lederer (1908-1988) from CNRS in France, creator of *«magic bullets»* consisting of muramyl dipeptides that stimulated the immune response against viruses, bacteria, protozoan parasites, as well as against antigens tumors. Reid Hunt (1870-1948), head of the Laboratory of Hygiene of the Public Health Service of the United States, precursor entity of NIH and his student Carl Voegtlin (1879-1960), hard supporters of chemotherapy against infectious diseases over the vaccines or serum, and the 1988 Nobel Prize George Hitchings and 1967 Manfred Eigen also were devoted to the development of new *«magic bullets»*.

With his discovery of prions, Stanley Prusiner, a researcher at the University of California, discovered the fascinating field of brain proteins that, through changes in their three-dimensional structure could become *«magic bullets»* causing infection. This job game him the award of Paul Erhlich´s prize in 1995 and the Nobel Prize in 1979.

It is evident that among the findings made by Ehrlich in the therapeutic field we can find the seed that inspired the design of synthetic pharmacological agents used in current research and medical therapy.

The *«magic bullets»* of salvarsan to treat syphilis, in which he noted his principle of «selective affinity» (to eliminate the germ causing disease without body injury), meant the glory and led to further medicine development such as sulfonamide, antibiotics and more recently, antitumor medicines including recombinant peptides, as well as cytotoxic or radioactive agents which may be marked on a selective way with monocional antibodies.

His persevering character was demonstrated by the insistence on that his disciples and collaborators repeated trials conducted for a particular result, over and over again, before it was published.

Always interested in the wellbeing of his assistants, he did not lose his simplicity nor his proverbial affability, despite the multiple awards and academic honors he received throughout his existence. In addition to the Nobel Prize for Physiology and Medicine, he received *honoris causa* doctorates at universities of Oxford, Gottingen and Chicago, Cameron Prizes at the University of Edinburgh, Honorary of Chemists from Germany and Honorary Congressional Medical Lisbon prizes, as well as medals from several countries around the world and honorary memberships in associations and science academies[12].

Being a strong smoker, his health suffered for several years after supervising a large-scale delivery of salvarsan and serum to German army during the First World War until, in a state of physical and mental exhaustion he died of a heart attack at 1915[12].

The deep respect and admiration inspired by Paul Erhlich to his contemporaries were embodied in the obituary that Professor Arnold Berliner wrote then in the newspaper «Naturwissenschaften»[13]:

«At dawn of history,» so Goethe tells us, «men held a solemn and sometimes terrifying belief. They imagined their ancestors seated in silent communion in great caves in a circle of thrones. When a new soul entered this company, they would stand and bow to welcome him if he was worthy enough. The ancestors are the great men whose services to humanity are recorded in the Book of Eternity. We can be sure that they will bow deeply in profound veneration to the man now entering their presence.»[13]

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