Medicine in Stamps

Paul Ehrlich (1854–1915): man with the magic bullet

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"It is because we are not exact that we fail." ~ Paul Ehrlich

Let's paint a picture of a man fascinated by colours and chemistry, whose imagination enabled the deduction of theories and cures years beyond his contemporaries. Add to this an unyielding enthusiasm and perseverance, and we have Paul Ehrlich, Nobel laureate for contributions in adaptive and acquired immunity. Born on March 14, 1854 in Strehlen, Germany, to wealthy German-Jew parents, Ehrlich studied medicine at Breslau, and was a mediocre student who refused to memorise the ten thousand and fifty medical terms necessary to graduate. He earned his MD in 1878 and began his career in the department of internal medicine at Charite Hospital in Berlin under Friedrich, a liberal whose motto was "only free birds sing, those in captivity don't." At Charite, Ehrlich showcased a lifelong habit of unrelenting work and smoking strong black cigars. He exercised little and drank much, frequently with colleagues in order to engage them in lively discussions of his favourite topic, chemistry. His self-depreciating humour earned him many friends, often men in high places.

HISTOLOGY Early in his career, the chemist in Ehrlich took note of Carl Weitgert's use of aniline dyes as biological stains, which caused him to ponder on the link between a dye's chemical structure and its selectivity for certain tissues. At 23, he published his first paper, "Contributions to the Theory and Practice of Histological Staining", which advanced the novel argument that both the colouring of fabrics and the staining of cells were fundamentally the result of a true chemical reaction. His expertise in histology and meticulous work ethic led to the eventual description of the various granulocytes and mast cells. Ehrlich used drawings and colour to present his ideas. In his frantic enthusiasm, he would scribble on any available surface: laboratory walls, tablecloths, the bottom of his shoes and the shirts of colleagues. Colour allowed Ehrlich to better understand the chemical underpinnings of biology. This obsession led to a few peculiarities: his pocket overflowed with sharpened coloured pencils, his laboratory brimmed with vibrantly coloured test tubes, and his research ideas were preserved on large coloured note cards.

TUBERCULOSIS Ehrlich's most "gripping experience" was his realisation, at a lecture by Koch, that he had seen the tuberculosis organism while staining a diseased liver. That night, he rushed to his laboratory to improve the acid-fast staining method for mycobacterium, which he demonstrated to Robert Koch the next day. Today, the Ziehl-Neelsen stain for acid-fast bacteria is a direct descendant of his method. That year, 1882, marked the start of a lifelong friendship and mutual intellectual admiration between these two pioneers of medicine. In 1885, Ehrlich discovered, to his chagrin, the presence of mycobacteria in his own sputum. As was the standard cure at that time, he went to Egypt for two years to rest his lungs. Meanwhile, Koch thought he had found a cure, and administered it to his friend. Fortunately, Ehrlich survived despite Koch's ineffective and dangerous treatment.

IMMUNOLOGY In 1885, Ehrlich published a paper on the requirement of the organism for oxygen, which proposed that cells have a multitude of specific receptors that enable them to take up necessary molecular nutrients. Harmful compounds could mimic nutrients and bind to these receptors. Despite a few missing details, his bold hypothesis gradually evolved; both living cells and dye molecules possess side chains that define their

properties and interactions. In 1900, Ehrlich described his famous side chain theory of antibody formation, proposing that antigens bind to pre-existing side chains on the cell surface, stimulating the synthesis of additional side chains that are then secreted into the extracellular fluid to neutralise the instigating antigen. He described these antibodies as "magic bullets" in search of toxins. Ehrlich drew his inspiration from Emil Fisher, who had proposed that enzymes fit their substrates like a lock and key. Ehrlich went further, adding that cells were capable of producing receptors *prior to*, not after, contact with foreign proteins, although later studies showed that the full spectrum of receptors is not present on every cell.

Unfortunately, Ehrlich's colleagues did not always understand his detailed diagrams and erratic explanations, and some openly mocked him. Convinced that mathematics governed toxin-antitoxin reactions, he searched for simple formulas, but lapsed into complex and complicated explanations. Despite these shortcomings, the core idea of his side chain theory firmly laid the foundation for modern-day truisms governing immunity. In 1908, he shared the Nobel Prize with Elie Metchnikoff.

MAGIC BULLETS In 1896, Germany established the Institute for Serum Research and Serum Testing. There, Ehrlich worked with colleagues Emil von Behring, Nobel winner for diphtheria therapy, and Shibasaburo Kitasato, who isolated the tetanus bacterium. Ehrlich's insistence on precision led to the quantifying and standardising of the antisera for diphtheria and tetanus, and optimised their immunisation regimen.

In 1901, with the help of bacteriologist Kiyoshi Shiga, Ehrlich tested hundreds of dyes on mice, in search of the magic bullet to target the large trypanosome that causes sleeping sickness. Earlier efforts by Alphonse Laveran with subcutaneous injections of arsenic had failed. After two years of frustrating work, Ehrlich and Shiga finally created a red dye modified with sulfo-groups, verified its effectiveness, and subsequently released it as Trypan Red in 1904 as a cure for sleeping sickness.

In 1906, Ehrlich, now the director of the Georg-Speyer-Haus, turned his attention to malaria. Together with Bertheim, the resident chief chemist, he developed hundreds of derivatives of Atoxyl, a toxic drug that caused blindness, before discovering a gold powder, code-named Compound 606. He had found another magic bullet, one capable of killing the malaria organism without corresponding host toxicity. In 1909, Ehrlich tested Compound 606 on a syphilis-infected rabbit, and demonstrated the killing of the spirochaetes with a single dose. At the time, the standard therapy for syphilis was a two-to-four-year regimen of mercury injections. His experimental success led to clinical trials with Compound 606; terminal patients with dementia began to improve and early stage patients with infected sores recovered. 400,000 doses were distributed in approved clinics before Compound 606 was publicly released as Salvarsan in 1910. Unfortunately, adverse neurological side effects, including convulsions and death, led to harsh criticisms. Further toiling in the laboratory yielded the 914th compound – a less toxic, albeit less effective alternative to Salvarsan named Neosalvarsan, which was released in 1913. These remained the most effective syphilis treatments until antibiotics were available in the 1940s.

DEATH AT 61 Ehrlich eventually developed diabetes and suffered two strokes – the second causing his death on August 20, 1915. He was buried in Frankfurt, where the citizens named a street in his honour. Von Behring, who became an adversary after allegedly failing to honour a commercial contract for antiserum production, had these words of farewell: "If we have hurt you, forgive us." Paul Ehrlich, the average student who resisted the learning of medical terms, had unlocked the secrets of magic bullets and vindicated himself with words of his own making such as hapten, toxin, complement and chemotherapy.

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