Paul Ehrlich: Nobel laureate and father of modern chemotherapy

This year marks the centenary of the death of Paul Ehrlich, whose brilliant studies at the beginning of the 20th century resulted in the first effective drug treatment of syphilis, then a worldwide and greatly feared disease.

Until his work there were only two effective agents in the treatment of parasitic infectious diseases; quinine, an alkaloid obtained from the bark of the cinchona tree, which was used in the treatment of malaria, and ipecacuanha, which contains the alkaloid emetine, which was found to be effective in the treatment of amoebic dysentery. In 1907, Ehrlich reported the successful use of the organic arsenical compound salvarsan in the treatment of syphilis in the animal model. The drug came into worldwide clinical use in 1911. Ehrlich received the Nobel Prize for Medicine (together with Elie Metchnikoff, who had described phagocytosis of bacteria by leucocytes) in 1908.

Ehrlich introduced the term 'chemotherapy' to describe chemical agents that would act like a 'magic bullet', that would kill a certain group of organisms without damaging the host's tissues. (The word chemotherapy has been stolen in recent years by oncologists to describe anti-cancer drugs; a kinder but less accurate label than the more threatening term 'cytotoxic agents'.)

Paul Ehrlich was born of Jewish parentage on 14 March 1854 in the small Silesian German town of Strehlen (now named Stzelin, and situated across the border in Poland), some 20 miles south of Breslau. He studied medicine in Breslau and Strasbourg, then part of Germany, and qualified in 1877. Even as a student, he was much more interested in the chemical aspects of medicine than in clinical work, and this was to remain his passion throughout his life.

In 1878, just a year after his qualification, he was appointed chief resident at Professor Frerichs' medical clinic in Berlin and remained there for 7 years. Here he relied heavily on his juniors for the clinical management of his patients, while he occupied himself in the laboratory.

It was during these early years that Ehrlich made his first important discovery. He was among the first to use the newly synthesized aniline dyes for tissue staining in microscopy; this led to his description of the mast cells in blood.

By 1884, he received the title of Professor in Berlin, but 4 years later developed tuberculosis, probably as result of his experiments with the mycobacterium. For over a year he was off work and was among those treated with Robert Koch's newly discovered (but clinically ineffective) tuberculin. Ehrlich returned to work in Berlin in 1890 with the title of 'Professor extraordinary' and took up the study of toxins and antitoxins. In 1887 he published his important work on the standardization of Emil Behring's diphtheria antitoxin, which placed the dosage of this important antiserum on a sound practical basis. In 1899 he moved to the large Royal Institute at Frankfort-on-Main, having been appointed Medical Privy Councillor, and here he remained for the rest of his days. His wide and very separate interests included haemolysis, malignant tumours in mice and then, in 1906, finally turned to the application of synthetic chemistry to therapeutics. It was this, of course, which led to his most important work, the treatment of syphilis.

The inspiration for his work on the organic compounds of arsenic came from the discovery at the Liverpool School of Tropical Medicine that the arsenical-containing drug atoxyl was more effective in the experimental animal (and later in man) in the treatment of trypanosomal infections than were inorganic arsenical drugs. Meantime, another vital step in the story had been made – in 1905, Fritz Schaudin and Paul Hoffmann discovered the causative organism of syphilis, *Spirochaeta pallida* (later renamed *Treponema pallidum*), which could only be visualized under the microscope by dark ground illumination.

Ehrlich and his team set out to modify the chemistry of atoxyl in the hope of producing an agent effective against other trypanosomes, in particular the treponeme of syphilis. By 1907, over 600 compounds had been synthesized and were being studied in the animal model. Ehrlich was now joined by the Japanese bacteriologist Sahachiro Hata, who was an expert at transmitting syphilis to rabbits. Hata was set to work re-testing the whole series of arsenical organic compounds; the 606th compound, named salvarsan, was found to be highly active in the rabbit model. In 1911 it was used clinically, found to be effective, and passed rapidly into worldwide use. If you look up the medical journals of that period, you will see article after article extolling the efficacy of this agent.

However, salvarsan was far from being Ehrlich's magic bullet – it was poorly soluble and had to be given as an intravenous drip in large amounts of solvent; moreover it was relatively toxic. Further work on dozens more synthetic arsenicals resulted in the discovery of the more soluble and less toxic 'neosalvarsan', later called 'neoarsphenamine'. As a medical student in Oxford in 1946, I saw this drug still being in standard use in the venereal diseases clinic, shortly to be replaced by penicillin.

By all accounts, Ehrlich was a remarkable, lovable, rather eccentric, absent-minded professor, working with single-minded enthusiasm. A photograph of him in his office shows him, short and bearded, surrounded by books, journals and papers, which cover his desk, fill his shelves and spread all over the floor. He delighted in devising mottos for his team. His favourite was 'there are four requirements for successful research – aptitude, patience, luck and money'. This sounds better in German – 'Geschick, Geduld, Glück und Geld'.

He died after a short illness on 20 August 1915. BJHM

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