

a history of medicine in pictures

by George A. Bender

painting by Robert A. Thom

Ehrlich: Chemotherapy is Launched

"WE MUST SEARCH for magic bullets. We must strike the parasites, and the parasites only, if possible, and to do this, we must learn to aim with chemical substances!"

Paul Ehrlich's words were no hollow phrases; he backed them with intensive laboratory experimentation. From his work, and of even more importance, from application by others of the principles which he developed, medicine gained many "magic bullets." The new science of chemotherapy owed its growth largely to stimuli arising from Paul Ehrlich's work in Frankfurt, Germany, during the early years of the twentieth century.

There is hardly a field of medicine that has not benefited from Ehrlich's work. In clinical medicine he contributed studies on blood, and the use of methylene blue in malaria. His methods for staining bacteria were of great importance to bacteriology. His work on immunity made practical the application of Behring's findings: it was Ehrlich who standardized diphtheritic antitoxin, and who recognized the existence and role of toxoids. Finally, Ehrlich's originality and discipline of objective experimentation resulted in synthesis of antisyphilitic drugs and launched the age of chemotherapy.

Paul Ehrlich was born March 14, 1854, in the small town of Strehlen, in Silesia, Germany (now a part of Poland). He was the only son of a well-to-do Jewish





family. At ten years of age, Paul was sent to preparatory school at Breslau, where he became a classmate of Albert Neisser, who in later life was to become discoverer of the gonococcus bacillus. From 1872 to 1878 Ehrlich studied medicine in Strasbourg, Freiburg, and Breslau. Though generally his scholastic work was undistinguished, he continued to experiment in his own way. All of Ehrlich's research developed as offshoots of his preoccupation with one problem: why do different tissues have different affinities to the same dye? In Strasbourg he worked under the anatomist Waldeyer; in Breslau, under the physiologist Heidenhain and the pathologist Cohnheim. It was the latter's assistant, Ehrlich's older cousin Karl Weigert, who introduced Ehrlich to use of aniline dyes, greatly increasing the range of his research in staining. It was at the Cohnheim laboratory, too, that Ehrlich befriended William H. Welch, later the man most responsible for development of The Johns Hopkins School of Medicine in Baltimore.

While still a student, Ehrlich began to prepare papers for publication on the morphology of blood. This was an outgrowth of his ceaseless preoccupation with dyestuffs—he was able to differentiate the elements of blood by color analysis. This work laid the foundation for modern hematology.

Ehrlich presented his doctoral dissertation in 1878 at the University of Leipzig. The twenty-four-year-old research specialist received his medical degree for a thesis entitled: "Contributions to the Theory and Practice of Histological Staining." In it, Ehrlich laid down a basic principle that was to pervade his work—that pharmacological activity is based on the affinity of molecules of living matter for various chemical substances when brought into relationship with them.

In 1878, Ehrlich became an assistant to Professor von Frerichs at the Second Medical Clinic of Charité Hospital in Berlin. Von Frerichs recognized his talent, and Ehrlich was permitted to continue his research. In the course of ten years he produced more than forty articles, and published his first book on the "Oxygen Requirements of the Organism." He married Hedwig Pinkus in 1883, and received the title of professor, in 1884, at the University of Berlin. This happy decade came to an end with a change in policy which followed the death of von Frerichs. Also, an attack of pulmonary tuberculosis forced Ehrlich to spend parts of 1888 and 1889 recuperating in Egypt.

In 1890, Robert Koch, famous for his work in bacteriology, invited Ehrlich to work with him. Koch had not forgotten Ehrlich's success in 1882 in inventing a staining method for the tubercle bacillus. At Koch's newly founded Institute for Infectious Diseases, in Berlin, Ehrlich entered upon a new phase of his work: bacteriology and immunology. There, too, he began to work with Emil Behring. In 1892, Behring discovered specific immune substances which developed in blood serum of animals infected with diphtheria or with tetanus bacilli. It was Ehrlich, drawing upon his broad experience and his unprecedented experiments, who supplied practical procedures that enabled Behring to develop effective antitoxins.

During the course of his immunologic studies, Ehrlich developed his famous "side-chain" theory of immunity—an idea revealing the close relationship in which the scientist held his ideas of chemistry and of biology. Essentially, Ehrlich believed that "side-chains," produced in profusion by the body during infection (or supplied artificially when antitoxins were injected), unite with toxins released from bacteria, chemically neutralizing them.

In 1896, Ehrlich was named director of the State Institute for Serum Research and Testing at Steglitz. This makeshift institute provided meager facilities, but Ehrlich continued his researches. "As long as I have a water-tap, a flame, and some blotting paper," he told a friend, "I can work just as well in a barn!" Shortly thereafter, through efforts of Dr. Franz Adickes, Lord Mayor of Frankfurt am Main, there was created in that city a large Institute for Experimental Therapy. In 1899, Ehrlich accepted an invitation to become

its director. There he was destined to work for the remaining sixteen years of his life, and to make the greatest of his discoveries. For the first time, he had fine laboratories, modern equipment, and capable assistants.

In Frankfurt, though a part of his work had to do with cancer research and with evaluation of serums for the government, Ehrlich's efforts were largely directed toward the field of chemotherapy. Indefatigable in his laboratory work, Ehrlich was original and daring. He had an uncanny way of being able to visualize chemical structures in his mind, even before they had been synthesized. In his own laboratory, there was seeming disarray and disorder, but Ehrlich knew just where to find everything. Of his assistants, however, he demanded strictest adherence to order and to his directions. These he laid out for each person, daily, on his "blocks"—small colored cards, on which were scrawled, with pencils of various colors, brief, cryptic directions or questions. Ehrlich demanded immediate attention to these orders, and daily progress reports from subordinates. Kindly, friendly, almost shy, the small-statured, cigar-smoking director could go into a fury of rage when his instructions were not followed. Chemists unwilling to use methods which he directed, however incredible they seemed, did not remain long at the Institute.

Ehrlich naturally began his studies with his beloved dyes. Methylene blue, with which as a student he had so well demonstrated nerve fibers, proved to have antimalarial properties. By 1904, through continuous chemical variation, he had succeeded in producing a dye known as trypan-red which proved effective against trypanosomes, particularly those causing sleeping sickness.

The side-chain theory continued to intrigue Ehrlich. Behring's antitoxins, he reasoned, were the first effective specific remedies for infectious diseases. They were natural products, created within the body. Would it be possible to produce a similar effect with chemical compounds? Would it be possible to find chemicals which would kill specific disease-producing microbes before they would seriously harm the cells of the patient? Most research men were pessimistic. But Ehrlich, supported by the knowledge he had gained during immunity studies plus his boundless optimism, set out to find those "magic bullets," as he called them.

The work which Ehrlich was doing in the field of chemotherapy received a big boost in 1906, when the richly endowed Georg Speyer

House was built next to his Institute and placed under his direction. In 1908, Ehrlich, together with Elie Metchnikoff of the Pasteur Institute, Paris, shared the Nobel Prize in Medicine "In recognition of his work on immunity."

Continuing his search for "magic bullets" which could be aimed at specific invaders without injury to the body, Ehrlich turned his attention to Atoxyl, an arsenical compound discovered in 1906 by Thomas and Breinl, working in Liverpool, England. Atoxyl had been found to be effective against certain trypanosomes, but at the same time to be highly toxic to optic nerves. Ehrlich disagreed with most contemporary chemists regarding the structural formula of Atoxyl, proved his theory correct, and set his assistants to work on a busy schedule of creating chemical variants—seeking always a compound that would possess maximum killing power against organisms of disease with minimum damage to cells of the host. "Parasitotropic they must be, but not organotropic," Ehrlich continually reminded his associates.

Starting with Atoxyl, Ehrlich and his co-workers created 418 separate compounds built around an arsenic radical and tested each thoroughly on animals before one was found that seemed to fulfill his specifications. No. 418, arsenophenylglycine, proved most effective against tropical diseases caused by trypanosomes. The research continued until, in 1907, compound No. 606 was created—the hydrochloride of dioxy-diamino-arseno-benzene. Ehrlich was optimistic about this compound; but an assistant erroneously reported that it had no effect whatsoever on trypanosomes, and so it was laid aside.

Two events contributed to the advancement of Ehrlich's chemotherapeutic endeavors. In 1905, Professors Fritz R. Schaudinn and Erich Hoffmann had discovered the spirochete, *Treponema pallidum*, to be the cause of syphilis. This pale, corkscrew-shaped organism had wrought immeasurable damage upon the human race for centuries, virtually unchecked by any drug or therapy. Its discoverers believed there was a relationship between spirochetes and trypanosomes, and, because of the far greater significance of the disease, Ehrlich began to study syphilis. Second event was the arrival at the Institute's laboratories, in 1909, of Dr. Sahachiro Hata, a pupil of Ehrlich's friend, Professor Kitasato, bacteriologist of Tokyo. Dr. Hata had been working experimentally with syphilis in rabbits, and had been sent to Frankfurt

the picture In his crowded laboratory at Frankfurt's Institute of Experimental Therapy, German research scientist Paul Ehrlich (1854-1915) habitually scrawled work orders to associates with stubby colored pencils on "blocks" of note paper. Dr. Ehrlich and his Japanese assistant, Dr. Sahachiro Hata, announced Salvarsan (606) to the world in 1910 as a "chemical bullet" for treatment of syphilis. Dr. Ehrlich's success with chemical synthesis gave impetus to a new medical science, chemotherapy. Though his greatest achievements were in this field, Dr. Ehrlich contributed to many branches of medicine and shared in a 1908 Nobel Prize for his work on immunology.

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for further study. His first assignment at the Institute was to test on syphilis-infected animals every compound, old and new, that had been developed in the laboratories. The patient Japanese set about the task with characteristic thoroughness. Eventually, Hata came to compound 606. He reported to Ehrlich that it was by far the most effective and least toxic of all compounds tested against syphilitic infections.

Ehrlich was pleased, but he demanded further tests, hundreds of tests. Hata made them. Then, tests were begun on humans, conducted by cooperating physicians at nearby hospitals. Hundreds more tests were required to determine effective doses, safe doses; to determine whether the relief was permanent, or whether relapses would occur. Meantime, Professor Iversen at the St. Petersburg Hospital for Men reported that 606 completely cured patients with relapsing fever.

Drs. Ehrlich and Hata reported development of 606 and their experiments with the compound to medical men from many countries at the Congress for Internal Medicine, at Wiesbaden, Germany, April 19, 1910. Dr. Schreiber of Magdeburg Hospital gave an account of the first successful treatment of syphilitic patients at his hospital with 606. The announcements had an electrifying effect upon the medical world. Demands and entreaties for the drug poured in on Ehrlich. The name, Salvarsan, was given to compound 606, and it was registered with the patent office. Facilities at Georg Speyer House were put to making the drug in quantity; the Höchst Chemical Works began to build facilities for its manufacture—but for some time demand far exceeded supply. Ehrlich insisted on keeping a close check on any irregularity arising from the use of 606. He devised a method for intravenous injection to get away from tissue damage and danger of infection—and then had to educate the medical profession to its use. He continued to search for more and better compounds. Finally, in No. 914, he found what he needed: the drug was not quite so active against the spirochete—but it was far safer, and much less difficult for physicians to administer. No. 914 became Neosalvarsan—and, for three decades, until the introduction of penicillin, Neosalvarsan (nearsphenamine) and Salvarsan (arsphenamine) remained dominant as remedies for syphilis. In Paris, Ernest Fourneau at the Pasteur Institute applied Ehrlich's techniques to bismuth, creating several anti-syphilitic compounds which paralleled and supplemented the arsenicals.

Ehrlich, at last, had created his "magic bullets." Regrettably, his success, while winning him many honors and much fame, also brought attacks. Some were from crackpots, who accused him of trying to poison people.

Some were acts of jealousy. Some were anti-Semitic in character. These attacks greatly perturbed the kindly scientist, who wanted only to help the sick. In the scientific field, he could deftly answer any challenge; but these unfounded, unwarranted, unscientific attacks were beyond his understanding. These, together with worries attendant with the beginning of World War I, in August, 1914, undoubtedly contributed to shortening Ehrlich's life. A first stroke, late in 1914, was followed by a second, fatal attack on August 20, 1915. He was buried in the Jewish Cemetery of Frankfurt.

Paul Ehrlich has been variously described by different writers. Some have emphasized his eccentricities, his absent-minded habits, his disregard for conventional order. Some have portrayed him as an unscientific experimenter whose "shots in the dark" luckily hit some marks. But the facts remain: his wealth of ideas, his enthusiasm for biochemistry, his courage to try new avenues and his general creativity, combined with great gifts for organization and for harmonious direction, earned him the title of genius. Medicine has been heir to many "magic bullets" since 1915, created by men who followed in Ehrlich's footsteps in creative chemistry: among them, the antimalarials, the sulfonamides, the anti-histamines, the ataraxic drugs.

A modest, kind, faithful man, respected by true scientists and medical men world-wide, beloved not only by his family but by his laboratory assistants, his faithful custodian Kadereit, and his secretary, Martha Marquardt, Paul Ehrlich was one of the greatest figures in medicine in the first half of the twentieth century.

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