Paul Ehrlich: pioneer of chemotherapy and cure by arsenic (1854-1915)

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SUMMARY  Paul Ehrlich's experiments in staining techniques at the end of the nineteenth century resulted in many discoveries which help to form the basis of present research work. Ehrlich's chemotherapy research led to his formulating the arsenic compound, Salvarsan, which was used in the treatment of syphilis during the first half of this century until it was superseded by penicillin.

Background

This remarkable man came of Jewish stock. He was born in Strzelin, Silesia, Germany, schooled at Breslau College, and went to the University there. He later transferred to the newly founded University of Strasbourg, where he entered the medical faculty and met the great Robert Koch.

Ehrlich had an air of alertness and animation and was mildly humorous, kind and, never pompous. He took little exercise, smoking twenty strong cigars daily, and invariably used a cab to and from the laboratory. He read little outside his own scientific range, but was an ardent reader of the Sherlock Holmes stories of Sir Arthur Conan Doyle.

Career

He completed his studies at Leipzig University with a degree thesis on the value and significance in medicine of staining with aniline dyes. This perceptive work was the groundwork for his side chain theory and showed his essential genius, becoming, in time, the basis of his entire life's work on chemotherapy.

In 1877 after working in a hospital pathology department, he secured an internship at the Charité Hospital, Berlin, where he set up a primitive laboratory in a disused wing. Showing a colleague a pot containing an excised primary chancre, he said "when the microbe causing syphilis is found, I must be prepared". He was to wait until 1905, when Schaudinn and Hoffmann discovered the spirochaete with the new Zeiss ultra powerful lens.

After graduating, he became interested in staining reactions of tissues and discovered mast cells. He later devised a classification of leukaemias which remains in use to this day, and established the function of bone marrow as a tissue of defence. In 1882, fired with Koch's discovery of the tubercle bacillus, he started experimenting on selected stains which quickly and easily identified the rod shaped organism. This earned him Koch's delight and admiration, and so established a lasting friendship.

Ehrlich married a Prussian lady called Hedwig Pinkus, but shortly afterwards contracted pulmonary tuberculosis. He resigned from his appointment and travelled to Egypt accompanied by his young wife,
where he made a complete recovery after two years’
treatment with Koch’s tuberculin. He had resumed
intensive experiments on serum antitoxins, when he
saw and heard of Von Behring’s antitoxin serum for
diphtheria. Ehrlich’s standardisation of its unit
potency has become the accepted basis for diphtheria
serum.

For several years Ehrlich experimented extensively
with the organic dye, methylene blue, as a better and
cheaper substitute for quinine in treating malaria,
but it did not succeed clinically. When quinine
supplies were cut off in the second world war,
however, Bayer laboratories found Ehrlich’s work
helpful in producing the successful compounds
known as Plasmoquin and Atebrin.

Ehrlich became Head of the Royal Institute of
Experimental Therapy, Frankfurt, in 1899, and it
was here that his career reached its climax.
The following year he gave the Croonian Lecture. He
selected a brilliant team of researchers, including C J
Browning who was later to become Professor of
Bacteriology at the University of Glasgow.

In 1906 Wasserman discovered his reaction for the
diagnosis of syphilis, and publicly acknowledged that
this was thanks to Ehrlich’s pioneer work on
haemolysins and the studies of Bordet and Gengou
on antibodies. Ehrlich told his workers that,
although their past five years’ research work on try-
panosomiasis had not led to any usable result, they
had extended knowledge on protozoa. They now had
to make efforts based on Breinl and Thomas’
researches at Liverpool University on arsenical
organic compounds to find the “silver bullet” (as he
called it) against the syphilis spirochaete. These two
researchers had produced a pentavalent arsenic
compound (Atoxyl) which had been used in treating
trypanosomiasis, but had been discontinued as its
high arsenic content had caused optic atrophy. The
therapeutic problem was how to obtain maximum
effect on the parasite with minimum effect on the
body tissues. In 1907, Ehrlich produced his six
hundred and sixth preparation of an arsenobenzene
compound. For some unaccountable reason its
potential was overlooked for two years, but later bi-
ological work with it on syphilitic rabbits convinced
him of its importance. He believed he had found his
“silver bullet”.

As well as having the best resources of the
synthetic chemical industry, Ehrlich had patho-
logists, biological chemists, bacteriologists, and
organic chemists at his call. In retrospect, the scale
and magnitude of his operations are quite difficult
for us to comprehend. The whole series of trials had
taken over four years of patient, painstaking, and
devoted scientific investigation by the best brains in
Germany. At last the whole world would have a cure
for syphilis.

When the chemical firm of Hoechst eventually
gained his approval to market Salvarsan (healing
arsenic), sometimes called “606”, a total of 65,000
free samples were sent to doctors in all parts of the
world. At a Congress for Internal Medicine in 1910 at
Wiesbaden, he announced the promising results he
had achieved with Salvarsan. He was especially fond
of telling colleagues of a patient severely crippled
with tabes, who was so improved after treatment he
could jump on to a moving tramcar. The newspapers
carried the good news with banner headlines and
international scientific periodicals were equally
enthusiastic. Within six months medical men all over
the world clamoured for supplies. Ehrlich con-
tinually warned them that it might be harmful
because of its very powerful action, and urged
caution with intravenous injections. The chemical
structure of the “silver bullet” was based on 32%
arsonic, and was thus closely related to the poison
generally associated with murder cases. Professor
Herxheimer, Director of Dermatology at Frankfurt
Hospital, also warned colleagues about dosage and,
in a thesis based on clinical results, reminded them
of reactions after primary injection. Proceedings
against Ehrlich on grounds of criminal negligence
were started by one Carl Wassman, who slandered
Ehrlich publicly and libelled him in newspapers.
Ehrlich shrank from defending himself, but
Herxheimer brought Wassman to court, where he
was sentenced to one year’s imprisonment.

After the start of the first world war Ehrlich was
under great strain, supervising supplies of Salvarsan
and serum on a huge scale for the German army. By
1915 he had physically and mentally exhausted,
and died in that year on 20 August from a stroke. He
was buried in Frankfurt, the city of which he was a
freeman. His obituary in The Times said “He opened
doors to the unknown, and the whole world at
this hour is his debtor”. He had received the greatest
academic honours, including the Nobel Prize for
Medicine, honorary doctorates from the universities
of Oxford, Gottingen, and Chicago, the Prize of
 Honour of German Chemists, gold medals from
eleven countries as far apart as Norway and Japan,
the Cameron Prize of the University of Edinburgh,
and the Prize of Honour at the Lisbon Congress of
Medicine.

Salvarsan, and its less toxic derivative Neo-
salvarsan continued to be widely used in Europe until
they were replaced by penicillin in the late 1940s.
Their use against yaws carried on even later in the Far
East where penicillin was not easily available and
exorbitantly priced.

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