

Ehrlich's Magic Bullet - and the Curse of Injections

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Abstract

Ehrlich made more than 600 arsenic compounds, one of which, Salvarsan, cured the disease of syphilis. Later, one injection was found to cure in ten days, the terrible, disfiguring, tropical yaws. This Magic Bullet seemed a miracle, but the injection itself was absorbed into local cultures so that all treatments were given with injections. However, hepatitis and HIV were transmitted to tens of millions by injections. Probably 16 billion injections are made every year, many unnecessary and unsterile. WHO has adopted a campaign for the use of 'once only' syringes, but most injections are given outside the health services, and syringes are used many times without cleaning or sterilizing. It is these injections which must be stopped.

Keywords: Ehrlich; Injections; Polio; Yaws; Syphilis

Introduction

Paul Ehrlich, the inventor of the Magic Bullet died, regretting the slaughter of the First World War. As biology students in the early 1940's we all knew one important number, 606, the name of the first man-made drug, Salvarsan or the Magic Bullet. A German doctor, Paul Ehrlich, had noticed that different dyes would stain tissues and even bacteria and parasites. He noticed that methylene blue stained nerve endings, even in living tissues and hoped that use of the dye in patients might subdue pain. In this, he was disappointed although he continued to use dyes against trypanosome infected mice.

He wondered if he could attach a toxic chemical, like arsenic, to a dye which would then stain only the disease organism and kill it. He tried unsuccessfully until in 1909, the 606th compound cured rabbits infected with syphilis. Forty years later when I was studying for my Ph.D., men, but not women, in the cardiac wards were secretly given the Kahn and Wasserman tests for evidence of past infection. About one in ten was positive and had probably been treated for the disease in the first world war. Some years later this same compound was found to kill the related organism which caused the horrible disfiguring tropical disease of yaws. The disease was cured in ten days! It was another two decades before another German, Domagk, discovered Prontosil, the first of the sulphonamide drugs which were effective against child birth fever.

Ehrlich was a pioneer who recognized that the inventor of a new drug must check that it is safe as well as effective. Salvarsan was an effective drug, but he realized that with its poisonous arsenic content, it might have serious side-effects. He rejected some of the early batches and improved the manufacturing processes. In 1909 Ehrlich himself tested nearly 400,000 ampoules of his Salvarsan for strength before they were tested on more than 20,000 cases (he presumably tested the batches although the biography is ambiguous about this [1]). Ehrlich did not release the drug for general use until he had received reports on its use with test cases. He only sent his ampoules of the drug to known and trusted doctors who were obliged to send him reports of all adverse effects suffered by patients. These doctors promised to use the drug only according to his instructions. They had to promise to: 'select carefully the cases, only cases in the primary state of the disease... watch the treated cases with the utmost care, make a note in their records of the slightest change in the patients' general condition, and send Ehrlich a detailed report of everything that happened'.

A major cause of distress was the use of aged distilled water in which there were bacterial contaminants causing endotoxic reactions. When some patients died of septicaemia, Ehrlich thought that although the doctors were distilling the water to be used to prepare his compound, they were keeping it until needed and contaminating bacteria were multiplying. Other doctors were using distilled water bought from their local pharmacy, which stored the water in large containers until the next batch was required. He insisted that only freshly distilled water should be used and no more deaths occurred.

We are fortunate to have two fine biographies of Ehrlich. Martha Marquardt was his secretary for 13 years and wrote a 'lively and highly personal portrait of his complex character' [2]. Baumler wrote an absorbing biography not only of his scientific and medical work, but also of the anti-semitic discrimination and the social and scientific prejudices which clouded his life (and that of his widow) [1]. Ehrlich was the final scientist in Paul de Kruif's widely read and influential 'Microbe Hunters' [3].

Ehrlich was born in 1854 in the town of Strehlen in Upper Silesia of parents who kept an inn. At school he excelled in Latin but his 'German composition was wretchedly bad' and he very nearly failed his matriculation examination because of it. Visiting his elder cousin Carl Weigert, young Ehrlich was shown a slide with parts of some cells stained with a dye. He recognized that dyes could be used to probe the different components of cells. From then on, even as a schoolboy, he worked for hours on staining tissues. He studied at four universities and at Breslau he was present at the historic and momentous demonstration by Koch of his experiments with photographs of the germination of anthrax spores and their bacteria. Later, Koch was able to stain the bacteria of tuberculosis in tissues, but Ehrlich was unable to repeat it with new dye. He realized that the old dye had been changed by ammonia in the laboratory air.

In 1878, as a doctor of medicine and already with a reputation for

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histological staining, he was appointed to the famous Charite, an East Berlin hospital. One night he put the stained slides with organs and sputa from tuberculosis patients on top of his small, but cold stove, to dry. In the morning, his cleaner lit the stove without moving the slides. By chance, Ehrlich had discovered a new and important method of staining the tubercle bacterium! [2] The technique we use today is a modification of that staining. Five years later, he used that stain to discover to his horror that he was himself infected. Fortunately he recovered.

Ehrlich was an extraordinary doctor and scientist who is justly remembered for his major works on the understanding of the immune system, Salvarsan and the magic bullet. Yet he was far in advance of his time with other pioneering work. Paul de Kruif did not mention his early work on the testing and control of the antitoxins used against diphtheria and tetanus. In 1896 Ehrlich was appointed to head the 'State Institute for the investigation and control of sera' which would monitor the levels of antitoxin which were produced for clinical use. Ehrlich established the therapeutic dose and realized that the preparations needed to be checked against a standard concentration of toxin so that the antibodies neutralized all of the toxin and so would be therapeutically reliable.

Dr. Shiga had found the bacterium that causes dysentery and came to work with Ehrlich. Together, they cured a single mouse infected with sleeping sickness by using the dye trypan red. Sadly, the treatment did not work in humans. Ehrlich was not satisfied with his 606: he went on searching for a better drug. He tested another 300 variants and found a newer and better version – NeoSalvarsan. It was easier to make and easier to use.

Nearly 30 years later there was no such control over two vaccines used in the USA. In 1935 three American doctors produced two supposed polio 'vaccines' and with highly dubious testing allowed them to be used to 'immunize' children. The vaccines were sent to doctors with no checks or records. The doctors themselves kept no records of the patients or of their health. The 'vaccines' were only tested by injection into the CNS in suitable primates, as feeding and other routes were negative for the live virus. The 'vaccines' probably contained virulent poliovirus if injected into the CNS although not otherwise infectious for humans and were certainly ineffective. And nearly 50 years later, the batches of Salk vaccine were not tested for safety, resulting in many cases of paralysis and some deaths. Even forty years later, the makers of thalidomide in Germany did not monitor the safety of their drug.

In 1908, Ehrlich was awarded the Nobel Prize, with Elie Metchnikoff, a Russian bacteriologist from the Institute Pasteur, Paris. A Google search for Ehrlich gives a first response to 'bio. True story' which states that Metchnikoff was Ehrlich's partner and that they worked together; neither statement is correct, they met for the first time in Stockholm at the Nobel ceremony. Among those who worked with Ehrlich was a Swiss, Dr. Paul Karrer, who left to become Professor of Chemistry in Zurich in 1918. He was awarded a Nobel Prize in 1937 for his work on vitamin synthesis: his son, Heinz, was a famous electron microscopist.

Unexpected Complications of Injections

Ehrlich was a careful worker who looked for adverse reactions to the use of his drug. However, sometimes an adverse reaction is not recognized because it represents a new (and unknowable) reaction. In 1914, when Ehrlich was already 'exhausted from overwork and depression' [2], Dr Hans Kern reported an outbreak of poliomyelitis

in children with congenital syphilis in a home in Germany [4]. Five children, aged between one and three years developed paralysis during treatment with NeoSalvarsan, Salvarsan and other drugs: 23% of the children under treatment. This was the first instance of what was reported as provocation polio in 1950. There was no way that reports of such incidents from 1914 onwards could have been regarded as anything other than coincident events following different injections [5].

The Magic Bullet, 606 cured many of disease, but another Bullet, the 303 fired from a Rifle, killed millions in the First World War. Unfortunately, another consequence of the use of Salvarsan has been the belief of the magic of injections in the third world following the magical cures of the hideous sores of yaws within ten days or so after the injection of Salvarsan. People dismissed the role of the injected drug and instead focussed on the evident (and no doubt painful) physical action of the injection. Accounts of the campaigns against yaws in the whole of the tropics and other regions used the word 'magical' to describe these cures. Lambert recorded that his assistants in Samoa would clamour for injections of surplus Neoarsphenamine (a later variant of Salvarsan) at the end of the day. The Samoans would trek long distances with illnesses not susceptible to the drug, in order to be given the injection [6]. Of course, there were many drugs which also fostered the popularity of injections, but no other accounts use the extravagant terms of 'magic' [7]. One study found that syringes were used 600 times without cleaning or sterilizing. The popularity of injections has increased over the years and WHO has recently estimated that there are 16 billion injections given every year – many are unnecessary and also unsterile. They are given outside the health services. These injections have transmitted hepatitis and HIV to millions of people and have caused polio paralysis for hundreds of thousands of children [7,8]. Again, no-one could have foreseen the consequences of treating yaws with injections of the Magic Bullet.

But this year WHO has announced a campaign to end the reuse of syringes by 2020. WHO hopes that single use syringes, which cannot be reused, will be the only ones in use by then. We should remember Ehrlich, a very great scientist, but especially this year when WHO is set to control the use of unnecessary injections [9].

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