Of Rabbits and Men: The Tale of Paul Ehrlich

In our modern world of chemotherapy, antibiotics and antivirals, it might come as a surprise to find that the origin of all these treatments can be traced back to rabbits; the cute and fluffy kind. To understand why, we need to go all the way back to 1882 Berlin. A talented, if aimless, young German doctor, Paul Ehrlich, had just met the great microbiologist Robert Koch. Koch was giving a lecture in which he identified the pathogen responsible for tuberculosis. Ehrlich was instantly fascinated by Koch and microbiology. Unknown to himself, he had just taken the first step on a path that would help change the way disease is tackled forever[1].

The late 1800's were a time of dynamic change in the sciences. Charles Darwin had proposed his Theory of Natural Selection and Thomas Edison had given us the light bulb. Amongst the many fashionable topics of the time, some biologists were fascinated by dyes; specifically the staining of living tissue. Spending all day bent over a microscope looking at the pretty colours might not seem like worthwhile science by modern standards, but these dyes had interesting properties. Dyes displayed a high level of specificity; they would only stain certain structures and pass through others. Ehrlich noticed this and soon started to think of applications for these properties.

These were times when catching a chill could kill. Many well-known individuals of the time were killed in their prime due to infectious disease. Emily Brontë died from tuberculosis[2], René Descartes from pneumonia[3] and Pyotr Tchaikovsky died from cholera[4]. However, one of the most notorious and stigmatising diseases out there by far was syphilis.

Syphilis is a bacterial sexually transmitted disease (STD) and was known at the time as the great pox. As the name suggests, the disease was characterised by pus-filled pustules. Untreated, the disease could lead to heart conditions, deformities and death [5]. Dr. Ehrlich believed that the selectivity observed with dyes could be harnessed to attack the bacterial organism responsible for syphilis, without damaging human tissue. Being an avid hunter, he likened it to having a "magic bullet" to kill the bacteria.

Magic bullets made from dyes do not sound like the most promising start for serious science, but this was a different age. Walking into a pharmacy in the 1800's would be a very

interesting experience. Is your child teething and won't stop crying? No problem! The hefty dose of morphine in our all purpose soothing syrup should do the trick. Not to mention the use of mercury for STDs, bloodletting with leeches and the prescription of heroin for a cough[6]. To say that these had mixed results is an understatement, although by all accounts, heroin was excellent at dealing with a cough. Common side effects could include increased tolerance, addiction[7] and sudden loss of self-respect.

So what about the rabbits? You were promised fluffy and cute and the story delivers. Unfortunately for the rabbits, it is in a thoroughly unpleasant fashion. By 1899, Erhlich had been appointed director of the Royal Institute of Experimental Therapy in Frankfurt. In this role, he had free reign to explore his idea of "magic bullets" to attack disease. His work was initially unfocused and he worked on parasitic infections as well as bacterial infections. It was his work with sleeping sickness, a parasitic disease spread by the tsetse fly[8], which helped him identify an anti-parasitic arsenic compound called Atoxyl. This discovery encouraged Ehrlich in his search for a compound to treat and cure syphilis. The rabbits had the unfortunate job of being his test subjects[1].

Rabbits were known to be susceptible to syphilis and so made excellent test animals. However, to the rabbits' added misery, Ehrlich had no idea which arsenic compound would be effective as a magic bullet. Arsenic, as we all know, is not something to be adding to your tea. Often referred to as the inheritor's powder, arsenic trioxide was *the* poison of choice in the 19th century[9]. How could such a dangerous substance ever be thought of as a cure? The answer is that not all arsenic compounds are poisonous to mammals. Ehrlich knew this, and set out to find one that would attack the infecting bacteria but not the rabbits.

His approach largely relied on meticulous testing, strict organisation and a good helping of wishful thinking. Not knowing which arsenic-based dye would do the trick, he and his Japanese assistant, Dr. Sahachiro Hata, had to test them all. Things were pretty bleak for the bunnies. If they were *lucky* they would have survived the poisoning, only to still be suffering from syphilis. The unlucky ones would be killed by the compounds used, all in the name of science.

In 1908 Ehrlich was awarded a Nobel Prize for medicine and physiology. He had built a reputation as an expert in immunology and was well respected in his field. However the

magic bullet still eluded him[1]. By 1909, the two microbiologists had gone through 605 different variations of arsenic molecules, testing them all on the infected rabbits. Compound 606, arsphenamine, finally displayed the properties the two scientists (and hundreds of rabbits) had been hoping to find. Ehrlich and Hata had stumbled upon a chemical that cleared the syphilis infection, but did not kill the rabbit. It would later be renamed as Salvarsan and be marketed as the first targeted treatment for syphilis. In later years, a new more soluble arsenic compound was also discovered by Ehrlich and Hata. Compound 914 was slightly less effective than Salvarsan, but it was easier to administer and was marketed as Neosalvarsan[10].

Unfortunately the establishment, as is so frequently the case, was slow to realise the importance of Ehrlich's work. Ehrlich being Jewish, this reluctance was in no small measure due to anti-Semitic feeling within some sections of society. Additionally, many people considered syphilis a just punishment for those with a less than wholesome lifestyle. It was believed that the availability of a cure would lead to generalised debauchery and loose morals. Nonetheless, the step had been taken and both Salvarsan and Neosalvarsan would go on to help millions of people[11]. However, more significant was the attitude change brought about by Ehrlich and his work. He inspired many future researchers, including Alexander Fleming, who discovered penicillin. From this point on, science would strive to find more "magic bullets" and attempt to directly target the cause of disease. His meticulous approach towards drug discovery would also change the way new medicines were tested. Medicine took its first steps out of the dark ages thanks to Ehrlich and his rabbits. The age of chemotherapy had arrived.

References

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