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extra

The original 'magic bullet' is 100 years old

Frank Heynick

Today, even long-retired psychiatrists are unlikely to recall having seen more than some occasional cases of syphilis-induced paralytic dementia. But not many generations earlier, 'general paresis of the insane' accounted for some 10% – even as much as a third – of the admissions to mental hospitals in Europe and the USA. All that began to change on the day in August of 1909 when Paul Ehrlich fired the first 'magic bullet'.

Dyes

Born in 1854 to a middle-class Jewish family in Strehlen, Germany, Ehrlich came on the scene at the right time and place, for it was the dawn of the 'heroic age of medicine' and, not coincidentally, an era of rapid advances in the chemical industry. While chemists were revolutionising textile manufacturing through the development of a new spectrum of synthetic dyes such as mauve and indigo, medical microscopists, especially in Germany, were using the new aniline stains to tease out the secrets of sub-visible life, particularly the identification and classification of microbial pathogens.

Already as a young boy, Paul Ehrlich was fascinated by the dyestuffs and colours of the nearby Silesian textile plants. His doctoral dissertation at the University of Leipzig introduced the concept of counterstaining *in vitro* and he soon went on to develop dynamic vital staining *in vivo*.

As professor in Berlin and Frankfurt, the physician/chemist Ehrlich pioneered the fields of haematology, serum therapy, oncology and, most notably, the molecular side-chain theory of immunity that would be honoured with the Nobel prize.

However, the triumph for which Ehrlich would forever be remembered was yet to come. As director of the new Royal Institute of Experimental Therapy in Frankfurt early in the new century, Ehrlich returned to his youthful dream of developing a chemotherapeutic antibiotic or, as he called it, *Zauberkugel* – magic bullet.

Arsenic

Put simply: Ehrlich envisioned a very selective dye-like compound – it could even be colourless – which, when injected into the bloodstream, would home in on specific pathogens and deliver a fatal blow, while leaving the other cells of the body undisturbed.

Arsenic could be found in the *materia medica* since medieval times. French, British and American scientists had recently been experimenting on its use for combating the trypanosomes of sleeping sickness. Ehrlich joined in the hunt for a safe antimicrobial arsenical 'dye'.

But the downside to this approach was obvious. Arsenic was, after all, the favourite poison of murderers and assassins. Ehrlich's critics publicly cartooned him as 'Dr Phantasus' and several of his master chemists quit in frustration. Ehrlich himself began questioning the value of further investment of money, time and effort on sleeping sickness, which was, after all, a tropical disease of peripheral concern to Europeans.

606

Then, in 1905, came the news of the discovery by the German microscopist Fritz Schaudinn of the tiny, ghostly pale, corkscrew-shaped causative agent of syphilis *Treponema pallidium*. On the basis of morphological similarity Schaudinn took the dubious liberty of relating it to the trypanosome of sleeping sickness, and therefore perhaps susceptible to similar chemotherapeutic agents.

This gave renewed vigour to Ehrlich's quest for the magic bullet. Having already experienced several hundred failures, he was ready to tolerate several hundred more.

On 31 August 1909 came the breakthrough, as the 606th arsenical compound rapidly cured a rabbit of syphilis and produced no side-effects. There followed tests with a few human patients and subsequently a historically unprecedented clinical trial with 65 000 doses. The overall results were astounding. Only then was Salvarsan (the trade name, meaning 'safe' or 'saving arsenic') put on the market.

Within a decade, the incidence of syphilis in many countries was slashed by three-quarters and more. Most important from the psychiatric standpoint: admissions to mental hospitals of patients with neurosyphilis were beginning to be a thing of the past.

The magic bullet, let it be said, was not free from backfiring: liver and kidney dysfunction and occasional fatal shock. Yet Salvarsan – and Ehrlich's later variant, Neosalvarsan – would remain the treatment of choice for syphilis until the advent of penicillin in the Second World War.

Dream

In today's post-industrialised world, the challenges facing medicine – cardiovascular disease, cancers, genetic defects, and geriatric care – are more complex than the targeting of pathogens in the heyday of the 'microbe-hunters'. This is all the more so with regard to the array of mental and psychosomatic afflictions confronting so many members of our society.

Yet the dream lives on of chemotherapeutic wonder-drugs that may alleviate depression (or reverse senile dementia, or dry up various cancers) in such a specifically targeted way as to have minimal side-effects. This is in the spirit of Paul Ehrlich and the first magic bullet created a century ago.

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