Gerhard Domagk: a Nobel laureate pioneer of chemotherapy

This year marks the 50th anniversary of the death of Gerhard Domagk, on 24 April 1964, whose work was an important step in the development of the effective chemotherapy of bacterial infections.

Since Louis Pasteur's studies in the 1860s and 70s on the bacterial basis of wound infection, and those of Joseph Lister on the antiseptic treatment of wounds, in which chemical agents were used to kill the contaminating bacteria, medical scientists dreamed of the possibility of the discovery of an agent that would destroy the invading microbes without, at the same time, damaging the patient's own healthy tissues. Indeed, mercury had been introduced for the treatment of syphilis in 1495 and quinine for malaria around 1630, long before the aetiology of these diseases was understood.

Paul Ehrlich, of Frankfurt am Main, Germany, introduced the term 'chemotherapy' in 1905 in reference to a synthetic chemical compound that would be a specific antidote to a disease produced by a particular micro-organism. Three years later he received the Nobel Prize for his work on immunity. Ehrlich then commenced an exhaustive study of a large series of newly synthesized compounds of arsenic for the treatment of syphilis. Eventually compound number 606, which he named 'salvarsan', was shown to be effective against the spirochaete of syphilis in the rabbit. It was first put to clinical use in 1911. Salvarsan is poorly soluble and large amounts of the dilute solution had to be given by intravenous drip. A later compound, neosalvarsan (neoarsphenamine), was developed, which was more soluble and for decades was the standard treatment for this disease. I saw it being used in the venereal diseases clinic (as it was then called) when I was a clinical student in Oxford in 1946.

Ehrlich coined the term 'the magic bullet' – an agent that would kill the invading organisms without injury to the host. Neosalvarsan was hardly the perfect bullet, since it was a toxic drug with unpleasant side effects.

Another example of a specific but unpleasant drug was emetine, developed in the 1920s by Sir Leonard Rogers for the treatment of amoebic dysentery, which continued in use until the fairly recent introduction of the much less toxic metronidazole.

The next major step in chemotherapy again came from Germany. Gerhard Domagk, the subject of this anniversary, was born in Brandenburg in 1885. His medical studies at the University of Kiel were interrupted after a few months by the outbreak of the First World War in 1914, when he enlisted in the army as a grenadier. He was wounded on the Western Front and, after recovery, was posted to the Medical Corps. After the war, he returned to medical school and graduated in 1921.

In 1925 Domagk was appointed to a readership in pathology at the University of Munster, where he studied new chemical substances and their power of disinfection. At the age of 32 years he was appointed Director of Research at the giant chemical works of I.G. Farben, near Dusseldorf, where his task was to investigate the vast numbers of new synthetic dyes being produced by the dye chemists for their possible useful medical purposes.

Among these compounds, in 1932 he studied the red dye Prontosil rubra. Although inactive in vitro, it was shown to protect mice from streptococcal infection when given by nasogastric tube. It was soon shown to be highly effective in clinical practice in dealing with streptococcal infections, with the disadvantage that it (temporarily) also stained the patients red!

These important results were published in February 1935. Within weeks of this publication, workers at the Pasteur Institute in Paris showed that it was the sulphanilamide fraction of the prontosil molecule that was the active agent, both in vivo and in vitro. By 1936, Leonard Colebrook at Queen Charlotte's Hospital London used sulphanilamide on 64 women with severe, life-threatening, puerperal sepsis with only three deaths.

There is an interesting question to be answered. Domagk's exciting mouse experiments were performed in 1932 and the first clinical use of prontosil was in December of that year, yet these important results were not published till February 1935. The 'official' reason given is that the results seemed too good to be true and that more time was needed for intensive research. However, the bacteriologist Professor Ronald Hare (1970), in his book *The Birth of Penicillin*, had another explanation – Domagk and his chemists were almost certainly using sulphanilamide in the process of synthesizing Prontosil. Sulphanilamide had itself been synthesized by Paul Gelmo for his PhD in Vienna in 1908 and therefore could not be patented. The most obvious solution would be to hold off publication while attempting to produce compounds having formulae sufficiently different from sulphanilamide for them to be capable of being protected by patents.

Although Domagk does not emerge with much credit from this explanation, it could well be that he was not a free agent and was doing only what his commercial employers demanded of him.

Domagk was awarded the Nobel Prize for Medicine in 1939; amazingly, Hitler forbad him to accept the honour. However, in 1947 he was able to attend the ceremony in Stockholm to receive his award.

In his later years, Domagk continued his work, with studies of the thiosemicarbazones in the treatment of tuberculous infections, but he will be remembered for his important investigations which led to the sulphonamide drugs and later to the isolation of penicillin and the subsequent antibiotics. **BJHM**

Professor Harold Ellis *is Emeritus Professor of Surgery, Guy's, King's and St Thomas' School of Biomedical Sciences, London SE1 1UL*

Conflict of interest: none.

Hare R (1970) *The Birth of Penicillin.* Allen and Unwin, London