The birth of the antibiotic era

Just 75 years ago, on 16 August 1941, *The Lancet* published a paper entitled 'Further observations on Penicillin'. Its authors were given alphabetically as EP Abraham, E Chain, CM Fletcher, HW Florey, AD Gardner, NG Heatley and MA Jennings. There is no doubt that this paper represents one of the great landmarks in medical history and, for practical purposes, marks the birth of the antibiotic era.

Since the work of Louis Pasteur and Joseph Lister, medical scientists had dreamed of the possibility of drugs that would destroy invading microbes without damage to the patient's healthy tissues.

Paul Ehrlich, of Frankfurt, Germany, introduced the term 'chemotherapy' in about 1905 – a synthetic chemical that would be specific for a disease produced by a micro-organism without damage to the healthy tissues of the recipient. Already mercury had been used for the treatment of syphilis and quinine for the treatment of malaria, long before the aetiology of these diseases was understood. Ehrlich began an exhaustive study of the newly synthesized organic compounds of arsenic in the treatment of syphilis.

Eventually compound number 606, which he named salvarsan, was shown to be effective, first in the rabbit and then, in 1911, in clinical studies in man. A later compound, neosalvarsan, renamed neoarsphenamine, was synthesized, which was more water-soluble and less toxic. As a medical student in my first clinical year in 1945, I saw neoarsphenamine being used routinely in the Venereal Disease Clinic at the old Radcliffe Infirmary in Oxford.

The next major landmark was the introduction of the sulphonamide drugs by Gerhard Domagk in Germany in 1935, and shown to be highly effective against spreading streptococcal infections. By 1936, Leonard Colebrook at Queen Charlotte's Hospital, London, had used sulphanilamide on 38 almost hopeless cases of puerperal fever with only three deaths. The next 26 cases were treated without a single fatality.

So, by the end of the 1930s, the concept of systemic chemical agents that would be Ehrlich's 'magic bullets' was now well established. But what about antimicrobial agents from fungi and bacteria, the antibiotics? Most people think that the story begins with Alexander Fleming's description of penicillin in 1928, but it goes back much further than this.

In 1870, John Burdon Sanderson, while working as Medical Officer of Health in London (he subsequently became professor of medicine in Oxford), showed that bacteria would not grow in culture fluid containing visible mould.

Using urine as a culture medium, Joseph Lister noted that glasses of urine containing a heavy growth of mould could show complete absence of bacteria.

In 1928, Alexander Fleming, at St Mary's Hospital London, noted the lysis of staphylococcal colonies on culture plates contaminated with *Penicillium notatum*. The work was published the following year but attempts by Fleming and his colleagues failed to concentrate what was now named penicillin.

In 1938, Howard Florey, Professor of Pathology at Oxford, together with a young German-Jewish refugee, the biochemist Ernst Boris Chain, determined to study and try to extract known natural antibiotic substances. From Chain's review of the many reports of this phenomenon, penicillin seemed the most promising. They were joined by Norman Heatley, who devised a technique to assay culture samples to see whether they contained more concentrated samples of penicillin.

By 25 May 1940, enough penicillin was available for a critical experiment. Remember, this was the time of the German invasion of Holland and Belgium, soon to be followed by the Dunkirk evacuation. Four mice were injected with a lethal dose of streptococci and received subcutaneous penicillin. Four controls did not receive penicillin. All the controls died while the treated animals survived. Two days later, a further ten mice were injected with streptococci; all six of the treated animals survived, three of the four controls died.

By the beginning of 1941, Florey had enough penicillin for a clinical trial. The first patient was a 43-year-old policeman dying of a combined staphylococcal and streptococcal septicaemia, multiple lung abscesses and osteomyelitis of the left humerus. Within a day of treatment with penicillin given by intravenous drip his condition had improved and after 5 days he was vastly better, but by now the supply of penicillin was exhausted and the poor fellow died a month later. The total dose given had been 220 000 units – today, a small single injection.

The next patient, a boy of 15 years with a sulphonamide-resistant streptococcal septic arthritis of the hip, rapidly recovered. The third, a man with a large carbuncle on his back, responded rapidly. Next, a boy dying with a septic cavernous sinus thrombosis from an infected eyelid made a remarkable recovery but a week later became unconscious and died of a ruptured intracranial mycotic aneurysm. The final patient was a boy aged 14 years with a staphylococcal osteomyelitis of the femur with involvement of the hip joint. The prognosis seemed hopeless. After 2 weeks of penicillin he was completely cured. This small series of patients established that fatal staphylococcal septicaemia could be cured and that penicillin, unlike the sulphonamides, could act in the presence of pus. The evidence was sufficient to initiate the large-scale production of penicillin. By the time of the allied landings in Sicily, enough precious penicillin was available to treat staphylococcal infection of war wounds with dramatic results.

Howard Florey was knighted in 1944. The following year the Nobel Prize for Physiology and Medicine was awarded to Florey, Fleming and Chain. Surely that article of August 1941 deserves its place in the history of medicine. **BJHM**

Conflict of interest: none.

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