The last year before the dawn of antibiotics

Pick up any bound volume of a general medical journal of 1934 (75 years ago – within the memory of old members of the profession), and there are likely to be papers concerning the dreaded effects of the Gram positive cocci. The pneumococcus, causing often fatal lobar pneumonia in previously fit young people, and the beta-haemolytic streptococcus, producing erysipelas, septicaemia and puerperal sepsis, were especially dangerous. Volume one of the *Lancet* for that year, for example, contains no less than four papers on different trials of treatment for streptococcal infection as well as a long and learned leading article.

Treatment of streptococcal infections consisted of general nursing care, drainage of obvious pus collections, and trials of vaccines, blood transfusions and of various drugs, including the arsenicals.

Workers at St. Mary's Hospital, London (then a major centre for the study of vaccine therapy), describe their trial of blood transfusions from donors inoculated with a vaccine made from streptococci obtained from the patient's blood in two patients; both recovered. Of course, this was long before the days of controlled clinical trials, the authors simply stating 'outside the group occuring in the puerperium, spontaneous recovery from acute haemolytic streptococcal infection is rarely noted'. A study from the National Temperance Hospital reports two patients with streptococcal septicaemia treated with anti-streptococcal serum manufactured by Burroughs Wellcome with recovery in both instances. Both, it should be noted, had their abscesses drained. A trial from Hastings records 12 patients with streptococcal septicaemia treated with fresh blood or serum transfusion in addition to anti-streptococcal serum: 'in ten cases there was improvement' even though none had been seen after the antiserum alone.

The most interesting paper came from Queen Charlotte's Maternity Hospital. Its authors, Leonard Colebrook and Ronald Hare, both achieved distinction in later years. They based their work on the observation that, following the injection of arsenical drugs in the treatment of syphilis, the patient's blood acquired the power to destroy *Streptococcus pyogenes* in vitro. Their study comprised 66 women with streptococcal puerperal sepsis who were given four to six injections of these drugs. The only additional treatment, apart from supportive nursing care, was instillation of glycerine into the uterus in an attempt to promote the flow of lymph carrying the arsenical through the infected tissues, Comparison was made with 38 cases treated without the arsenicals. Disappointingly, this careful comparison, stratifying the cases according to their severity, revealed no advantage in the treated group.

The leader in the *Lancet* starts with the bold statement that 'It is a remarkable fact, a fact worth close attention, that the discovery of the relationship of bacteria to disease has led to little improvement in the control of the common infections'. It goes on later to say 'The fact remains that tragic cases of fulminating septicaemia are seen every week in every large hospital and something must be done to meet their need'. It points out that blood transfusion and antitoxic serum seem to have some effect, but notes that animal experiments had shown that antitoxic sera are effective only when given before the infection has occured and not when infection has become established. It notes that anti-tetanus serum is routinely given in cases of wounds resulting from street accidents etc. and suggests that the use of anti-streptococcal serum might be routine in all those cases of abnormal labour in which the incidence of puerperal infection is high.

All this work and all this suffering. Very few people knew the closely guarded secret that a specific treatment was about to be announced.

Gerhard Domagk (1895–1964), a bacteriologist, was Director of Research at I.G. Farben, the great chemical works outside Dusseldorf, Germany. His task was to investigate the vast number of synthetic compounds produced by the dye chemists for possible medical use. In 1932 he found that the dye Prontosil Rubra, although inactive in vivo, protected mice from streptococcal infection when given by nasogastric tube. By December 1932 the drug was found to be effective in clinical practice against the dreaded streptococcal infections in spite of the disadvantage that the dye stained the patient, fortunately only temporarily, a bright red colour. These exciting finding were not published until February 1935. Within weeks, workers at the Pasteur Institute, Paris showed that it was the colourless sulphanilamide moiety of the molecule which was the active agent and indeed active in vitro against the streptococci. Sulphanilamide had itself been synthesized by Paul Gelmo in Vienna way back in 1908, although its invaluable antibacterial properties had not been investigated.

Why the long delay in reporting these exciting findings? The official explanation is that they seemed too good to be true and that two more years were needed to confirm them. Another explanation is that Domagk and his chemists were working for a commercial firm. They almost certainly used sulphanilamide in the synthesis of Prontosil Rubra and it is unreasonable to imagine that they did not discover for themselves its chemotherapeutic properties. Yet sulphanilamide itself had already been synthesized many years before and could not be patented. The obvious commercial thing to do would be to withhold publication until effective sulpha compounds sufficiently different to sulphanilamide could be synthesized and patented. Whatever the truth, Domagk was awarded a Nobel Prize in 1939.

By 1936, Leonard Colebrook at Queen Charlotte's used sulphanilamide on 38 almost hopeless cases of puerperal fever with only three deaths. The next 26 were treated without a single loss of life. It is interesting that he decided against the original protocol of treating alternate patients with the drug because he could not bring himself to withhold the agent in these desperately ill young women.

Surely 2009 marks the 75th anniversary of the end of the pre-antibiotic era – but it could have ended a couple of years earlier. **BJHM**

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