bacterial infections was now found to be false. Nevertheless, this example shows how a research team can be motivated by a convincing idea—something upon which research has always relied.

On the other hand, Domagk is completely vindicated in his view that a 'therapia magna sterilans' is not the decisive criterion for successful antibacterial chemotherapy, but that chemotherapeutic intervention should influence the host-pathogen interaction in such a way that the host's defence mechanisms become able to eliminate the pathogen. These ideas are once again becoming highly topical in connection with the growing problems of immunodeficiency in infectious diseases. Domagk could not have given a clearer demonstration of his ideas about the treatment of infections than by developing the sulphonamides as the classical example of bacteriostatic chemotherapeutics.

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Editorial Note
Dr Hinrich Otten was Domagk's youngest associate and one of his last collaborators, and still works at the Institute of Chemotherapy of Bayer AG Pharma Research Centre in Wuppertal.

The sulphonamides: an early British perspective
It is not easy to cast ones mind back to the prechemotherapeutic era, but essential to do so if we are to understand why the sulphonamides, as the first truly effective antibacterial agents, received a rather cautious welcome. Leonard Colebrook, the first Briton to report on the sulphonamides had been involved in other, ineffective, chemotherapeutic trials and knew that some patients recovered despite the treatment they received. He was also aware of one other problem, that of an apparent decrease in the virulence of the streptococcus.

In the 1870s when the Metropolitan Asylums Board (MAB) opened its London fever hospitals, scarlet fever was very prevalent and was frequently fatal. Alexander Collie (1887) personally treated 10,185 patients with scarlet fever admitted to the Eastern Fever Hospitals, where he was Medical Superintendent, over a period of ten years. He recorded a 12% mortality rate amongst these patients. However the death rate for MAB hospital admissions of scarlet fever declined steadily from 1871 to 1931; the following mortality rates are derived from Ayers (1971): 1871–80 12.8%, 1881–1890 9.4%, 1891–1900 4.8%, 1901–1910 3.0%, 1911–1920 1.5%, 1921–1929 1.0%. There had been no specific advances in treatment during this period although the MAB felt that, by concentrating cases, a degree of expertise in general patient management had been built up. In all probability the general health of the nation was improving and the changes were socio-economic and patient centred rather than due to a specific decline in the streptococcus; nevertheless this made changes in death rates due to streptococcal infection more difficult to assess.

Attempts at chemotherapy had occurred sporadically throughout Colebrook's career. As a young man in South Africa with Sir Almroth Wright, Colebrook had witnessed the abandoning of Optochin (ethyl hydrocuprein) as a treatment for pneumococcal infection because it was reported to cause blindness. Arsenical compounds had proved of value in syphilis and Colebrook had been involved with Alexander Fleming in work (and clinical practice) on the arsenical compound, Salvarsan (Fleming & Colebrook, 1911). In an era when a clinician could inject lysol into a patient's veins on the grounds that it killed bacteria in vitro and might therefore do so in vivo, and when the injection of milk into the buttocks to induce leukocytosis was a serious attempt at chemotherapy, it is little wonder that Colebrook initially followed a rather leisurely programme in regard to chemotherapy of puerperal sepsis due to streptococci.

Douglas & Colebrook (1916) had reported that Salvarsan would render blood or serum bactericidal and suggested that this might have a beneficial effect on wound infections or septicemias. Colebrook returned to this idea 12 years later in a report to the MRC (Colebrook, 1928) largely describing in-vitro work and again suggesting that clinical trials might be of value. The clinical trials were reported in 1934 by Colebrook & Hare and were clearly disappointing. Eleven (40%) of a group of 28 treated patients with streptococcal septicemia but no peritonitis recovered and in three of these patients arsenicals seemed to have played a part; however a 40% recovery rate was experienced in those not treated.
Further, nine patients with diffuse peritonitis treated with arsenicals all died. Colebrook & Hare remarked that only two chemical agents had been found capable of increasing the bactericidal power of the blood for more than a few minutes, the arsenicals and Optochin. They commented, 'The search for such agents should, we think, be the immediate objective in future chemotherapeutic work on streptococcal infections'.

Colebrook & Hare had tried other substances. In 1927 they described in-vitro studies on mercurochrome concluding that it was useless to attempt therapy. Referring to instances in which administration of mercurochrome had been claimed by others to achieve a therapeutic effect, they attributed the patient's recovery to 'the formidable constitutional disturbances, as shown by the occurrence of haematuria, violent purging, rigors and stomatitis'. An attempt to treat puerperal sepsis with antistreptococcal serum was considered misguided by Colebrook (1935) since there was no evidence of efficacy and even some suggestion that administration of antiserum interfered with the normal immune mechanisms.

The Interim Report of the Departmental Committee on Maternal Mortality and Morbidity published in 1930 could offer little under the heading Methods of Treatment in its chapter on puerperal sepsis. In cases of mild type general measures for increasing the cial effect. Later the same year Colebrook & Purdie's (1937) paper revealed the overall mood 'Striking results have followed the treatment of streptococcal puerperal sepsis by the two diazo compounds...'.

The age of effective chemotherapy had begun.

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References
Figure 1. Professor Gerhard Domagk in his Laboratory at Elberfeld. Figure 2. Two pages of Domagk's laboratory notebooks: left, Prontosil rubrum; right, Prontosil solubile. Figure 3. Prontosil for intramuscular injection. Figure 4. Leonard Colebrook. (Figures 1–3 by permission of Bayer AG., Wuppertal, West Germany; Figure 4 from CoP—Great Healer of Men, by W.C. Noble, 1974, Heinemann, London.