Leading articles

Domagk and the development of the sulphonamides

The introduction of sulphonamides over 50 years ago as antibacterial chemotherapeutic agents is remembered as one of the greatest advances in the development of medical science. Gerhard Domagk (1895–1964), who in 1939 was awarded the Nobel Prize for the discovery of Prontosil, the first sulphonamide used in clinical practice, once said that it was futile to discuss who deserved the greatest credit for the discovery of sulphonamides—chemists, medical researchers or bedside physicians. The success achieved was the result of a team effort. This attitude was undoubtedly essential for success and provides a good example of the teamwork often planned today for the solution of problems.

It is now difficult to imagine the important position occupied by streptococcal infections such as pneumonia, erysipelas, etc., before the advent of antibacterial therapy. Drug research at that time was aimed at finding a possible solution to this major therapeutic problem. At the research laboratories of the then Farbenfabriken Bayer in Elberfeld excellent therapeutic principles had been demonstrated with the development of Germanin for the treatment of sleeping sickness, and of Atebrin for malaria, and attention was directed towards tracking down analogous modes of action between chemotherapeutic agents and bacterial pathogens.

It is thanks to Heinrich Hörlein (1882–1954), then head of pharmaceutical research at Farbenfabriken Bayer, that young scientists working at Elberfeld in 1927 became involved in the search for effective antibacterial therapy.

Domagk’s essential basis for success in discovery of the sulphonamides can be traced back to his earlier work, in which he used animal experiments to assess the course of an infection, certainly necessary when investigating different processes in histological examinations. As the head of the department of Experimental Pathology (set up for him at Bayer in 1927) and of Bacteriology (added in 1929) Domagk had a strictly delineated research programme to the goals of which he dedicated himself completely in an exceptionally successful career until his retirement in 1960.

Soon after Prontosil had achieved sweeping worldwide success shortly after being placed on the market, Domagk himself when questioned about the discovery said: 'The question is hard to answer because it is difficult to say how much luck had to do with it. Even so it was no chance discovery... Hope and disappointment alternated month by month, until at once we made a considerable step forward by testing a sulphonamide-containing azo compound. Now for the first time we had in our hands a compound (Kl 695, October 1932) (Josef Klarer, 1898–1953) that gave reproducible results not only in vitro but also in living animals... There again we asked ourselves whether we would be able to help sick people by using the results obtained in animal experiments.'

The rapid success of Prontosil as a chemotherapeutic agent marked the beginning of a tempestuous development of other sulphonamides, and from the sulphonamide era developed the age of chemotherapy for infectious diseases.

While this success crowned the work at the Bayer laboratories, insights into the mechanisms of action of the sulphonamides (achieved by the work of Trefouel, Nitti and Bovet) caused a profound disappointment. It became clear that the sulphonamide group introduced into an azo dye did not have the intended function of improving the activity as had been seen with textile dyes. Rather, linking it to an azo dye seemed to be superfluous, as the chemotherapeutic effect could be achieved by use of sulphanilamide alone. The working hypothesis which had been so successful in bringing about development of therapy for
Leading articles

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.

H. OTTEN
Institut für Chemotherapie,
Bayer AG,
Postfach 101709,
D 5600 Wuppertal 1,
West Germany

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 septicaemias. 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 septicaemia 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.