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Making *British* Cortisone: Glaxo and the development of Corticosteroids in Britain in the 1950s–1960s

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Abstract

Following the announcement in 1949 in the USA that cortisone offered rheumatoid arthritis sufferers effective treatment for their crippling disease, the Ministry of Health came under considerable pressure from the medical profession and the public to make cortisone available in Britain. The Ministry, therefore, urged British companies to start manufacturing cortisone. Among the several pharmaceutical firms responding to the Ministry's request, Glaxo's expertise in the field of vitamins gave them a head start. This paper describes the varied and flexible strategy that enabled Glaxo to maintain this head start, and the scientific and technical capabilities which the company subsequently built up, enabling them to dominate the market for corticosteroids in Britain.

Among the drugs to emerge out of the Glaxo project to manufacture cortisone, which began in 1950 and later became a wider R&D programme on steroids, was the topical steroid Betnovate, launched in 1963, which remains a best-seller today. However, although it led to successful new products, Glaxo's programme had limitations. The paper identifies a missed opportunity, in the shape of the biosynthetic route to steroid drugs, often considered as a milestone in the development of the new biotechnology. Whether or not this missed opportunity proved costly to the company is uncertain. However, it illustrates the role of technological path-dependence, and the importance of the integration between different scientific disciplines, in this case chemistry and biology, in pharmaceutical innovation.

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1. Introduction

In May 1949, Philip Hench of the Mayo Clinic announced at the 7th International Congress of Rheumatology in New York that certain corticosteroids[1] were able to reverse many of the acute manifestations of rheumatoid arthritis. In the words of the British rheumatologist John Glyn,

> no matter what therapeutic disappointments and frustrations were to beset us later, the proof that rheumatoid inflammation was potentially reversible attracted interest from scientists and clinicians from a wide diversity of interests and skill and this enabled basic research into the rheumatic diseases to develop as never before.[2]

The drug that produced these dramatic effects, in which previously crippled patients were seen to get up and walk or even dance,[3] was compound E, later renamed cortisone. It had been manufactured in small quantities by Lewis Sarrett at Merck using a method developed by Hench's colleague, Edward Kendall, from desoxycholic acid (from ox bile).[4] Such was the impact of these achievements, that only one year after the announcement Hench and Kendall received the Nobel Prize for Physiology or Medicine, which was awarded jointly to the Swiss chemist Tadeus Reichstein.[5]

There followed a veritable 'outpouring of steroidal investigations',[6] bringing together steroid chemists, biochemists, endocrinologists, and clinicians from many different specialties.[7] The 1949 announcement gave tremendous impetus, in particular, to steroid chemistry—a field that was born in the nineteenth century, grew between the wars in connection with the newly discovered ergosterol (vitamin D) and steroid hormones, and was to play a key role in the development of corticosteroid drugs in the 1950s and 1960s. After 1949, it entered what Louis and Mary Fieser have called the 'third phase' of steroid research, that is to say one of 'intensive effort in partial and total synthesis by a rapidly expanding corps of chemists newly initiated into the steroid field'.[8] By the mid-1950s, the serious side effects brought on by the high dosage levels required to treat rheumatoid arthritis had led to the development of analogues with reduced toxicity and enhanced physiological activity. Moreover, shortages of bile acids and of dollars outside the USA had stimulated a search

[1] Corticosteroids: any steroid hormone secreted by adrenal cortex. They exist in two types, glucocorticosteroids and mineralcorticosteroids. Glucocorticosteroids, which include cortisone, are essential for the utilisation of carbohydrate, fat, and protein by the body, and for a normal response to stress. NB: corticosteroids are often referred to simply as steroids. Martin (1998), p. 151.

[2] Kersley & Glyn (1991), p. 56. It was Philip Hench who developed the concept of 'potential reversibility' with respect to rheumatic diseases in the 1920s and 1930s, work for which he was awarded the Nobel Prize. See Sourkes (1967), pp. 278–290.

[3] On the role of drama in the portrayal of medical discoveries, see Cantor (1993a).

[4] See Sourkes (1967), pp. 280–283.

[5] Le Fanu (2000), pp. 22–23.

[6] Johns (1973), Preface.

[7] Cantor (1993a), p. 174.

[8] Steroids are a group of compounds with a common structure based on the steroid nucleus, consisting of three six-membered carbon rings and one five-membered carbon ring, which occur in plants and animals. Early studies were conducted with cholesterol, which was easily obtainable from gallstones, with bile acids, with ergosterol—vitamin D—and subsequently with the newly discovered steroid hormones, which include the sex hormones as well as the hormones of the adrenal cortex—corticosteroids. See Fieser & Fieser (1959), Ch. 1. Note that Shoppee, writing in 1956, had counted *five*, not three, phases in the chemistry and history of steroids (Shoppee, 1956).