BIOGRAPHICAL MEMOIRS

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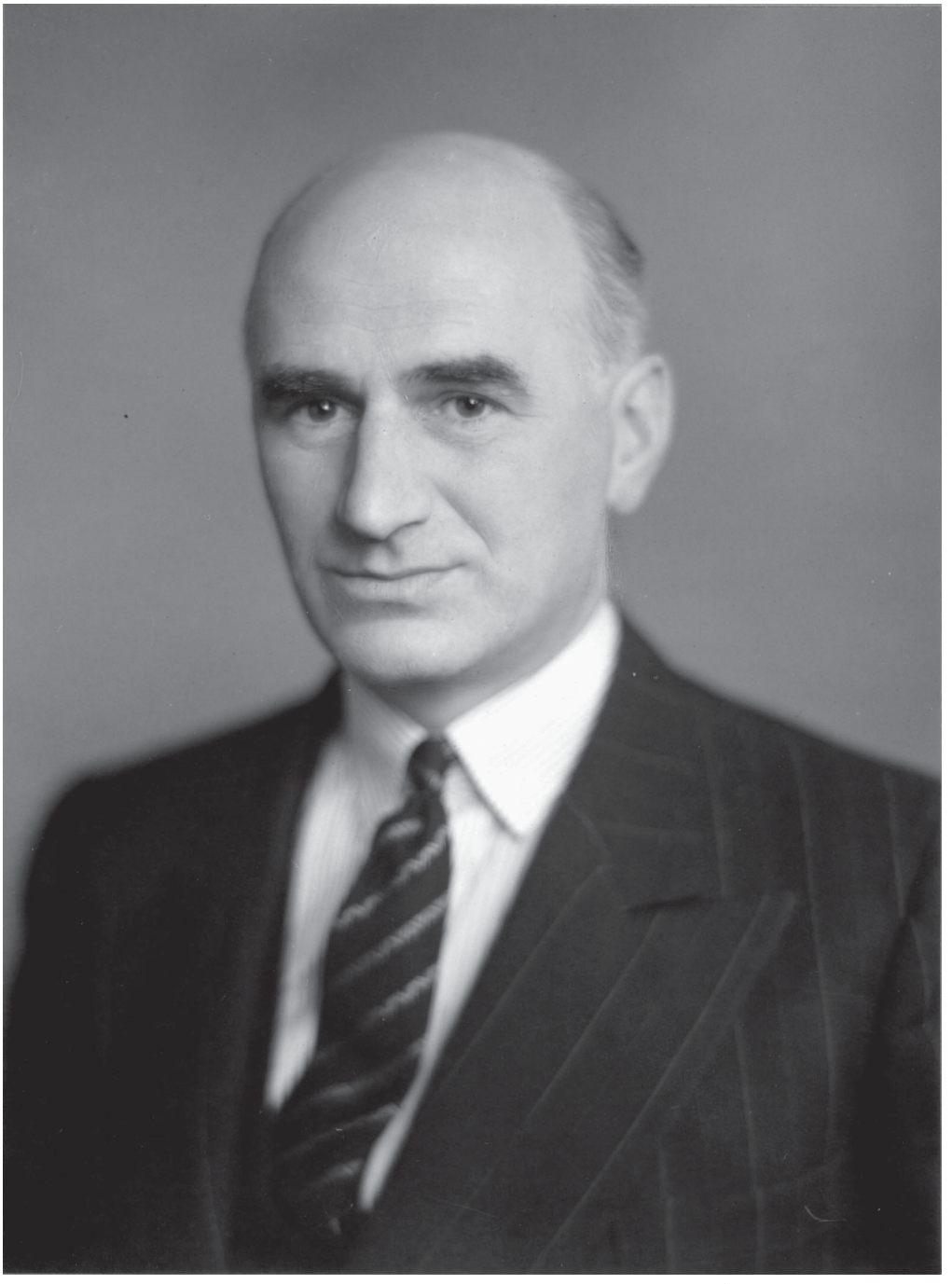

FRANK STUART SPRING

5 September 1907 — 2 March 1997

Elected FRS 1952

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Frank Spring was an organic chemist who made important contributions to our knowledge of the naturally occurring sterols, triterpenes and heterocyclic compounds. He investigated the structure of a large number of complex molecules, and proved his conclusions by synthesis. In the 1950s he was one of many researchers who contributed to the long series of transformations required for the synthesis of cortisone, his contribution being the evolution of mechanisms for the introduction of an oxygen atom at the 11-position of the steroid nucleus, and the development of routes for the synthesis of cortisone from ergosterol as a more convenient starting point than the bile acids previously used.

Early years

Frank Stuart Spring was born at Crosby, near Liverpool, on 5 September 1907, the fifth of a family of six children. His father, John Spring, was a Merchant Navy master whose ship, *Rhineland*, was sunk in the North Sea as a result of enemy action at the beginning of World War I, with the loss of all on board. Thus his mother Isabella was left on her own to bring up her large family under conditions of great hardship, and in later life Spring and his siblings would often enjoy a joke about their mother's many stringent domestic economies. However, it is to her great credit that all four sons grew up to follow careers of professional distinction, and the happy marriages of both daughters ensured that they too lived fulfilled and accomplished lives.

The experience of growing up in those difficult times was reinforced as Spring reached maturity in the Liverpool of the post-World War I depression. He never forgot the sight of men queuing for work outside factories, and this imbued him with a strong work ethic that was to last his lifetime. He was educated at Waterloo with Seaforth Secondary School, gaining

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admission to the University of Liverpool in 1924. With the support of a grant for academically gifted children from a Merchant Navy trust he graduated BSc with first-class honours in chemistry in July 1928, and after the award of a United Alkali Research Scholarship, supplemented in the second year by a university fellowship, he graduated PhD two years later, in 1930.

During his undergraduate and postgraduate years Spring joined fully in the social life of the university. For one year he was the President of the University of Liverpool Chemical Society, and contributed with wit and humour to the society's magazine. He loved cricket and enjoyed playing for the University XI; there is a story, perhaps apocryphal, that on one occasion he made an unbeaten century. There is even record of his treading the boards in Christmas pantomime, and it was in fancy dress on a students' rag day that he met his future wife, Mary Mackintosh, the second of three daughters of a Presbyterian minister from Heswall. Theirs was a very happy marriage, and when Spring died in 1997 he and Mary were about to celebrate their 65th wedding anniversary. A son, John, was born in 1934 and a daughter, Vivien, in 1938.

Sterols, 1928–39

The subject of Spring's postgraduate research at Liverpool was the chemistry of the sterols, naturally occurring compounds comprising the four fused rings of the steroid nucleus with a hydroxyl group at the 3-position. Ian (later Sir Ian) Heilbron (FRS 1931) was the head of the department, and his research school initially studied cholesterol, the most important of the animal sterols.

Spring's first postdoctoral position in 1930 was as a junior lecturer, later senior lecturer, in the Chemistry Department at Manchester University, and by good fortune Heilbron 'followed' him by becoming head of department at Manchester in 1933, so that collaboration between master and student progressed with little break in continuity. In a long series of papers starting at Liverpool with 'Studies in the sterol group. Part I' (Heilbron *et al*. 1928), and continuing at Manchester up to part XLII (Heilbron *et al*. 1940), the research group under Heilbron published their results in *Journal of the Chemical Society*, and Spring was joint author in 24 of these 42 papers between parts IV in 1929 (1)* and XXXIX in 1939 (5).

After the initial focus on cholesterol, its reactions and its derivatives, the work moved on to ergosterol, a sterol with a C_9H_{17} side chain at the 17-position, which is present in yeasts, fungal membranes and fish-liver oils and which yields calciferol (vitamin D_2) on irradiation. A radical new proposal about the structure of the sterols was put forward by Rosenheim & King (1932*a*, *b*) and by other workers; Heilbron and Spring, who had already established the empirical formula of ergosterol as $C_{28}H_{44}O$, deduced its structure in agreement with the new theory, publishing their result in 'Studies in the sterol group. Part XIX' in 1934 (3). Thereafter the group extended its studies to other sterols, in particular fucosterol, the sterol of the seaweeds, and lumisterol, one of the products of the irradiation of ergosterol.

Triterpenes, 1933–61

A second major interest was the chemistry of the triterpenes, naturally occurring compounds with molecular skeletons containing 30 carbon atoms arranged in a variable number of rings,

* Numbers in this form refer to the bibliography at the end of the text.

usually six-membered. Heilbron had first encountered this group in 1926, when he recognized that squalene, an open-chained polyalkene whose empirical formula is $C_{30}H_{50}$ and which is found in fish-liver oils, could easily be transformed into cyclic compounds (Heilbron *et al*. 1926*a–c*). Starting in 1933, Spring was joint author in the majority of a long numbered series of papers, initially as Heilbron's junior colleague but later as head of his own department, comprising 'The resinols. Part I' in 1933 (2) to part V in 1938 (4), the continuation series 'Triterpene resinols and related acids. Part VI' in 1939 (6) to part XXX in 1954 (13) and the further continuation series 'Triterpenoids. Part XXXII' in 1955 (14) to part LVIII in 1961 (16). The interest thus spanned the whole of his academic career and was pursued in parallel with his many other interests. The work was largely concerned with the chemistry of α- and β-amyrin and related compounds, one example being the determination of the structure of brein, first isolated from elemi resin in 1851, shown to be a product of extensive rearrangement of α-amyrin.

Heterocyclic compounds, 1945–52

The third main group of organic compounds that engaged Spring's attention was that of the heterocyclics, molecules with five-membered or six-membered rings containing one or more atoms other than carbon. Publication started in 1945 with 'The application of the Hofmann reaction to the synthesis of heterocyclic compounds. Part I' (7), and the series continued up to part VII in 1949 (9), covering the synthesis of xanthine, purine nucleosides and pyrimidine and related compounds. There followed a connected second series of papers, 'Pyrazine derivatives. Part I' in 1947 (8) to part XIV in 1952 (11), which explored the chemistry of for example alkyl-, chloro- and amino-pyrazines related to aspergillic acid, and derived the latter's structure.

Royal Technical College, Glasgow

In 1946 Spring was appointed Freeland Professor of Chemistry at the Royal Technical College, Glasgow, which became the Royal College of Science and Technology in 1956 and the University of Strathclyde in 1964. He inherited a department that had been allowed to run down under wartime conditions, and bringing it up to date called for his full reserves of tact, persuasion and inspiration. Spring always gave warm credit to Sir John Anderson, Principal of the college, for giving him much-appreciated support in his work of reconstruction. New and up-to-date laboratories were fitted out and before long Spring was in charge of his own research group of enthusiastic postgraduates who continued the work on triterpenes and heterocyclic compounds. In 1952 Spring was elected a Fellow of the Royal Society, the citation saying that

> he has made major contributions to our knowledge of the sterols, with particular reference to the structures of ergosterol and vitamin D_2. Over eighteen years he has carried out important systematic work on the triterpene resinols and related acids. He has also applied himself to a study of a variety of heterocyclic systems including the elaboration of new syntheses of pyrazine and purine derivatives.

Steroids and cortisone, 1952–55

Soon after his move to Glasgow, Spring returned to research on the steroids and initiated another numbered series of papers, 'Steroids. Part I' in 1952 (10) to part XV in 1955 (15), which covered the synthesis of ergosteryl compounds, cholegenin and progesterone. He first encountered cortisone, a steroid hormone with empirical formula $C_{21}H_{28}O_5$, during the early work on sterols at Liverpool and Manchester. There was a sudden resurgence of interest in 1949 when Kendall and others published clinical evidence showing that cortisone eased the symptoms of rheumatoid arthritis (Hench *et al*. 1949*a*, *b*), thus laying down a challenge that many research chemists all over the world eagerly took up. The first route for the synthesis of cortisone started from deoxycholic acid, a constituent of the bile acid of the cow, and proceeded through 32 steps, the varying degrees of yield at each stage resulting in 1000 lb (about 450 kg) of bile duct—itself not a convenient starting point—yielding about 200 mg of cortisone. This meant that pioneering use of the drug as a treatment for rheumatism sufferers was prohibitively expensive, but improvements made with the first efforts at commercial production brought the yield up to 938 g from 1270 lb (about 575 kg) of bile duct, and the price was set at $200 per gram. Lively competition between American drug manufacturers, with much experimentation on different routes of synthesis, meant further reductions to $10 per gram in 1951 and eventually to $3.50 per gram. In a masterly summary published in 1953, 'The partial synthesis of cortisone and related compounds from accessible steroids' (12), Spring set out the problems and listed the available alternatives, including his own routes from the much more convenient starting point of ergosterol, easily available from yeast. His contribution centred on the need to introduce an oxygen atom at the 11-position of the steroid nucleus.

Many organic chemists throughout the world made a contribution to these syntheses, but their efforts were overtaken by soil microorganisms, and ironically the preferred method of manufacture now uses enzymes carefully marshalled to perform the necessary conversions.

Industry

In 1959, at the age of 52 years and at the peak of his achievement as an academic researcher in organic chemistry, Spring surprised all his colleagues by resigning his chair at the Royal College of Science and Technology and becoming research director at the chemical manufacturing company Laporte Industries. Laporte was a bulk manufacturer of a limited number of 'commodity' inorganic chemicals, especially hydrogen peroxide at Luton, sulphuric acid at Warrington and titanium dioxide at Immingham. It was perhaps recognized by the directors of the company that their product range offered limited future growth and that they would fall behind without a concerted push into new markets and in particular into higher value-added products, including fine chemicals and organics. Spring established the company's first group research laboratory at Luton and piloted the move into these new fields, with the result that Laporte became an important supplier of a range of successful new products, such as coatings for the modern compact disc industry and specialized chemicals used in circuit board manufacture.

Consultancy

During World War II, Spring was called on to advise the authorities on the protection of the civilian population against gas attack, an event that fortunately never materialized. One result of this was that in the search for suitable treatments he came into contact with Frank Moore, managing director of Herts Pharmaceuticals, the manufacturer of Nivea Creme and a company of German origin that had been taken under management by the Custodian of Enemy Property. This was the start of a productive and valuable connection that lasted throughout Spring's career, and he advised the company on their postwar research programme, participating in their development of anti-tubercular drugs. In due course Herts Pharmaceuticals was taken over by Smith & Nephew, and Spring was involved in the consolidation of the research functions of the two firms into a new and separate company, Smith & Nephew Research Ltd, a procedure that proved a highly satisfactory model for the unification of different research departments.

Later years

From his first discovery of the Lake District as a teenager, Spring had a great love of the countryside and of walking. He made many walking expeditions in retirement, often in the company of his son, including traverses of the Black Mount and the Lairig Ghru. In his 80th year he completed the organized three-day walk around Chichester Harbour, for which he received a certificate from the chairman of the Harbour Conservancy and a rousing cheer from the other participants. He was a member of the MCC (Marylebone Cricket Club) and in retirement he was never happier than when spending a whole summer's day at a Lord's cricket match. Well into his eighties he took pleasure in a daily morning walk with his dog around the full perimeter of Hyde Park.

Acknowledgement

The frontispiece photograph was received taken in 1952 by Walter Bird and is reproduced here with the permission of Godfrey Argent.

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