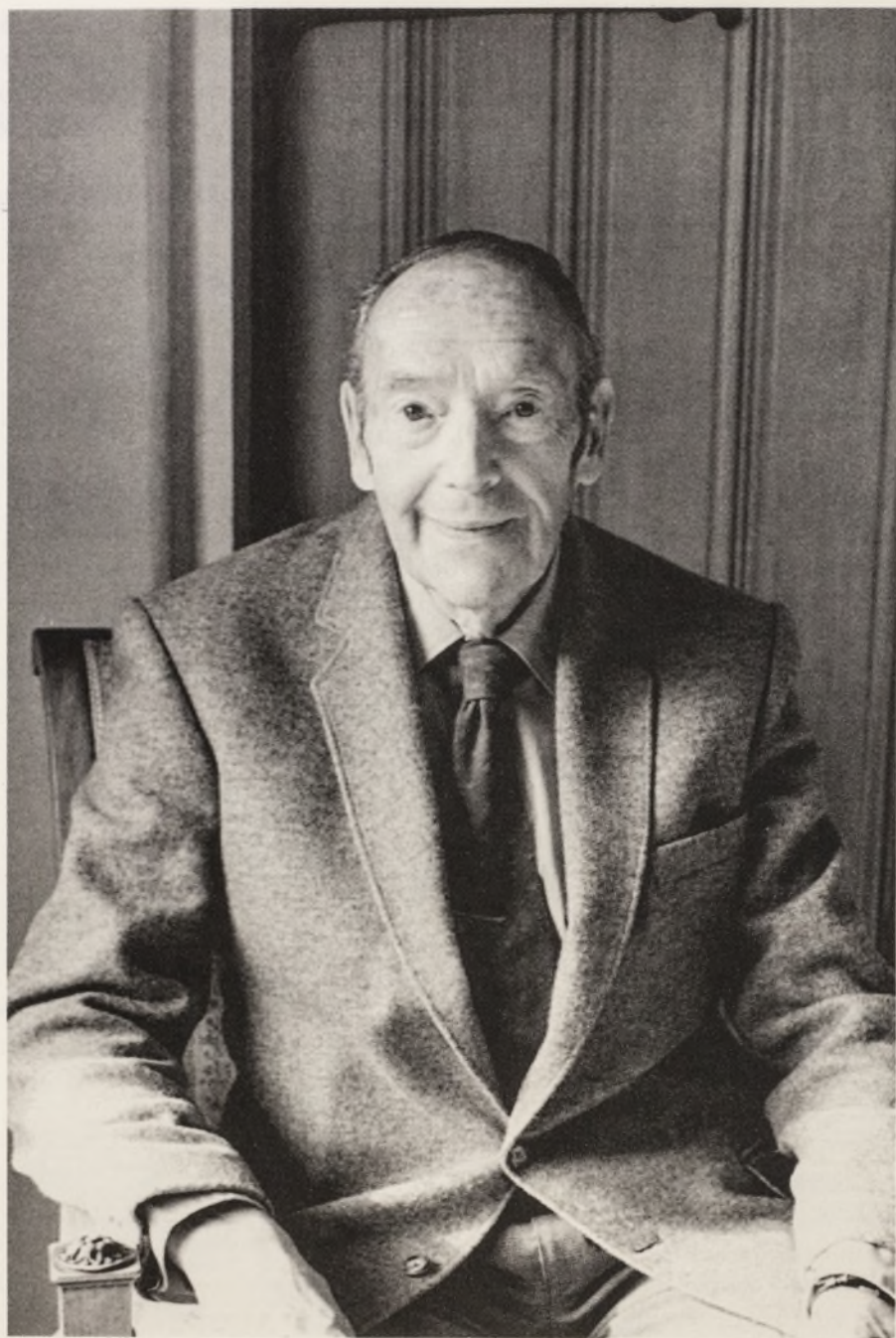


FRANZ BERGEL

13 February 1900—1 January 1987



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Elected F.R.S. 1959

BY LORD TODD, O.M., F.R.S.

FRANZ BERGEL was born on 13 February 1900 in the Alsergrund quarter of Vienna and lived there until 1908 when the Bergel family (parents, Franz and his younger brother, Otto, born in 1904) moved to permanent residence in the Viennese suburban area of Doebbling. His father was born and brought up in Hungary of peasant forebears and only came to Vienna at the age of 16 where, with his elder brother, he established a wine-importing business specializing in Hungarian wines. Presumably he was a native Magyar speaker because, according to Franz, although he spoke the Viennese dialect fluently, he never really mastered the German language. In marked contrast, Franz's mother was born in Teplitz-Schönau (now Teplice) in Bohemia (now Czechoslovakia); she was bilingual in Czech and German although German was always the language of the Bergel family, and I doubt whether Franz Bergel could speak either Czech or Magyar with any fluency. Unlike her husband, Franz's mother came of bourgeois stock, her family having a variety of business and professional interests. Her father was a successful carpet manufacturer who, unfortunately, fell victim to an incurable and incapacitating disease that confined him to a wheelchair and forced him to give up his business in the late 1880s. Undaunted, his wife—Franz Bergel's grandmother—moved with her husband and family to Vienna where she developed a small but successful business selling Bohemian glass and porcelain. Also in Vienna lived her sister, Hedwig (Franz's great-aunt), who was married to a Bohemian maker of wickerwork furniture and other goods whose business in Austria was so successful that he and his family settled in Vienna and lived in rather opulent circumstances on the outskirts of the city. Franz's mother lived during the latter part of her girlhood with her Aunt Hedwig; indeed, it was while living there that she met the young Hungarian wine merchant, Moritz Bergel, whom she later married.

Franz Bergel was thus born and, since his father's wine business flourished, brought up in comfortable middle-class circumstances in Vienna during the final decadent years of that remarkable phenomenon, the Austro-Hungarian Empire. His parents, although born into the Jewish faith, never adhered to its formal practice and, after marriage, they abandoned it, were baptized, and thereafter adhered to the Lutheran church.

The young Franz had the normal upbringing of his class: governesses until six years of age followed by five years of *Volkschule* and then five more in a *Realgymnasium*; his course at the *Realgymnasium* was interrupted by military service in the year 1917–18 so that the completion of his matriculation studies was delayed until late 1918. In the days before World War I Vienna was a gay and fascinating city and, as a boy, Bergel certainly enjoyed life in a society where music, learning and the arts all flourished and the great days of the Viennese operettas began. (I remember Franz telling me he remembered that, during his early boyhood, Franz Lehar conducted the military band that played nightly on the Prater.)

Things changed with the outbreak of war in 1914 but, from Bergel's own account, the effect on the life of the civilian population was relatively small until in the later stages food became bad and increasingly scarce. True, there was war work for civilians, but it does not seem to have been too arduous at least until 1918. As a schoolboy Bergel first worked with the Red Cross helping to deal with wounded soldiers, but later served as a part-time messenger at the office of the Lord Lieutenant controlling the City of Vienna and Lower Austria; in this position he seems to have been largely concerned with the treatment of aliens. All this was, of course, abruptly halted when, at the beginning of 1918, he was called up and put through the training course of an officer-cadet in a cavalry regiment. His fellow-warriors seem to have comprised a remarkable collection of young sprigs of the nobility, most, despite their youth, already dissolute womanizers. His six month's training completed, Bergel's regiment was ordered to the Italian front, but before it could get there the whole Isonzo–Piave front collapsed and with it, in due course, the whole Austro-Hungarian Empire. Despite, or perhaps because of, the weak and clumsy efforts of the Archduke Ferdinand and the Emperor Karl, there arose the chaos of the so-called National Successor States (all at one another's throats) and finally, in early November 1918, the present Austrian state was set up, following a musical comedy-style revolution.

Bergel and his fellow officer-cadets who had been called up from school shortly before they were due to take their final (i.e. matriculation) examination, were ordered back to school to complete their courses and take the examination before they could get final release from the army. This return of the warriors caused mayhem in the schools where 'wine, women and song' had never before been part of either the curriculum or

social life. However, Bergel did pass the examination with distinction only to find that the universities were so swamped by demobilized soldiers that he could not enrol as a full-time student of medicine or of chemistry, which had been his intention. He did, however, contrive to get admission to a course of lectures on chemistry for medical students given by Hans Fischer (later famous for his work on porphyrins) who encouraged the young Bergel to persevere with chemical studies.

During this period Franz Bergel, with two ex-cadet friends, seems to have led a very bohemian existence that developed in him some, perhaps latent, 'playboy' characteristics that undoubtedly affected adversely the development of his remarkable scientific talent and, indeed, he did not really rid himself of the effects of these riotous Vienna days until much later, after he had settled down in the United Kingdom.

After about a year, tiring of the gay life that occupied most of his time, Bergel decided to take his studies seriously and, having completed two semesters with Fischer, he left Vienna in January 1920 and went to Würzburg in Germany as a student of chemistry under Dimroth, and there took the *Erstes Verbandsexamen* before leaving in 1921 to continue his chemical studies under Heinrich Wieland, who had just come to Freiburg from the Technische Hochschule in Munich. In Freiburg he completed his undergraduate studies and, following the *Zweites Verbandsexamen*, he proceeded to work under Wieland's direction for his doctorate (Dr. phil. nat.), which he completed with distinction (*Summa cum laude*) in 1924, the subject of his dissertation being amino-acid oxidation. During this period he published some excellent work but, after Wieland's departure in 1925, his interests moved in the direction of natural products with physiological activity. In particular, he became interested in the constituents of *Cannabis* resin and in the alkaloids of *Solanum* species; but the high quality and promise of his earlier research with Wieland was not fully maintained, although in the next few years he published a number of papers with junior collaborators and, having taken the *Venia Legendi* in 1929 became Privatdozent in charge of the chemical course for medical students (and indeed wrote a small textbook for that course). Franz Bergel was never on very good terms with Heinrich Wieland's successor in Freiburg (Hermann Staudinger) but they seem to have developed some kind of *modus vivendi* for Bergel remained as Privatdozent in the Freiburg Chemistry Department until he left for Edinburgh in 1933.

Taken as a whole, Bergel's period in Freiburg after Wieland's departure (i.e. 1925–33) was not very productive chemically, despite his outstanding scientific potential. For this there were, I believe, a variety of reasons. First of all this was the period of social and political collapse associated with hyperinflation in Germany followed by unsuccessful attempts to introduce stable democratic government leading to the rise of extremist organizations such as the Stahlhelm, and the Communist and

National Socialist parties. All these were, in Bergel's case, overlaid by a series of, usually short-lived, affairs of the heart that reached their climax in 1928 when a whirlwind affair with the young wife of a medical professor in Freiburg led to a divorce and to her and Bergel setting up house together. The lady concerned, whose maiden name was Niddy Impekoven, came originally from Frankfurt am Maine where she had acquired a great reputation as a child solo dancer. Although she had given up dancing on her marriage she took it up again after the divorce and soon became an international figure in solo-dancing, which was at that time very popular in Europe (although it never had any great hold in Britain). One consequence of this was that from 1928 until 1933 she and Bergel spent a great deal of their time touring the major cities of Europe, he acting as a kind of impresario, greatly to the detriment of his chemistry. The couple were married in 1930 when about to go off on a prolonged visit to the Orient where Bergel arranged to spend some time as a visiting Professor in Colombo while combining this assignment with a dance tour of Indonesia arranged for his wife.

The result of this tour was predictable. Bergel spent little time in Colombo and achieved correspondingly meagre chemical progress although he did acquire, through the cooperation of the Colombo police, a substantial amount of *Cannabis* (in the form of the sweetmeat *ganja*) from which he prepared and distilled a large amount of active *Cannabis* resin that formed the raw material for research done much later with the author of this memoir in London and Manchester. The Bergel-Impekoven marriage was terminated by divorce in 1933 partly, I imagine (but only partly) because of the rise to power of the National Socialists with consequent difficulties for his German wife arising from Bergel's racial origin and his unconcealed desire to leave Germany as soon as possible.

From the earliest days of the National Socialist movement in Munich Bergel (who could be described politically as a 'liberal democrat') was violently opposed to it and to all it stood for, and his dislike of it grew steadily stronger over the years. After the accession of Hitler to power in 1933 Bergel could stand it no longer and, although being an Austrian national he was in no immediate danger, he resolved to emigrate. This decision brought with it, of course, the double problem of where to go and how to finance the move. Fortunately he had, some years previously, made the acquaintance of Dr Marcus Guggenheim, Director of Research at Hoffmann-La Roche & Co. of Basle, who was a close friend of George Barger, Professor of Medical Chemistry in Edinburgh; as a result Bergel, who was also recommended to Barger by Heinrich Wieland, was invited to join Barger's laboratory in Edinburgh and a small maintenance grant was later provided for him there by Hoffmann-La Roche, the initial costs of moving and settling in being partly defrayed by the Society for the Protection of Science and Learning, an organization set up by Professor

A. V. Hill to help *émigré* scholars from Germany, and actively run by Esther Simpson of whom Bergel always spoke with the highest regard.

EDINBURGH AND LONDON, 1933–38

Bergel left Freiburg in September 1933 and proceeded first of all to London where he spent a short time and renewed acquaintance with R. S. Cahn, whom he had met a couple of years before while accompanying his wife on one of her dance tours. Cahn had worked on *Cannabis* resin before leaving University College Bangor to become editor of the *Journal of the Chemical Society* in London; it was, of course, their common interest in *Cannabis* that had brought Cahn and Bergel together in the first place. At the end of September Bergel left London and, after an overnight rail journey, arrived in Edinburgh where he was to spend most of the next three years. On the following day he visited the Department of Medical Chemistry where he was to work; he was appalled by the ill-equipped and poorly designed laboratories located in the old pre-clinical building of the Edinburgh University Medical School and most of all by the almost complete lack of interest in chemical research shown by most of their few inhabitants. When, added to this, he had to contend with Edinburgh itself—cold, grey and forbidding to a man of his origin and upbringing—and its Calvinistic society, it is easy to understand how his reaction to Edinburgh was one of extreme dislike and, although he gradually became acclimatized, he never came to like the city and he left it with relief in 1936 almost exactly three years after his initial contact with it.

George Barger, Professor of Medical Chemistry and head of the department, was a man in his mid-fifties at the time of Bergel's arrival in Edinburgh. He carried on some rather desultory research in the alkaloid field but had probably passed his peak chemically. However, he enjoyed a great reputation based on a combination of respect for his earlier work (much of it associated with H. H. Dale), his mastery of foreign languages (he had a Dutch father and spoke seven languages more or less fluently), his left-wing political stance, and the total absence of any racial discrimination in his choice of friends and co-workers. The Department of Medical Chemistry was separated from the Chemistry Department of the university by about 2 miles and it provided teaching only for first-year students of medicine. As a result, research students coming to the department from the Edinburgh University school of chemistry were few and far between (I can recall only one, T. S. Work, during the period 1934–36) and Barger's modest little research school was peopled almost wholly by foreigners, many working on a short-term basis. So it was that, during his first academic year in Edinburgh, Bergel found that the only research students in the laboratory were a Japanese and an Indian (both of whom left after about 6 months) and a Hungarian refugee who was

quite inexperienced in research. Bergel found it hard to accommodate himself to Edinburgh and to the forlorn state of Medical Chemistry and he did no chemical work of any significance during the academic year 1933–34.

A major change occurred in the late summer of 1934—indeed, I would say a turning point in Bergel's career—when I arrived to join the Medical Chemistry Department. During that summer there was, by coincidence, a large increase in the research group through the arrival of H. Fraenkel Conrat, a Jewish refugee from Breslau; Dr Anni Jacob, a Frankfurt graduate who, although wholly 'Aryan' could not stomach the Nazi régime; Karimullah, a young Indian (later to become Professor of Chemistry at Lahore); and a Spaniard, Juan Madinaveitia, son of the Professor of Pharmacy in the University of Madrid. Madinaveitia came originally on a temporary basis as holder of a government research scholarship but, his family being staunchly Republican and forced to leave Spain after the Civil War, he became himself a refugee and settled in this country; some years later he married Dr Anni Jacob, joined ICI Ltd and the couple, with their children, lived near Macclesfield until his retirement and subsequent death. With that influx, together with T. S. Work, a new Edinburgh chemical graduate who came to work for his Ph.D. under Barger, and myself, things began to look rather different in Medical Chemistry.

In 1934 I, although only 27 years of age, had a fairly solid record of research achievement based on work in Frankfurt and Oxford on natural products, with a number of substantial publications mainly on bile acids, anthocyanin pigments and other natural colouring matters. I came to Edinburgh from Oxford at the invitation of Barger to take up the study of vitamin B₁, of which he had a few milligrams given him by his friend, B. C. P. Jansen of Amsterdam. Jansen, in 1927, was the first to isolate vitamin B₁ in crystalline form; he was anxious that the problems of structural determination and eventual synthesis of the vitamin should not be left solely to industry (work to that end was, he knew, already being undertaken by the I. G. Farbenindustrie in Germany and by Merck & Co. Inc. in the United States) and so, in 1934, he asked his friend Barger if he could help. Barger felt unable to undertake the work himself and, on the recommendation of Robert Robinson, he invited me to join him in Edinburgh and take up the study of vitamin B₁, supported by a modest grant from the Medical Research Council, a part-time demonstratorship and the promise of getting some rice concentrates to be obtained through the good offices of Hoffmann-La Roche & Co.

When I arrived in Edinburgh and saw the laboratories in which I would have to work my reaction was very similar to that of Bergel—I was appalled! When Bergel and I met we struck up an almost immediate *rapport* and, although he was some seven years my senior, we struck up a friendship that never faltered but grew stronger and stronger as time

went on. My youthful chemical vigour and enthusiasm seemed to infect him so that we quickly joined forces and set about a joint attack on vitamin B₁ aided by a small grant that Barger obtained for me from the Rockefeller Foundation and a supply of rice-concentrate from Hoffman-La Roche. In addition, most of the other newcomers in the laboratory—Fraenkel-Conrat, Jacob, Karimullah and a newly arrived Swiss named Keller—all wanted to join in the vitamin work so that, within a short time, we had a substantial group forming, with Bergel and myself, a useful team attacking the problem of structure and synthesis of vitamin B₁.

There is in my mind no doubt that both Bergel and I benefited enormously from our partnership, which grew ever stronger. For perhaps the first time in his postdoctoral career Franz Bergel devoted himself mainly to research and, doubtless spurred by the enthusiasm of his young new-found friend, began to show something of the great scientific talent he possessed and that had lain more or less dormant ever since he had parted company from Heinrich Wieland in Freiburg. True, some vestiges of his earlier playboy existence showed from time to time, but his lapses soon became less and less frequent. In the autumn of 1934 his former wife, Niddy Impekoven, came to Edinburgh, presumably in the hope of re-starting the marriage; the couple went together to Alsace at Easter 1935 but separated again thereafter and Bergel returned alone to Edinburgh; as a result of this brief reconciliation a child, Monica Renée, was born in 1936. (As far as I know this daughter uses her mother's surname (Impekoven) and now lives with her son in the neighbourhood of Basle, while her mother also resides in Switzerland at Bad Ragaz.)

Work on vitamin B₁ and its blue-fluorescent oxidation product, thiochrome, was intensively pursued by the whole Edinburgh group from early in 1935 and formed the basis of a series of publications (mainly in the *Journal of the Chemical Society*), culminating in the total synthesis of the vitamin itself and of a number of structural analogues (all physiologically inactive) as well as of thiochrome. In the actual synthesis of the vitamin the German workers associated with the I. G. Farbenindustrie completed their work a few weeks before we did. The natural feeling of disappointment by the little Edinburgh group was mitigated by the fact that their synthesis differed considerably from the German (and also the American) synthesis and included an entirely novel procedure in one of its key steps; it turned out, moreover, to be the most successful route for the large-scale production of the vitamin.

In the autumn of 1936 I moved to London to succeed J. M. Gulland at the Lister Institute of Preventive Medicine. Not only did Dr Anni Jacob and T. S. Work (who had just completed his Ph.D. under Barger's guidance) elect to move to London with me, but Franz Bergel (against, I believe, the advice of George Barger) also went with me, so that our Edinburgh team was not wholly dispersed and we were able to continue

its programmes in London; the group caused a considerable stir in the Lister Institute, which was, in those days, a rather sleepy place and did not take easily to people like us who regularly worked at night even during week-ends! In London the group (enlarged by the accession of Dr Hans Waldmann from Basle) first tidied up some loose ends of the vitamin B₁ work and helped to prepare and set up the International Standard for the vitamin. Thereafter, its main concern was with vitamin E. Using rice-germ oil as a source we isolated β -tocopherol, distinct (although closely related to) the α -tocopherol originally isolated by H. M. Evans and his collaborators in California. Our group was the first to postulate a bicyclic structure for the E vitamins, recognizing that they must be either chroman or coumaran derivatives. The final establishment of the chroman structure and the total synthesis of the tocopherols was not effected until 1938 when I had moved from London to become Professor of Chemistry in Manchester. During the Lister period Bergel and I also did some preliminary studies on *Cannabis* using the resin that (as already mentioned) he had obtained in Ceylon in 1930 and had brought to Edinburgh with him in 1933.

The close scientific partnership between Franz Bergel and myself came to an end in 1938 when I was appointed to Manchester (being accompanied there by Dr Anni Jacob and Juan Madinaveitia of the old Edinburgh group) and Bergel was appointed Director of Research at the fine new laboratories just being completed at Welwyn Garden City for Roche Products Ltd, the British subsidiary of the giant Swiss corporation Hoffmann-La Roche & Co. (which had, indeed, been supporting Bergel financially during his stay in Britain). During the early part of 1938 Bergel who, naturally enough, was having to divide his time between chemical work at the Lister Institute and the construction and equipping of the new laboratories of Roche Products Ltd, moved to a rented house in Welwyn Garden City where he lived for the next 14 years. Almost immediately, his former wife arrived at Welwyn Garden City with their little daughter and she and Bergel made a last effort to come together again. The attempt was quickly found to be hopeless and within a couple of months they separated, this time finally, and she returned to Switzerland and permanent residence there.

Bergel and I then went our separate ways in the early summer of 1938 and never actually worked together again, although a few further joint publications appeared: one or two on vitamin E and others on *Cannabis* and synthetic cannabinoids, which involved collaborative work done partly in Manchester and partly in Welwyn Garden City in which we sought (unsuccessfully) to find a therapeutic use for analogues of tetrahydrocannabinol. Looking back over this chapter in Bergel's life (i.e. Edinburgh and the Lister Institute) I think there can be no doubt that it was the time of his scientific awakening. He had great scientific talent but until he joined forces with me in Edinburgh it had never really been used.

It is perhaps ironic that his scientific career should have been essentially determined in a city that he so much disliked.

WELWYN GARDEN CITY

As indicated above, Franz Bergel's scientific awakening was begun in Edinburgh and completed at the Lister Institute; but vestiges of the old playboy still remained and it was clear that he really needed some permanent stabilizing influence if he was to make the success in professional life of which he was capable. In August 1938 he had the amazing good fortune to meet a young actress, Phyllis Thomas, at the home of a mutual friend. A love affair developed rapidly and on 6 April 1939 Franz Bergel and Phyllis Thomas were married at the Chelsea Registry Office. This event was the final turning-point in Bergel's life for the marriage was a very happy one; it gave him the peace of mind, the balance, and the companionship that he had hitherto lacked, and it endured—an outstandingly successful marriage—until Franz Bergel's death in 1987 ended the partnership.

The summer of 1938 was hardly the ideal time to start an entirely new career in an equally new and untried industrial research laboratory. Already the storm clouds were gathering over Europe and one felt that war could not be far away. Bergel's parents, finding life intolerable after Hitler's annexation of Austria, came to England early that year and joined an uncle of Franz's who had been living at Crouch End for some years. Also, in the autumn of that year, Bergel's brother, Otto, with his wife and two young daughters, stayed for a short time with him at Welwyn; they too could no longer tolerate life in Vienna and were *en route* to South Australia where they were to settle in the wine-growing area near Adelaide.

Nevertheless, Bergel did get things started quickly in the new Roche Laboratories so that they were in full operation before war actually broke out in 1939. He was extremely fortunate in his choice of a second-in-command. I doubt if he could have found anywhere a better man than Dr A. L. Morrison, an able and quite imperturbable Scot, who provided a perfect foil to the rather temperamental and volatile Bergel; Morrison did, indeed, succeed Bergel as Director when the latter resigned in 1952. By the summer of 1939 research was really getting under way at Welwyn when the war broke out and brought in its train modification of some, at least, of the current research programmes to accord with national needs.

In October 1939 Bergel's mother, who had been ailing for some time, died and, in due course, his father moved to Welwyn Garden City to live with his son and daughter-in-law; during the war he worked in a local department store and emigrated to Australia thereafter to join his younger son in Adelaide. When the so-called 'phoney war' ended in the

spring of 1940, the private lives of Bergel and his wife were greatly changed. She was busy throughout the ensuing war period with theatrical and allied work for the armed forces, while he, in addition to his work with Roche, held a commission in the Home Guard and acted throughout the war as an air-raid warden (positions that he was able to hold only because he had received full naturalization as a British subject in August 1939).

Bergel's chemical interests lay in the field of natural products with physiological action and in the synthesis and study of compounds that might be of value in medicine. These interests were, of course, central to the activities of Roche Products and its Swiss parent company. They were also clearly of potential interest to the war effort, so that the programme of work envisaged by him when he set up the Welwyn laboratories with four chemists in 1938, although somewhat modified, remained the backbone of the laboratories' work and, indeed, continued to dominate their activities until Bergel's resignation. It was, of course, necessary to do a lot of short-term research and development work during the war years when Roche Products was, in effect, cut off from its parent company; as a result, much of the work done was limited in scope and, although of excellent quality, it does not lend itself to detailed discussion; most of it is recorded in a substantial series of patent specifications and papers that are listed in the bibliography. A brief outline of the main fields of research follows.

Synthetic analgesics

Considerable effort was devoted to the synthesis of compounds that might be of value as substitutes for morphine and its derivatives. No new compounds with high activity emerged but the group had a not inconsiderable success in the discovery and development of a new and industrially usable synthesis of the widely used analgesic pethidine.

Cannabinoids

Mention has already been made of Bergel's early interest in the constituents of *Cannabis* and his procurement of a substantial quantity of active *Cannabis* resin during his stay in Colombo in 1930. He brought this material to Edinburgh in 1933 and, during his sojourn at the Lister Institute, he and the author of this memoir did some preliminary work on the drug and showed that cannabiniol, the only pure compound that could be isolated from it with the techniques then available, was devoid of physiological activity, all of which appeared to reside in the intractable resin remaining after the separation of cannabiniol from the natural drug. Although it was established that cannabiniol was a dibenzopyran derivative, its precise structure remained in doubt until it was synthesized

independently in 1940 by Adams in the United States and Todd in Manchester. A key intermediate in the Todd synthesis, Δ^3 -tetrahydrocannabinol, showed marked hashish activity in animal tests, although the degree of activity was much less than that of the natural drug. At the time I held the view that the active portion of *Cannabis* resin consisted of a mixture of isometric tetrahydrocannabinols but, owing to pressure of other work, did not pursue further study of the natural material. (My view was indeed vindicated some 15 years later through the brilliant work of Mechulam and his colleagues, who showed that the most active component of the mixture was Δ^6 -3,4-*trans*-tetrahydrocannabinol.)

Following completion of the cannabinol synthesis in Manchester, a rather desultory collaborative effort was made throughout the war years between Welwyn and Manchester in which a large number of analogues (including some water-soluble examples) of Δ^3 -tetrahydrocannabinol were synthesized and tested as anti-depressants. The results of clinical tests with these materials were, at best, ambiguous, and nothing likely to be of real therapeutic value emerged. This collaboration ended following the re-establishment of the controlling body of Hoffmann-La Roche in Basle at the end of the war. Roche did not follow up these researches, not so much (according to Bergel) because of the negative results obtained up to that point, but because the Hoffmann-La Roche management did not wish to be in any way associated with *Cannabis*, which had come to the fore about that time as a proscribed drug of addiction. Whatever the reason for the decision, the firm lost nothing by keeping clear of *Cannabis* for, despite efforts made by various groups over the years since then, no success has yet been achieved in discovering therapeutically useful cannabinoids.

Antibacterials

During the war years the Welwyn laboratories did a substantial amount of work on antibacterial substances as part of the national effort. Among natural antibiotics they devoted their main attention to patulin (clavatin), which they obtained from *Penicillium patulum* and geodin (from *Aspergillus terreus*). Although chemically interesting, these materials were completely overshadowed by penicillin, to the production of which the Welwyn group made only minor contributions. In parallel with this work on naturally occurring materials, synthetic studies were made on a variety of compounds, e.g. thiophanones, derivatives of patulin and a series of benzylacrylic acids. Most of the compounds made had antibacterial activity but none warranted commercial development.

Vitamins

By the outbreak of World War II the Hoffmann-La Roche group of companies had become the leading supplier of synthetic vitamins and

much of its research effort was devoted to the vitamin field. Not unnaturally, therefore, during the enforced wartime separation from Basle, Bergel and his colleagues had to devote a substantial amount of effort to process control and development and to the study of the various new vitamins that were discovered or whose existence was postulated during these years; this work concerned mainly vitamins B, C and E, with pantothenic acid and the so-called 'vitamin P'.

Other work

Alongside the studies briefly outlined above, a variety of smaller investigations were undertaken, for example on adrenergic drugs and on organic phosphates. No outstanding results of practical value emerged from these investigations and the substantial effort made by Bergel and his colleagues to synthesize lysergic acid after the war was frustrated by the prior synthesis of that compound by R. B. Woodward.

At the time Franz Bergel joined Roche Products Ltd, the Hoffmann-La Roche group of companies was very tightly controlled from the group headquarters in Basle. The chairman and chief executive in 1938 was Dr E. C. Barell, who continued to occupy that position until his death in 1953. He was a strict disciplinarian who insisted upon being involved, not only in appointments to, but also in the detailed running of, the Swiss, British and, during the war years at least, American subsidiary companies. So it was that Barell, usually accompanied by a senior Swiss colleague, visited the Welwyn laboratories frequently between early 1938 and the outbreak of war. Bergel found these visits extremely irksome and it was a great relief to him when Dr Barell and his colleagues moved to the United States during the war years and so could no longer interfere directly with the day-to-day work of his research group. Had it not been for this relief it is doubtful whether Bergel would have remained with Roche, so strong was his dislike of Dr Barell and his methods. Rigid control from Basle was re-introduced upon the return of Dr Barell and his colleagues to Switzerland after the war, and it was (in Bergel's opinion) rendered even more unpalatable by the appointment of a new managing director of Roche Products Ltd with whom he (Bergel) was frequently at loggerheads. As a result, in the years following the war's end, Bergel became increasingly frustrated and finally, in 1952, decided he could stand it no longer; accordingly, he travelled to Basle and, after a stormy interview with Dr Barell, resigned.

It is true that Bergel had seriously considered leaving Roche in 1946 when he was offered a Chair of Chemistry at the Free University of Brussels; his rejection of that offer followed a visit to Belgium where the deep divisions brought about by the wartime experience both within and without the University were all too evident, and, he felt, would have nullified any effort he might make to develop a strong school of chemistry there.

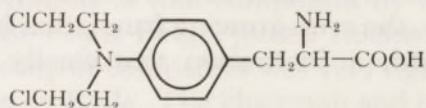
During the six and a half postwar years during which he remained with Roche Products, Bergel became increasingly involved in extramural activities. Following his wartime experiences he became involved in a variety of more or less local affairs (especially in education) in Welwyn Garden City and further afield in Hertfordshire. Nationally, his scientific stature, especially in the fields of pharmacological chemistry and nutrition, were becoming increasingly recognized and he was appointed to an Honorary Lectureship in the Department of Pharmacology, University College London, in 1946, a position he held until 1972. He served on the Council of both the Chemical Society and the Society of the Chemical Industry. He was a founding member of the Fine Chemicals Group of the Society of the Chemical Industry set up by Sir Jack Drummond, whom Bergel later succeeded as chairman. He also succeeded Sir Charles Harington as chairman of the Coordinating Committee for Symposia on Drug Action. These activities, with attendance at symposia and delivery of invited lectures, certainly helped to ease, but could not eliminate, the ever-growing frustration he felt in his post with Roche Products Ltd, a frustration that finally led to his resignation in 1952.

As it turned out, Bergel was very fortunate in the timing of his resignation from Roche. In 1951 Professor G. A. R. Kon, Head of the Chemistry Department of the Chester Beatty Research Institute in the Royal Cancer Hospital, London, had died and, shortly after Bergel's resignation from Roche, it was decided to seek a successor to Kon and the Chair was advertised. Bergel applied and (he always maintained), much to his surprise, was appointed. He took up his new duties in the autumn of 1952, coincident with a reorganization and consolidation of activities relating to cancer research not only in the Chester Beatty Institute but also in its associated hospital, the Royal Marsden. Bergel's new department was concerned essentially with organic chemistry and enzymology, there being separate departments of physical chemistry and biochemistry.

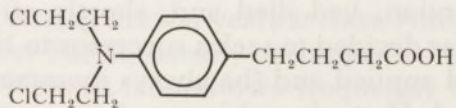
THE CHESTER BEATTY RESEARCH INSTITUTE

Bergel's appointment to the Chester Beatty Research Institute with the title of Professor in the University of London gave him the right to accept and supervise postgraduate students for the degree of Ph.D., and his Honorary Lectureship at University College enabled him to keep in touch with undergraduate teaching. Altogether, it would be difficult to think of any other position so appropriate to a man of his abilities and temperament. His previous interest and experience in natural product work and in the synthesis of potential therapeutic agents led him to concentrate on the chemotherapy of cancer, a subject that was then only in its infancy and to which he was to make great contributions during his 14 years at the Chester Beatty. His predecessor, G. A. R. Kon, had,

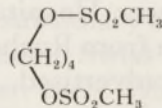
shortly before his death in 1951, begun a programme of work on derivatives of 'nitrogen-mustard' (di- β -chloroethyl-methylamine) as possible chemotherapeutic agents for cancer, but it had not proceeded very far and had enjoyed little in the way of success. Bergel took over this programme enlarging and expanding it on the basis of his idea that a useful approach might be to study compounds in which a nitrogen-mustard derivative was attached to an amino acid or a peptide carrier thereby, perhaps, enhancing its selective entry into tumours. This work led not only to a substantial series of scientific papers but also to several therapeutically important compounds, e.g. melphalan (4-[bis-(2-chloroethyl)amino]-L-phenylalanine) (1) (with J. Stock) in 1960 (1)* and also the related chlorambucil (4-[bis-2 chloroethyl amino]-phenylbutyric acid) (2), and *myleran* (1:4-dimethanesulphonyloxy-*n*-butane) (3) (3). It is worth noting that all three of these compounds still feature prominently in the armament of the clinical oncologist.



1



2



3

In addition to his work on alkylating agents, Bergel also initiated and developed a substantial programme of research aimed at developing therapeutic measures based on the biochemical properties of tumours. In particular, he sought to exploit the emphasis of tumours on anabolic rather than catabolic pathways, and also to use enzyme therapy to deprive particular tumours of essential nutrients. His attention was focused primarily on the enzyme xanthine oxidase (the 'Schardinger enzyme') although he also did some work with guanase and cysteine desulphydrase. This initiative was certainly visionary and was well ahead of developments elsewhere that established a role for asparaginase in the enzyme therapy of leukaemia. Special mention should be made of the work of Bergel with Bray on the isolation and crystallization of xanthine oxidase from cow's milk, and the establishment of the electron pathway in this metallo-flavoprotein and the elucidation of its reaction mechanism. Alongside the work on xanthine oxidase, Bergel set up a companion study on assays for circulating enzymes as indicators of the presence of tumours and their

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

response to treatment, and, in 1961, he published a comprehensive monograph, *Chemistry of enzymes in cancer* (2), in which he reviewed all that was then known about the role of enzymes in cancer and the potential of some of them as therapeutic agents.

Throughout the period of Bergel's stay at the Chester Beatty its Director was Alexander Haddow with whom he developed a close friendship. Their intimacy and mutual respect, both scientifically and personally, had much to do with the orientation of Bergel's scientific work and the latter in turn undoubtedly influenced Haddow's approach on the clinical side of the Institute's research. The interaction between the two men emerges clearly in the comprehensive account of Alexander Haddow's life and work written by Bergel and published in *Biographical Memoirs* (4). It was through Haddow that Bergel first met Sidney Farber, a leading figure in the cancer field in the 1950s and, at the time, Director of the Children's Cancer Research Foundation in Boston, Massachusetts (now called the Dana-Farber Cancer Institute and reorganized in two parts: The Sidney Farber Cancer Institute and the Charles A. Dana Cancer Center). Bergel spent an enjoyable and profitable sabbatical year in Farber's laboratory in 1959-60 and was subsequently a frequent visitor to the Institute, initially as a consultant and then, from 1966 to 1971, as a member of its Scientific Advisory Board, frequently spending one or two months at a time there during this period.

Dr George E. Foley, a previous Administrative Director of the Sidney Farber Institute, has written of Bergel's association with the Institute:

Franz often spent one or two months in residence. He was interested in all aspects of the Foundation and its development. His major interest, of course, was the program in chemotherapy but he provided invaluable wisdom and advice to all members of the Staff—he was 'at home' with all of them irrespective of their discipline, and he was always interested in young people and their ideas on how to advance our knowledge of neoplastic disease.

Through his work at the Chester Beatty, Bergel rapidly acquired an international reputation in cancer research. He was frequently an invited participant in major international symposia and he lectured widely on cancer chemotherapy. In 1965 he was responsible for founding the Coordinating Committee for Human Tumour Investigations, which provided a much-needed forum for the coordination and integration of laboratory and clinical studies in oncology. He was elected to the Royal Society in 1959 and, during his career at the Chester Beatty, he was not only Deputy Director of the Institute itself but served on all its major committees as well as acting as Dean from 1963 until his retirement in 1966.

Regarding his time at the Chester Beatty, Professor K. R. Harrap has written:

Franz Bergel's achievements in medicinal chemistry were many and varied, and those who were privileged to know and to work with him could not fail to be influenced by his captivating enthusiasm for scientific enquiry. He believed implicitly in the value and importance of interdisciplinary collaboration in cancer research and encouraged his colleagues to focus their attention consistently on the urgent need for new cancer treatments, and he was always ready to promote their ideas. He always maintained a close personal interest in the work of his Department at the Chester Beatty Institute and started his daily rounds of the laboratories punctually at 9 a.m. and 6 p.m. Invariably these visits revealed his staggering command of the literature across the whole spectrum of the Department's work; if something particularly exciting was happening he would, almost literally, camp in the laboratory concerned, despite his many other duties.

In recognition of his services to the Institute and of his scientific distinction, the library on its new Sutton campus was dedicated to his memory in his presence on 25 April 1980, a ceremony that, incidentally, marked his last visit to the Institute from the service of which he retired in 1966, and that he had served so well.

Following his retirement Bergel moved to Jersey where, at Bel Royal, he and Phyllis lived happily and peacefully together until his death in January 1987, only a few weeks before what would have been his 87th birthday. Although retired and living in Jersey, Bergel maintained a keen interest in the Chester Beatty and continued for a number of years to maintain contact with cancer research there and elsewhere by writing, by visits to meetings on the mainland, and by his continuing association with the Dana Farber Cancer Institute. This activity following his official retirement and, perhaps even more, his highly productive and active career in cancer research, is the more remarkable when one recalls that in 1957 Franz Bergel underwent a surgical operation for rectal cancer involving a colostomy; it says a great deal indeed for his courage and dedication that the permanent handicap he thus acquired should have had so little obvious effect on his career; he certainly never complained of his lot, and continued to the end of his days as if the problem of a colostomy did not exist.

Essentially a humanist, Franz Bergel was a kind, compassionate and gentle man. He always nurtured the careers of his staff and associates and was much concerned for the welfare of their families. In return he was respected by all who knew him for his scientific distinction, and loved for his friendship and consideration for others, whatever their status. Widely read outside science, and with an active interest in European languages, he was an engaging conversationalist and an amateur artist of considerable talent. The comments from Professor Harrap and the brief appreciation from Dr Foley that I have quoted give a fair, if brief, impression of the man whom his colleagues and friends, among whom I am proud to count myself, knew and loved. His passing is a loss to science but his

achievements and his stimulation, especially of research on the chemotherapy of cancer, remain a permanent tribute to him.

Franz Bergel will not be readily replaced in research and still less in the minds and hearts of those of us who were privileged to know him.

ACKNOWLEDGEMENTS

Rough autobiographical notes left by Professor Bergel and made available to me through the kindness of his widow, Mrs Phyllis Bergel, have been of the greatest assistance in the preparation of this memoir. I am also indebted to many of his friends and former associates for details of his life and work, and especially to Professor K. R. Harrap, Professor C. H. Hassall, F.R.S., and Dr George Foley. I am also deeply indebted to Miss G. M. Davies, Librarian of the Chester Beatty Research Institute, for compiling the bibliography.

The photograph was taken in 1959 by Robert Tilling.

PAPERS BY BERGEL REFERRED TO IN THE TEXT*

- (1) 1960 (With J. A. STOCK) Cytoactive amino-acids and peptides. Part 8. N alpha-acyl, amide, ester and peptide derivatives of melphalan. *J. chem. Soc.*, p. 3658.
- (2) 1961 *Chemistry of enzymes in cancer*, Springfield, 111. C. C. Thomas.
- (3) 1963 (With S. S. BROWN, C. L. LEESE, G. M. TIMMIS & R. WADE) Some potentially cytotoxic methylnitrosoamines. *J. chem. Soc.*, p. 846.
- (4) 1977 Alexander Haddow 1907-1958. *Biogr. Mem. Fell. R. Soc.* **23**, 133-191.

* The complete bibliography appears on the accompanying microfiche no. 1.