Berthold Halpern 1923-1980

By D. Danks, A. Duffield, and A. Sargeson

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Bert Halpern was born in Vienna (18 June 1923) educated at the University of Sydney and majored in organic chemistry. He did an honours degree (1950) under the tutelage of G.K. Hughes and E. Ritchie who led a flourishing research group in Australian natural product chemistry which was largely devoted to the extraction, degradation, structural analysis and synthesis of alkaloids. This aspect of Australian chemistry was strong at the time and the group was one of the leaders, both locally and internationally. In retrospect, it is easy to see how a man with Halpern's abilities chose his mentors so accurately and they clearly contributed to his life time interest in natural products

Lectureships in organic chemistry were scarce at the time and the PhD degree had only just been introduced into the University of Sydney. Industry, however, was anxious to employ organic chemists and it was not surprising therefore that Halpern accepted a post as a Research Chemist with Monsanto Chemicals (Aust.) Ltd and quickly became a group leader. He worked on chloromycetin chemistry and the application of fluidised technology to the production of organic chemicals. Monsanto thought so highly of him that they encouraged him to take up a Salters Scholarship to work for a PhD (1957-59) with Professor Derek Barton at the Imperial College of the University of London (subsequently knighted for his services to chemistry and awarded a Nobel Prize). His research project involved syntheses in a then new area of polycylic antibiotic compounds, namely tetracycline, and this work was finally published in 1971. Halpern returned to Monsanto as Research Manager and some of his previous and subsequent research is only published in the form of patents relating to agricultural chemical formulations, anthelminthics, resolution of amino acids and the synthesis of a potentially new range of antibacterial agents The last activity is an interesting chemical story and a sad commentary on the relationship between science and commerce in the implementation of useful discoveries.

In the 1950s, Professor Frank Dwyer was captivated by the potential of coordination complexes for influencing biological systems, especially those likely to retain their integrity in biological systems (i.e. those kinetically inert to dissociation of their ligands). Coordination complexes had been used before but it was never clear whether the complex was the effective agent or the organic molecule which dissociated from the complex. Dwyer advanced the notion that large organic amines such as 1,l0 phenanthroline bound to metal ions to give positively charged complexes would have some of the characteristics of cationic alkaloids and might have other interesting properties as well. He was so convinced that he persuaded some colleagues at the time and himself to taste nickel (II) tris (1,10-phenanthroline) sulphate. In fact, the

complex ion has a strong bitter taste even though it is not a potent as strychnine or brucine. This was enough for Dwyer to encourage several biological colleagues and notably Drs Rogers and Koch at the McMaster Laboratories of CSIRO to scan likely systems for activity. The complexes turned out to be potent acetyl cholinesterase inhibitors and finally some of them were shown to be effective antibacterial agents. However, the cost of the phenanthroline ligands was substantial (£1 per gm) so Dwyer and Albert Shulman and others succeeded in getting Halpern, Jackson and Berger, of Monsanto Chemicals (Aust.) interested in the potential use of the compounds and in developing new and more active ligands and new and cheaper methods of making the substituted 1,l0 phenanthrolines.

The Monsanto side of the project was directed by Halpern and proved extremely interesting. By extensively methylating the ring system of the base the antibacterial activity was increased handsomely. In addition, the cost of the substituted ligand which had previously been prohibitive was reduced by a factor of forty. Moreover, the synthetic design and changes from traditional methods of making phenanthrolines were largely due to Halpern. A wide-range testing program for the compounds was undertaken by Dr A. Shulman, Professor R.D. Wright, Professor S. Rubbo and Dr M. White at the University of Melbourne for gram-positive and gram-negative bacteria, anti-viral activity and anti-tubercular activity. The effect on *Staphilococcus aureus,* for example, was so pronounced that a full-scale trial to protect new-born babies from this infection was carried out by Dr Hildred Butler at the Royal Women's Hospital, Melbourne, in competition with the most promising competitor at that time, hexachlorophene. The results of the trial were so promising that the ligand and complex syntheses and uses were patented by Monsanto and jointly by the Australian National University and the University of Melbourne respectively. Monsanto was given exclusive manufacturing rights. The nickel and iron complexes of a tetramethylphenanthroline derivative were found to be superior to hexachlorophene in activity and their abilities to induce mutants in the organism were at an extraordinarily low level. Their potential therefore for topical application on infected areas was very substantial and Monsanto attempted to persuade various pharmaceutical firms to take them up as a commercial development. The problem which arose in those negotiations was that the compounds, although better than hexachlorophene, were not sufficiently better than the firm's current research objectives in this area for them to be willing to invest. Not only did this attitude deprive the community of a valuable antibacterial agent but the subsequent history of problems with hexachlorophene makes the tale even more depressing. Those who were privileged to have access to the complexes still use them for preference on infections which are accessible for topical application.

In 1958, Dwyer moved to the ANU at Canberra to set up the Unit of Biological Inorganic Chemistry in the John Curtin School of Medical Research. This was probably the first time the terms Biological and Inorganic had been combined formally and Dwyer clearly saw the prophecy in the combination. Halpern was also persuaded that this aspect of chemistry was interesting and in 1962, he joined the Group as a Senior Research Fellow to work on the resolution and chiral syntheses of amino acids, using coordination complexes as resolving agents. Unfortunately, shortly after Halpern's arrival Dwyer died and since Halpern's appointment was not tenured and the future of the group was in jeopardy, he decided to accept a Syntex Research Fellowship in Mexico. Before leaving ANU, however, he completed several significant papers on peptide syntheses using a new type of protecting group, dimedone. He also contributed to the general understanding of the behaviour of amino acids bound to metal ions which later led to a peptide synthesis where the metal ion both activates and protects an amino acid ester.

This early work formed the basis for a lasting research interest in stereochemistry, natural product chemistry and amino acid and peptide chemistry. Such a background probably influenced his appointment to Syntex and it certainly influenced his appointment to Stanford later.

The use of dimedone as a protecting group for amino acid ester and peptide chemistry was continued by Syntex at Mexico City (1963-64) but in 1964, Halpern was invited by the Nobel Laureate, Professor Joshua Lederberg, to fill the position of Senior Scientist in the Instrumentation Research Laboratory of the Department of Genetics at Stanford University. Here he remained until he took up the foundation chair in chemistry at the University of Wollongong in 1970.

The main source of research support for the Instrumentation Research Laboratory was the US National Aeronautics and Space Administration. Their interests lay in the promotion of new instrumental methods appropriate for the detection of extraterrestrial life. Dr Halpern's group began by designing experiments for

the detection of amino acids and the detection of chirality in amino acids, using primarily mass spectrometry and gas chromatography. Halpern's background was peculiarly appropriate for this work on amino acids and peptides and from it the concept of the Pasteur Probe arose as an assay for the detection of life. It was a period of great activity, interesting and exciting experiments and it allowed Halpern ample time to work a full day with his own hands, an occupation he thoroughly enjoyed. His impressive success with the application of physical methods to amino acid and peptide chemistry resulted in research grants from the National Institute of Health as well as NASA. He was also appointed a Senior Investigator in the NASA Lunar Science Program and as the time approached for the manned landing on the moon, Halpern, as a member of the Lunar Lander Analysis Team, assumed co-responsibility for some of the chemical assays to be undertaken on the moon rocks. The strategies developed for this program were also applied to the study of enzyme stereo-specificity and to the monitoring of bacterial growth in soils. A study of the effect of solute and substrate structure on the chromatographic separation of diastereoisomers led to a new method for the determination of absolute configurations of organic molecules.

The application of gas chromatographic-mass spectrometric techniques to multi-component systems was clearly evident by 1965 but the coupled instrumentation available was not particularly suitable. A new automated GC-MS computer system was then developed by Halpern, W. Reynolds and associates which allowed biomedical applications of this technology to be attempted. In this development, the computer was made to drive a quadrupole analyser directly and the data collection and processing was thereby greatly facilitated. This approach was first taken up by the Finnigan Corporation and was basic to their most popular range of automated GC-MS systems. The new MS-computer system was used for analysis of the Apollo 11 and 12 Lunar samples to seek amino acids, peptides, chlorins, porphyrins, carbon and organic compounds in general. It was also used for sequencing small peptides and for a number of biological applications. Its simplicity, ease of operation and reliability made it an ideal laboratory instrument for routine chemical analyses.

From 1968 a steady stream of visitors passed through Halpern's laboratory to see the computerised mass spectrometer system in operation. His own experience with GC-MS had convinced him of the important role this methodology would play in the future, especially for the analysis of substances present in low concentrations in complex mixtures. However, he did not neglect other physical methods or synthesis as substantial aspects of his work. He used rotatory dispersion and nuclear magnetic resonance extensively and developed new synthetic methods for peptide chemistry and for handling non-volatile compounds in the mass spectrometer.

In 1970, he returned to Australia as Professor of Chemistry at the University of Wollongong and immediately installed, with the assistance of Peter Bolton, the new technology and activity in the Chemistry Department. Almost immediately a new and ingenious method of sequencing proteins was developed to compete with the chemically more cumbersome Edman process. A dipeptidase was used to cleave the protein into dipeptide fragments and the hydrolysate was derivatised on the probe in the mass specrometer, A terminal amino acid was then removed from the protein and the hydrolysis and analysis were repeated. The elegance and power of this approach was that essentially only three chemical operations were required. The remaining analysis was carried out by the mass spectrometer or, if necessary, a combined GC-MS method and the usual mapping techniques. Apart from the DNA approach to the sequencing problem, it is probably the most elegant way of sequencing peptides. It is applicable to small amounts of protein and very little handling of the material is required.

The success of Halpern's research activities at Wollongong can be measured to some extent by the equipment he was able to attract to his department. Following the initial GC-MS computer instrumentation, a second system was installed and to this he subsequently added a third system loaned by Varian-MAT. To these major acquisitions one must add the chromatographic system (gas and liquid) necessary to equip the laboratory for their most successful research on biomedical applications of GC-MS, especially their chemical diagnosis of inherited disease.

Halpern's direct involvement in the biomedical applications of mass spectrometry probably began after an association with Professor Barkas of the Department of Psychiatry at Stanford University. This was a time of intense interest in precise methods of identification of small amounts of biological compounds at Stanford and it attracted a young Norwegian chemist, Egil Jellum from the Institute of Chemical

Biochemistry Rikshospitalet, Oslo, Norway, to work with Halpern. He was a member of the team in Oslo which produced the first burst of significant discoveries in the field of inborn metabolic errors, using gas chromatography-mass spectrometry. The association contributed to a continuing interchange between Wollongong and Oslo, including a period of sabbatical leave for Halpem in the Oslo laboratory

In 1972 Halpern gave a very stimulating lecture on the potential of GC-MS in biomedical research in the Department of Chemistry at Melbourne University and after this lecture a mutual friend introduced him to Dr David Danks, Head of the Genetics Research Unit at the Royal Children's Hospital, thereby initiating a collaboration which was to continue very actively until Halpern's untimely death. The genetics group in Melbourne had just set up gas chromatography to analyse carboxylic acids extracted from urine in patients in whom a metabolic cause of mental retardation or other symptoms was suspected. The technique supplemented the methods they were already using for detection of amino acids in urine. Strategies were then developed in Wollongong which allowed the derivatised extract tested in Melbourne to be frozen and sent to Wollongong for immediate injection into the GC-MS system. This provided relatively rapid confirmation of the identification suggested by the GC run in Melbourne and allowed the workers in Wollongong to suggest structures of molecules which were not identified by the Melbourne system.

Part of the original urine sample was frozen and sent along with the derivatised extract so that other methods of extraction and derivatisation could be applied in Wollongong if necessary. The initial results proved that this approach was practicable, despite the five hundred rniles between the laboratories, and the National Health and Medical Research Council then funded a postdoctoral fellow to work in Wollongong to develop the collaboration. This support was quite critical to the final success of the venture.

Over the eight year period of the collaboration, samples were shipped from Melbourne to Sydney on an average of once or twice a week by refrigerated overnight road transport. The success of the system is a tribute to the energy and enthusiasm of the people concerned in Melbourne and in Wollongong, and to the efficiency of the road transport service. A specific example can be given as an illustration. A urine sample was sent by air from Perth early one morning received in Melbourne in the latter part of the morning analysed on the GC by mid-afternoon, confirming the existence of four unknown peaks already seen in Perth. The extract was shipped to Wollongong overnight and a tentative identification of all peaks was obtained by rnidday, approximately 30 hours after the sample left Perth. Tweny-four hours later, Halpern's team had synthesised the four compounds and confirmed the identification of the peaks. This case defined a new inborn metabolic error: 3-hydroxy-3-methylglutaric aciduria. Indeed, the overall efficiency of interchange of samples and discussion between the two laboratory groups throughout the eight years was equal to that in the best groups around the world where the two sets of expertise are in the same or adjacent laboratories.

As time went by, the doctors working with inborn metabolic errors in other cities realised the value of the resource now available in Wollongong and increasing numbers of samples were sent to Wollongong, or via the Melbourne laboratory. Halpern had already established a very good relationship with the chemical pathology department at the Wollongong Hospital and two of the biochemists from the Hospital (Drs I. Gan and G. Shier) did their doctoral degrees in Halpern's department An increasing liaison also developed with the Oliver Latham Laboratory at the North Ryde Psychiatric Centre in Sydney, which performed screening tests for metabolic diseases for the whole of New South Wales.

The collaborative efforts between Melbourne and Sydney identified five 'new' inborn metabolic errors during the eight years of the work and discovered previously unknown metabolites in a number of other diseases. This contribution to knowledge is equal to that of any other group using GC-MS methods to study inborn errors of metabolism, and greater than the productivity of most other groups over the period 1973-1980, following the first burst of new discoveries of organic acidurias. It also had a substantial social impact. Even the known disorders were identified rapidly and this allowed prompt treatment or early counselling of parents when effective treatment was not possible. The young postdoctoral fellows who held the NH and MRC grants in Halpern's laboratories received outstanding training in mass spectrometry, in organic chemistry and in the overall approach necessary for success in research. Two of them went on to further postdoctoral study in Professor Barkas' laboratory at Stanford; Dr Fauls stayed on there in a staff position and Dr Truscott returned to head a OC-MS unit in clinical pharmacology in Melbourne.

Halpern's outstanding success in this phase of his work and in his research in general can be attributed to his profound knowledge and ability, and especially to his infectious enthusiasm, his delightful personality and an unfailing 'sense of smell' which enabled him to choose which problem to attack with vigour and which to leave alone. In other words, he showed to an unusually high degree those characteristics essential to success in collaborative research and these talents led to his election to a Fellowship in the Academy in 1978.

It is interesting to trace the pattern of chance, influence and association in the development of any scientist's work and Halpern's is an especially interesting history because it spans such a variety of activity and areas. His industrial associations inevitably brought to his research a pragmatism which few academics have. He sought quickly the nub of the problem and then decided just as quickly if it was worth tackling. His whole day in the laboratory was devoted to effective experiments which he had thought about the previous evening. The early work on the resolution and chiral synthesis of amino acids arose because of the high cost, of what was at that time called 'unnatural forms', the D-isomers. No one could have foreseen how that initial pragmatism would subsequently involve him in the Lunar project, an important method of protein sequencing and finally the diagnosis of disease and its important social implications.

This combination of events does not detract from the man. The general body of results and their impact attests to his stature as a scientist. It implies an outstanding capacity to choose important problems but it does not say much about his personality. In that respect, he was quite delightful, enthusiastic, encouraging and unfailingly helpful and direct with his research associates. In his private life, Halpern was a quiet person who enjoyed his home life, family, friends and garden. He was staunchly encouraged and supported by his wife, Margaret, in all his activities. He was a good friend, with a delightful sense of humour, very tolerant, and he also had friends in many phases of human endeavour. Those of us who were fortunate to know him well remember him with affection and were desolated by his premature death on 15 November 1980. A small consolation is that his contributions to the pioneering work culminating in socio-medical achievements will be taken up by hospitals around the world and will be used for diagnosing a variety of diseases as well as detecting genetic deficiencies.

Professor D. Danks, Professor of Paediatrics, University of Melbourne.

Dr A. Duffield, Director, Biomedical Mass Spectrometry Unit, University of New South Wales.

Professor A. Sargeson, FAA, FRS, Professor of Chemistry, Australian National University.
