SIR LESLIE FOWDEN
13 October 1925 — 16 December 2008
Professor Sir Leslie Fowden was an organic chemist and one of the most influential plant scientists of his generation. He pioneered the new field of phytochemistry and was the world authority on plant amino acids. He was distinguished for the identification, characterization and biological function of a new category of nitrogen containing molecules in plants, the non-protein amino acids. During his research career, he isolated at least 50 of these compounds from a wide range of different plant genera and established their structural diversity, metabolic and toxic functions, and their scientific significance. In achieving this, he developed novel techniques for the rapid, quantitative separation of compounds by chromatography and electrophoresis, which were widely adopted in other disciplines. As Director of Rothamsted Experimental Station, he opened up new areas of research in plant biochemistry and molecular biology, and became an effective voice for the importance of agricultural research in the UK. He provided strategic leadership in the translational application of plant biochemistry to the agrichemical industry and to global crop resistance and production. His discoveries established the complexity and central role of plant nitrogen metabolism in plant growth and laid the foundations for current research in plant sciences aimed at improving both food security and the nutritional value of plants.
EARLY LIFE AND EDUCATION

Leslie Fowden was born in Rochdale in 1925, the only child of Herbert Fowden and Amy Dorothy Rabbich, who both came from large working class families. Herbert was a skilled iron turner of Lancastrian stock while Amy, the daughter of a baker and a cotton winder at the time of their marriage in 1923, was born in Devon. In 1930, the family moved into a newly built, semi-detached council house on the edge of town that overlooked the Manchester to Leeds railway line with the Pennines in the distance. The new house was near a good elementary school with a free school bus driven by Leslie’s older cousin. His parents encouraged his schoolwork as they were keen for him to make the most of his educational opportunities. He was a diligent, well-behaved pupil who excelled at mathematics and won a full, fee-paying scholarship to Rochdale Grammar School for Boys, where he studied from 1936 to 1943. Recognizing Leslie’s talent for logical reasoning, his teachers fostered his interests in mathematics and science. He took the School Certificate Examinations in eight subjects in 1940 with distinctions in mathematics, physics, chemistry, history and geography and credits in German and English literature but only a pass in English language. These results cemented his innate scientific inclination and began his trajectory of progressive academic distinction. Leslie spent three years in the sixth form as a school prefect, becoming head boy for 1942–1943 (figure 1a). Initially, his primary focus was on mathematics, in part driven by family hopes that he would become a bank manager like a wealthier uncle. However, Leslie became more interested in chemistry and read widely in the subject. For the 1942 Higher School Certificate (HSC) he took physics, chemistry and mathematics, and gained distinctions in all three. Still only 17, he remained in the sixth form, taking scholarship papers in chemistry and physics as well as repeating the ordinary level HSC examinations in physics, chemistry and mathematics. He gained distinctions in all five papers and was awarded a State Scholarship of £100 per annum for study at university.

UNIVERSITY EDUCATION

Leslie made applications for admission to the universities of Cambridge and London. He failed to gain admission to Cambridge owing to a poor performance in the compulsory Latin and German papers of the entry examination, although he also thought his strong Lancashire accent had not helped at interview. He fared better at the University of London and was offered a scholarship of £40 per annum to read chemistry at University College. University admission during the war depended on gaining permission to delay conscription into the armed forces, which was only given to limited numbers taking courses of national importance. Chemistry was one of these subjects. With his academic track record, Leslie was granted authority to join another 20 students following a two-year intensive degree course in chemistry at University College, University of London (UCL; now University College London) with an obligation to simultaneously participate in officer training.

Because of the sustained bombing of London, UCL’s chemistry department had been evacuated to Aberystwyth to share facilities with the University College of Wales, so Leslie began his undergraduate studies in 1943 at the University of London in Wales. Lectures in physics and chemistry were held every morning with practical classes for the remainder of the day, including Saturdays, and officer training on Sunday mornings. The Head of the
Chemistry Department was Professor (later Sir) Christopher Ingold FRS, who had a significant influence on Leslie’s early career. Lectures were of a variable standard, owing to the scarcity of qualified staff following military conscription, but the recommended texts were well chosen to provide a sound grounding in advanced chemistry. To compress the course into two years, the students were set a considerable amount of academic work to complete during the 1944 summer vacation alongside their military training.

For the following year, the UCL Chemistry Department returned to London. The buildings had been heavily bombed, but make-shift facilities were hurriedly prepared to run the same weekly timetable of academic and military activities as in the first year. Some of the more eminent UCL professors who had remained in London now gave the principal lectures, and one new student, Margaret (Peggy) Oakes, joined the chemistry class. She had transferred from a UCL joint mathematics–chemistry course that had been evacuated to Bangor and was now directed to Leslie for help in familiarizing herself with the first-year chemistry material that she had missed. This began a life-long relationship (see below).

Despite the continued ‘doodlebug’ bombings, central London had greater student appeal than Aberystwyth. There were more options for sport, plenty of cinemas and major museums as well as national theatre and opera at reasonable prices. Leslie made the most of all of these new opportunities. He played rugby and swam for the UCL teams, took up tennis and cycled around London from his digs where he shared a room with a school friend. Although working hard for their finals, Leslie and his friends joined the crowds thronging central London for the two days of celebrations marking the end of the war in Europe in May 1945.

Leslie was awarded a first class BSc degree in chemistry with honours and told that he was the top student in chemistry in the University of London as a whole (figure 1b). As a result, he was offered a State postgraduate studentship and the University of London Neil–Alnott fellowship for postgraduate education. However, with conscription still in force, Leslie did
not have a free choice about his postgraduate studies and was directed to research on organic reactions in UCL’s Department of Chemistry.

His PhD started in late 1945 and was supervised jointly by Professor Ingold and by Professor E. D. Hughes (FRS 1949) of the University College of Wales, Bangor. Professor Ingold was the UK authority on organic reaction mechanisms, and Leslie was set to work investigating nucleophilic substitution in alkyl halides as the alkyl group became progressively larger or more branched in structure. More specifically, he was tasked with identifying whether the substitution reaction occurred by the SN1 or SN2 mechanism and the extent to which secondary and tertiary alkyl halides caused steric hindrance during the substitution process. He learnt to synthesize alkyl halides and to determine the rate constants for halide substitutions and their $Q_{10}$ temperature coefficients, a measure of the rate of change of a chemical reaction with 10°C increments in temperature. This involved lengthy experiments, sometimes over weeks, across a wide range of temperatures, with the final stage of the process involving titration with a 10% solution of potassium cyanide, which he pipetted by mouth! As a result, he believed that he developed a tolerance to cyanide, possibly through induction of an enzyme forming $\beta$-cyanoalanine, a process that he later identified in plants (29)*.

Leslie’s project progressed smoothly, with minimal direct supervision and infrequent meetings with his professors. The experimental schedule required long hours in the laboratory on a regular basis, with 12 h reactions frequently starting and/or finishing at 21.00. He typed his own thesis and submitted it within two years. His viva, with Professor Hughes and a chemist from Kings College London, lasted all of 20 minutes including the pleasantries. His PhD degree in physical organic chemistry was awarded in early 1948, with his main findings included in two papers as part of a series of publications by Professor Ingold (9, 10). Although his PhD honed his practical skills and instilled an analytical approach to scientific questions, Leslie did not find the research very challenging intellectually or experimentally. He wanted work that had more direct benefit to society, and made the decision to move away from physical to biological chemistry for his future career. Consequently, in September 1947, he accepted a post as scientific officer in the Human Nutrition Research Unit of the Medical Research Council at Queen’s Square, London.

**ACADEMIC CAREER, SCIENTIFIC CONTRIBUTIONS AND IMPACT ON AGRICULTURAL RESEARCH**

*Discovery of non-protein amino acids in plants: Human Nutrition Research Unit, 1947–1950*

For the next three years, Leslie worked under the direction of the Unit’s Deputy Director, Dr R. A. Webb, on two projects. The first related to the Unit’s interests in kwashiorkor and investigated a growth-retarding factor in maize bran (1). The second project was a chromatographic study of peanut protein hydrolysates and their free amino acid content (2), which provided the stimulus for much of Leslie’s subsequent research. This project grew in prominence as a result of the Labour government’s Groundnut Scheme in Tanganyika, which was designed to improve post-war nutrition and the economy of Commonwealth countries in East Africa (Esselborn 2013).

* Numbers in this form refer to the bibliography at the end of the text.
Despite the ultimate failure of the scheme, Leslie’s work on the chemical composition of groundnuts (peanuts, *Arachis hypogaea*) demonstrated for the first time that amino acids could be separated quantitatively using the recently developed technique of paper chromatography. In collaboration with Dr Jim Done, he identified two unknown amino acids in the seeds, leaves and xylem sap of the peanut plant (5, 8). Having optimized the ninhydrin reaction (4), these two compounds appeared as yellow–brown spots distinct from all the other purple ones on the chromatograph. They were identified as \( \gamma \)-methylene-\( \text{l} \)-glutamine and \( \gamma \)-methylene-\( \text{l} \)-glutamic acid, the first aliphatic amino acids with unsaturated carbon bonds found to exist naturally (figure 2a,b; now known as 4-methyleneglutamine and 4-methyleneglutamate). Their identity was conclusively proved by the subsequent synthesis of both compounds (7). These compounds were not intermediate metabolites in protein amino acid synthesis or degradation and were the forerunners of a new class of soluble non-protein amino acids that now number in the hundreds (8, 57).

This discovery was controversial at the time because plants were believed to oxidize ethylene bonds quickly, but it led to Leslie’s life-long fascination with the unusual non-protein amino acids in plants. However, with the Unit’s changing research priorities, he felt that it was no longer the appropriate place to pursue a long-term career in the emerging field of phytochemistry. So, on the advice of Professor Ingold, he contacted Professor W. H. Pearsall FRS, the Head of the Department of Botany at UCL, who offered Leslie a lectureship in plant chemistry in the department from October 1950.
Plant nitrogen metabolism: Department of Botany, University College London, 1950–1973

The 1950s—identification and structural analysis of plant non-protein amino acids

The move back to UCL provided Leslie with greater freedom to pursue his scientific interests and establish his own laboratory. The Department of Botany was located on the top floor of the North Quad with the Slade School of Art below. The laboratories were antiquated and, although spacious, were not designed for chemical analyses. However, they offered the possibility of housing a research group of five or six people, so Leslie set about equipping them and recruiting PhD students and technical assistants. Initially, in collaboration with Professors Pearsall and Fogg (FRS 1965), he worked on marine and fresh water algae as possible sources of protein because protein deficiency was seen as a worldwide nutritional problem in the post-war years. More specifically, he studied algal ammonia uptake and protein composition across a range of species (3). Alongside this, he continued to develop his own line of research on the non-protein amino acids in plants. Indeed, identification and characterization of these compounds and their biosynthetic pathways became the major thrust of Leslie’s research for most of the 1950s. This was spurred on by Professor Pearsall’s advice to find a unique niche, free from competitors, that capitalized on Leslie’s acknowledged practical skills in synthetic organic chemistry.

First, Leslie concentrated on the structural analysis and biochemical synthesis of \( \gamma \)-methylene-\( L \)-glutamine and \( \gamma \)-methylene-\( L \)-glutamic acid in germinating peanut plants (6, 7). At the time, these compounds were not thought to exist in any other plant species, although they were subsequently identified in tulips (14). By measuring their concentrations in different parts of the groundnut plant during germination and seedling growth, Leslie concluded that they were formed during the processes of converting seed protein into vegetative tissue protein and that \( \gamma \)-methylene-\( L \)-glutamine was probably the main compound used to transport nitrogen within the plant (8). He identified a unique deamidase that metabolized \( \gamma \)-methylene-\( L \)-glutamine to \( \gamma \)-methylene-\( L \)-glutamic acid with the liberation of ammonia and a greater specificity for \( \gamma \)-methylene-\( L \)-glutamine than glutamine (11, 15). However, it was not until 1984 that this deamidase was finally purified and its properties studied in detail by Leslie’s group (55). The enzyme synthesizing \( \gamma \)-methylene-\( L \)-glutamine was not identified until 1986, when Winter and Dekker extracted it from germinating peanut cotyledons (Winter & Dekker 1986). They showed that it was insensitive to most inhibitors of glutamine synthetase, thereby demonstrating its specificity for \( \gamma \)-methylene-\( L \)-glutamine synthesis and completing the work begun by Leslie in 1952 on the metabolic cycle of ammonia during growth of the groundnut plant.

In pursuing his ‘unusual’ amino acid research programme, Leslie was joined by a succession of PhD students, postdoctoral research fellows and foreign visitors, many of whom went on to successful academic careers. With technical assistance, they discovered several new plant amino and imino acids, like azetidine-2-carboxylic acid (A2C) and \( \beta \)-pyrazol-1-ylalanine (now named 3-pyrazol-1-yl-alanine), which initially evoked surprise as plant constituents because their structures were new not only to the biological literature but also to the chemical literature more widely (12, 16, 19, 54) (figure 2c,d). The pyrazole ring, for instance, was not known to occur in any natural product at the time, but, by using biochemical synthesis and the new technique of nuclear magnetic resonance, Leslie’s group were able to provide definitive evidence for the pyrazole ring structure in the natural product (17, 22).
Similarly, to prove that A2C had been correctly identified, Leslie synthesized it by bromination of γ-aminobutyrate, which was followed by ring closure and elimination of HBr. The synthesized A2C product was then compared with the compound originally isolated from lily of the valley (Convallaria majalis, figure 3). In addition to direct chemical synthesis, Leslie’s group also identified the biochemical pathways and enzymes responsible for producing and metabolizing these non-protein amino acid in the plants (7, 11, 13) (figure 3). They also analysed the content and transport of A2C from the rhizomes and roots to the leaves of the growing plants (16, 18). As the decade advanced, Leslie isolated and characterized non-protein amino acids from more plants’ including tulips, maize, watermelon and various grasses, which emphasized their general importance in plant nitrogen metabolism (28). His research output was recognized by promotion to a readership in 1956.

Broadening his research to include more genera was stimulated, in part, by sabbatical visits that Leslie made to foreign laboratories. In 1955, he was awarded a Rockefeller Visiting Fellowship to work with Professor F. C. Steward (FRS 1957) at Cornell University in Ithaca. Professor Steward’s group had shown that A2C occurred in tulip plants using the authentic compound that Leslie had synthesized previously. In Cornell, Leslie began surveying the liliaceous species for substituted glutamic acids (14) (figure 4) and completed the work on the structure of A2C and its occurrence more widely in the plant kingdom (13). The research with Steward provided one of the earliest demonstrations of how chemical data could be used to establish phylogenetic relationships within and between plant families and their constituent genera (13, 26). In 1957, he visited Professor Virtanen at the Biochemical Institute in Helsinki for three months supported by a British Council Anglo-Finnish Fellowship. This trip successfully resolved the apparent disparity in the chemical structure of A2C isolated by Leslie in Convallaria majalis and by Professor Virtanen’s group in Polygonium multiflorum (Solomon’s seal) and, as a consequence, helped scientific acceptance of this new class of natural amino/imino acids (56). These visits also stimulated Leslie’s interest in foreign travel and ensured that he accepted every invitation to speak at international scientific meetings or undertake advisory tours abroad well into retirement.

The 1960s—characterization of the synthesis, metabolism and toxicity of non-protein amino acids

With Leslie’s laboratory and unique research field established by the end of the 1950s, the next decade was one of increasing productivity and scientific recognition, with an expanding research group, more conference invitations and foreign visitors, and election to the Fellowship of the Royal Society. His research group increased to six to ten people and his output of papers doubled with the influx of more senior fellows and foreign visitors (figure 5a). The research of this decade fell into three main inter-connected areas: first, the isolation and characterization of further novel non-protein amino acids across plant genera; second, the identification of their biosynthetic and metabolic pathways; and, finally, the discovery of their anti-metabolic activity in compromising protein synthesis by acting as structural analogues for protein amino acids. During this period, new amino acids characterized by Leslie’s group included the N⁴-substituted asparagines, the cyclopropylamino acids and C7 unsaturated aliphatic amino acids (19–22, 37, 40). In total, they identified about 50 additional non-protein amino acids, many of which had novel chemical structures that were again proved by direct chemical synthesis (13, 22, 47). In pursuing these areas of research, Leslie’s group developed new techniques for tracing metabolic pathways using labelled carbon isotopes and
Leslie's research had a significant impact on the burgeoning disciplines of chemotaxonomy and plant phylogeny, as taxonomic botanists used the new data to formalize a theoretical framework for plant classification. Leslie's analyses of nine plant families and more than 30 different genera from different parts of the world helped to confirm plant classifications based on morphology and cytology, although, in other instances, they highlighted anomalies in classification that supported a revised taxonomy (Jeffrey 1961). For instance, Leslie's...
Figure 4. Relative amounts of $\alpha$-amino or -imino nitrogen of each amino acid expressed as a percentage of the total amino and imino nitrogen present in all the acids, as shown in (13). (Reproduced with permission from Cambridge University Press).

| Plant             | Aspartic acid | Glutamic acid | Serine + Glycine | Arginine | Threonine | Alanine | Glutamine | Lysine | Asparagine-$2\alpha$ carboxylic acid | Proline | Valine | $\gamma$-Aminobutyric acid | Other amino acids |
|-------------------|---------------|---------------|------------------|----------|-----------|---------|-----------|--------|--------------------------------------|---------|--------|-----------------------------------|------------------|
| Convallaria majalis (leaf) | 3.3          | 5.4          | 1.0             | 1.5      | 0.2       | 2.4     | 7.3       | 0.1    | 75.7                                | 1.8     | 0.1    | 1.2                               | 0.1              |
| C. majalis (seed) | 0.8          | 5.0          | 1.0             | 0.5      | 0.3       | 1.4     | 0.2       | 0.1    | 70.1                                | 1.8     | 1.3    | 1.2                               | 15.4             |
| Maianthemum canadense (leaf) | 1.2          | 7.8          | 3.6             | 3.9      | 0.5       | 4.8     | 8.2       | 0.1    | 58.9                                | 0.1     | 1.0    | 1.8                               | 5.1              |
| M. canadense (seed) | 3.1          | 2.9          | 3.7             | 2.1      | 1.9       | 3.7     | 13.6      | 0.1    | 54.7                                | 4.3     | 1.9    | 5.9                               | 2.0              |
| Polygonatum sp. (leaf) | 3.3          | 8.1          | 3.5             | 1.7      | 0.4       | 3.6     | 10.7      | 0.1    | 58.9                                | 8.2     | 1.4    | 0.8                               | 1.2              |
| Rohdea japonica (leaf) | 0.4          | 3.9          | 4.5             | 1.9      | 0.7       | 5.7     | 0.7       | 0.1    | 66.5                                | 1.1     | 0.6    | 7.4                               | 0.2              |
| Ruscus aculeatus (leaf) | 0.9          | 0.4          | 4.1             | 0.6      | 0.6       | 17.1    | 1.9       | 1.8    | 64.7                                | 0.5     | 7.9    | 0.5                               | 14.6             |
| Bovista volubilis (stem) | 1.7          | 4.6          | 3.0             | 0.3      | 0.5       | 15.1    | 1.9       | 1.8    | 64.7                                | 0.5     | 7.9    | 0.5                               | 14.6             |
| Liriope muscarii (leaf) | 0.5          | 2.5          | 5.1             | 0.9      | 0.9       | 12.9    | 1.2       | 0.5    | 23.6                                | 21.8    | 9.9    | 18.7                              | 0.6              |
| L. opsicata (seed) | 1.7          | 4.7          | 3.2             | 0.6      | 0.7       | 9.3     | 13.3      | 0.7    | 36.1                                | 4.2     | 0.9    | 4.5                               | 0.2              |
| Danes racemosa (seed) | 0.7          | 0.4          | 1.8             | 1.7      | 0.5       | 4.6     | 18.3      | 0.8    | 56.9                                | 8.2     | 0.7    | 3.0                               | 1.3              |
| Lationia modesta (seed) | 0.9          | 5.9          | 5.6             | 10.0     | 2.3       | 10.0    | 15.1      | 1.1    | 21.6                                | 5.7     | 2.8    | 4.3                               | 6.2              |
| Hysta sieboldiana (seed) | 5.0          | 12.5         | 4.1             | 10.5     | 1.5       | 8.2     | 23.3      | 0.4    | 11.1                                | 6.4     | 3.7    | 3.6                               | 9.9              |
| Dracena fragrans | 3.5          | 14.8         | 4.3             | 0.3      | 1.3       | 11.3    | 3.8       | 1.8    | 34.6                                | 11.0    | 0.3    | 12.5                              | 0.6              |
| D. sandieriana (leaf) | 0.2          | 1.3          | 1.9             | 0.5      | 0.5       | 7.4     | 10.4      | 0.5    | 61.5                                | 10.9    | 0.2    | 5.1                               | 0.2              |
| D. godseffiana (leaf) | 1.6          | 9.1          | 22.1            | 0.3      | 1.1       | 13.0    | 19.3      | 0.3    | 16.4                                | 3.1     | 0.3    | 3.7                               | 9.8              |

Figure 5. (a) Leslie’s research group at University College London in the mid 1960s. (b) Leslie viewing a two-dimensional chromatograph of amino acids extracted from royal poinciana (Delonix regia). (Online version in colour.)

comparison of the free amino acid content of cucurbit seeds showed a close correlation between their chemical composition and the ways in which the tribes and sub-tribes within the Cucurbitaceae family were arranged (33, 35). Conversely, the difference in occurrence of $\beta$-pyrazol-1-ylalanine and its peptide between the seeds of Old and New World species of
Melothria (figure 6) suggested that the genus should be subdivided as Jeffrey had suggested on morphological grounds (30). When the Liliaceae and Agavaceae plants that Leslie had originally used to extract A2C were re-classified morphologically into seven sub-families of the Asparagaceae family (figure 4), the presence of A2C proved to be a good indicator of plant relatedness, as the species with high A2C contents were placed in a different sub-family (Nolinoideae) from those with low concentrations (Agavoideae). However, when Leslie later identified A2C in leaves of the flame tree (*Delonix regia*), a legume, and in large quantities of sugar beet extract (*Beta vulgaris*), the question was raised of whether all plants could synthesize small qualities of A2C (41, 50).

Analogues of protein amino acids had been produced synthetically by the 1960s, but A2C was the first natural compound to be discovered that had structural homology with a protein amino/imino acid (12, 13). Its structural similarity to proline and its high concentrations in certain plants (16) led Leslie to investigate the toxicity of A2C and its interaction with proline in protein synthesis (23). Administration of A2C was shown to inhibit growth of germinating seeds of several plants that did not produce it naturally (23). Mung beans (*Phaseolus aureus*) were particularly sensitive to the toxic effects of A2C, with low concentrations killing all the seedlings. At sub-lethal concentrations, A2C was shown to replace proline in the mung bean protein fraction, an effect that could be reversed partially by addition of proline (23). Similar inhibitory effects were observed on the growth of *Escherichia coli*, with the cells incorporating relatively more A2C and less proline into protein when cultured with A2C than in control A2C-free medium (figure 7). Normal growth and protein composition were restored when the A2C culture medium was supplemented with additional proline (figure 7). Leslie and his co-workers concluded that, in A2C sensitive plants, A2C could stoichiometrically replace proline in proteins, with consequent abnormalities in protein conformation and function that explained its toxicity (36). Subsequently, A2C was also shown to have a wide range of toxic and teratogenic effects in animals, including birds and several mammalian species (Rubenstein et al. 2008).

Leslie and his PhD student, Peter Peterson, then turned to investigating the mechanism by which A2C producing plants avoided autotoxicity (24, 36). These were pioneering studies involving extraction, purification and detailed characterization of the amino acid activating enzymes responsible for the first step in incorporating amino acids into protein (34, 44). They hypothesized that, in A2C producing plants, the enzyme involved in activating proline had developed a structure that only recognized proline and not A2C. They began by comparing the activity and substrate specificity of the proline activating enzyme of mung beans with that of Solomon’s seal, a plant with a fresh weight content of A2C 50 times that shown to be lethal to mung beans (24, 31). Using substrate dependent ATP-PPi exchange as a measure of enzyme activity, they showed that prolyl-tRNA synthetase from mung beans could use both proline and A2C as substrates, while the enzyme from Solomon’s seal used only proline (figure 8). This strict substrate specificity of the proline activating enzyme in Solomon’s seal explained its insensitivity to A2C and indicated that the tertiary structure of the enzyme’s active site had evolved to exclude A2C (28, 30, 36, 54).

These findings led on to a more detailed series of studies on the activity of other activating enzymes, starting with the phenylalanine activating enzyme and its interaction with the toxic non-protein amino acids mimosine and 2-amino-4-methylhex-4-enoic acid (34, 38, 42). In total, the substrate specificity of at least 10 different amino acid activating enzymes from a range of different plant families was examined using synthetic and naturally occurring...
Figure 6. Amino acid chromatograms prepared from extracts of seed of two Melothria species comparing an Old World variety (*Melothria japonica*) with a New World one (*Melothria pendula*). Note the differences in β-pyrazol-1-ylalanine (βPA), its peptide (Pept), carboxyphenylalanine (cφAl) and an unidentified molecule D between the Old and New World species.

analogues (38, 39, 45, 49, 51, 52). Many of the non-protein amino acids were found to act as alternative substrates, although usually with lower affinity than the protein homologue. These studies also showed that the toxicity of certain non-protein amino acids like mimosine was not due primarily to incorporation into protein but rather depended on metabolism to secondary products that inhibited or interfered with other chemical reactions (34, 38). Collectively, the anti-metabolic actions of the non-protein amino acids provided a new tool to investigate the normal molecular mechanisms of protein synthesis and other chemical reactions (32) as
Figure 7. Effect of azetidine-2-carboxylic acid on growth of *Escherichia coli* in culture. Additions (μg/ml): Culture 1, nil; Culture 2, L-azetidine-2-carboxylic acid, 100; Culture 3, L-azetidine-2-carboxylic acid, 100 + DL-proline, 100. A, point of sampling for protein analyses. (From (25), with permission from Elsevier.)

Figure 8. Effect of the concentrations of activating enzyme from protein fractions of (a) mung bean (*Phaseolus aureus*) and (b) Solomon’s seal (*Polygonatum multiflorum*) on L-proline (open symbols) and L-azetidine-2-carboxylic acid (filled symbols) on stimulated rates of ATP-PPi exchange. (From (24), with permission from *Nature.*)
well as offering translational applications as potential herbicides, fungicides and insecticides (34, 36). Leslie’s research on the non-protein amino acid analogues and the amino acid activating enzymes, therefore, had broader biochemical significance well beyond the field of phytochemistry.

In 1964 Leslie was elected to the Fellowship of the Royal Society, at a relatively early age for an experimental biochemist. The citation highlights his distinction in developing quantitative methods for recovery of amino acids and in discovering the non-protein amino acids in plants (Royal Society Archive n.d.). It also acknowledges his signal achievement in synthesizing many of these new compounds. By taking an interdisciplinary approach in applying his knowledge of organic chemistry to biological questions in botany and biochemistry, Leslie opened up a new field of research in soluble nitrogenous compounds and nitrogen metabolism in plants. Recognition of his scientific contributions by the Royal Society was swiftly followed by promotion to a personal research professorship in plant chemistry at UCL that carried a limited teaching load. These professional advances were inevitably accompanied by increasing administrative work both for the University (e.g. Chair of the Board of Studies in Botany) and for the Royal Society (e.g. Grant Board F and Sectional Committee 9). However, they also provided greater opportunities for international travel, with more invitations to collaborate, teach, attend conferences and visit foreign institutions.

In the early 1960s Leslie visited East Germany and the USSR on several occasions to attend specialist meetings on plant nitrogen metabolism and visit influential scientists of the Eastern Bloc, including Professor Vatslav Kretovich, at the Institute of Biochemistry of the USSR Academy of Sciences, and Professors Kurt Mothes (ForMemRS 1971) and Benno Parthier, successive presidents of the Deutsche Akademie der Naturforscher Leopoldina and directors of the Plant Biochemistry Institute in Halle. At the height of the Cold War these were not straightforward visits and involved being escorted at all times to avoid political embarrassment.

In 1961 he made his first visit to California to lecture at a specialist amino acid meeting and visit University of California campuses. During the conference, he met several academic staff from the University of California at Davis and set in motion the arrangements for a seven-month period of sabbatical leave there in 1963 as a visiting professor. At Davis, he taught a postgraduate course in plant biochemistry and worked in the laboratories of Professors Conn and Stumpf on the metabolism of cyanide to asparagine in several legume and cucurbit species (29). In the summers of 1969 and 1970 Leslie returned to Davis on a NATO Co-operative grant, awarded jointly with Mendel Mazelis, to analyse the biosynthetic pathways of the non-protein amino acids identified earlier in the Californian buckeye (Aesculus californica) using radioactively labelled precursor amino acids (37, 46).

Leslie was the first Royal Society visiting professor to the University of Hong Kong in 1967. During this four-month stay, he was attached to the Botany Department, where he gave a course of lectures on plant biochemistry to students of the Botany and Chemistry departments. His research in Hong Kong focused on the amino acid content of the local flora. Three amino acids containing the acetylenic bond were isolated from the seeds of Euphoria longan and identified as 2-amino-4-methylenehex-5-ynoic acid, 2-amino-4-hydroxymethylhex-5-ynoic and 2-amino-4-hydroxyhept-6-ynoic acids (40). These initial analyses were subsequently developed into a more detailed study of Delonix regia and Euphoria longan on his return to UCL (41, 47). While in Hong Kong he tried to obtain a sample of Aesculus chinensis to compare with other Aesculus varieties that he had already analysed, with little success until he
was provided with seeds by a Chinese medicine emporium. On analysis, the major constituents were found to be derived from β-pyrazol-1-ylalanine, a compound only known to occur in cucurbits, which confirmed Leslie’s doubts about the stated contents and likely health benefits of herbal remedies.

The early 1970s—championing phytochemistry as a distinct scientific discipline
With increasing travel and more administrative work, Leslie had less time for hands-on experimental work in the laboratory, although his output of papers was higher in the early 1970s than at any other time in his career. He consolidated his past two decades of research into a series of invited and plenary lectures, scientific papers and topical reviews, which highlighted the novel metabolic pathways, unique chemical properties and importance of the non-protein amino acids in plant nitrogen metabolism (53). He showed that these amino acids are used for nitrogen transport and can act as a large store of soluble nitrogen in seeds and rhizomes ready for mobilization during plant germination and growth (28). He identified their role as defence chemicals and discovered the molecular mechanisms of their toxicity to other plants, herbivorous insects and grazing animals (36). He established that comparative phytochemistry could aid plant taxonomy and that plants, like other organisms, evolve biochemically for selective advantage in their ecological niche (26, 50).

With his accumulated academic and scientific expertise, he was elected president of the Phytochemistry Society of Europe and appointed as Dean of Science at UCL in 1970. The work of the Dean was to oversee the development and financial status of the science departments in conjunction with the faculty sub-deans. Leslie also became more involved in the administrative work of the Royal Society. He sat on its Council and Travelling Expenses Committee from 1970 to 1972 and its Symbols Committee from 1970 for 17 years. These administrative roles broadened his knowledge of other areas of science and brought his organizational skills to the attention of senior scientific and governmental advisers. Consequently, by 1972, he was being head hunted for leadership roles in science governance and policy.

In summer 1972, the UK government published a White Paper with the recommendations of a review that it had commissioned on government-funded research (HMSO 1972). The paper had radical implications for agricultural and food research, and suggested creation of the post of Chief Scientist in each research-sponsoring government department, who would have the responsibility for commissioning research with funds diverted from the UK Research Councils (Parker 2016). The councils would oversee both this new ministry-commissioned applied research and the more strategic projects funded by grants made to the councils by the Department of Education and Science. On the day the White Paper was published, Leslie was invited to meet Lord Rothschild, who had carried out the review, and Sir Basil Engholm, the Permanent Secretary of the Ministry of Agriculture, and informally asked to consider becoming the first Chief Scientist of the new Ministry of Agriculture, Fisheries and Food (MAFF). He thought about this offer briefly, but decided that becoming a Whitehall policymaker was too great a step away from direct involvement in research for him to achieve successfully, particularly given the controversy over academic autonomy elicited by Rothschild’s report (Duffy 1986). However, in declining the offer, he let Sir Basil know that he would be interested in a senior post more directly aligned to agricultural science research. A few weeks later he was approached by the governing body of the Lawes Agricultural Trust
about the vacant directorship of Rothamsted Experimental Station, created by the sudden death of the previous Director earlier in 1972.

Leadership of agricultural research in the UK: Rothamsted Experimental Station and Institute of Crop Research, 1973–1988

Raising the profile of plant sciences in the UK’s research portfolio, Rothamsted Experimental Station: 1973–1986

Leslie took up the post of Director of the Rothamsted Experimental Station (now Rothamsted Research) on 1 April 1973, the day the new research commissioning process started formally. At the time of his appointment, Rothamsted was the largest and longest-running agricultural research institute in the UK and had a total staff of 700, of whom about 500 were research scientists. Its research spanned a broad range of scientific disciplines relating to agriculture, including soils, plant biology and crop production, disease and pests, which were divided into multiple small departments with independent administrations. However, by 1973, the research was no longer transformative and needed reinvigoration—and new investment—to regain its past reputation for scientific excellence. As Director, Leslie’s aims for Rothamsted were therefore threefold: first, to re-establish its research at the forefront of scientific developments by modernizing its research portfolio; second, to raise its research profile within the wider scientific community; and, finally, to improve the translational impact of its research on agronomy globally. This required a new research infrastructure and tight financial management, given the uncertainty of the new government scheme for funding research.

Internally, the fragmented departmental structure was reorganized into larger units under single management. The departments of Soil Chemistry, Pedology and Soil Microbiology were combined into an enlarged Soils Division. Similarly, there were mergers between the Botany and Biochemistry and between the Entomology and Nematology departments. These changes finally led to the creation of a new five-division management structure, which enhanced collaboration between the different disciplines. With Rothamsted’s historical expertise in field trials, the new structure led to novel cross-disciplinary field experiments on crop growth and yield, which maximized the efficient use of both the scientific and the land resources unique to the Station. Leslie’s restructuring of the Biochemistry Department and his appointment of Ben Miflin as its Head also led to two new fundamental discoveries in plant sciences, namely the pathway of nitrogen assimilation (Miflin & Lea 1976) and the photorespiratory nitrogen cycle (Keys 2006). This placed Rothamsted in a world-leading position in plant nitrogen metabolism, in line with Lawes’s original work on nitrogen fertilization, and provided the springboard for the Station’s research on the genetic modification of crops (Macdonald 2021).

In the mid 1970s, the opportunities for agricultural research provided by the new methods of genetic engineering led the Agricultural Research Council (ARC) to provide more staff positions to develop crop genetics as part of their agri-food agenda at both Rothamsted and the John Innes Centre. At Rothamsted, the new staff began work on using gene vectors to improve the potato. This rapidly proved successful and gene manipulation of plants became a major research programme of the Station. The Rothamsted team under the direction of Michael Elliott (FRS 1979) also had success in synthesizing a new, safer range of insecticides, the synthetic pyrethroids, which were developed by the agrichemical industry for commercial
use on crops and as household insecticides. Further development of a ‘second generation’ of these compounds at Rothamsted prolonged their activity in bright light while maintaining their low mammalian toxicity and faster biodegradation than previous chemical pesticides (Elliott 1976). The new synthetic pyrethroids were patented and licensed by the National Research Development Corporation, which retained all the royalties from commercialization. However, Leslie successfully petitioned the ARC to distribute a share of the royalties to the Rothamsted researchers who discovered the insecticidal properties of these compounds. The Station was awarded two Queens Awards for Technological Achievements and the UNESCO Science Medal in recognition of these discoveries.

With Rothamsted’s growing expertise in insecticide chemistry (Casida 2010), Leslie broadened the Station’s scientific remit and recruited John Pickett (FRS 1996) in 1976 to lead a new research programme on insect pheromones and their synergies with plant-derived semiochemicals directed at improving control of crop pests (Pickett et al. 2014).

Modernization of the scientific portfolio and divisional structure of Rothamsted was accompanied by a ten-year programme of improvements in its research infrastructure. This included provision of the latest high-end equipment, extended statistical and computing services and construction of major new laboratory and other specialized research buildings in addition to a conference centre seating 250 people. The grounds around the research buildings were landscaped into gardens to enhance the working environment and showcase some of the plants studied there. Rothamsted Manor house, the ancestral home of the Lawes family, was restored to provide elegant meeting rooms, social spaces and accommodation for postgraduate students and visiting scientists. Leslie had a major role in raising the finance for these developments, which came from a wide variety of sources, including the ARC, major charities, commercial organizations, philanthropic appeals and the Lawes Agricultural Trust. The Trust also funded the conservation and curation of the Rothamsted archives and many of the antiquarian books in the library. To publicize the Station’s work more widely, Leslie took the novel approach (for the time) of instituting public open days and media coverage of its latest discoveries.

In the late 1960s and early 1970s government funding for agricultural research increased in real terms and remained stable for about a decade. Thereafter, annual budgets declined as a result of a fall in MAFF-commissioned research. Quickly, operating economies were insufficient to balance Rothamsted’s budget, so permanent staff had to be lost, sometimes by forced redundancy, in order to maintain the Station’s high quality research and long-running field experiments. Alternative non-governmental sources of funding were found, often through commercial activities, and permanent contracts were replaced by short-term ones. The composition of Rothamsted’s staff therefore changed, with fewer support staff and more self-funded foreign visitors and young UK scientists on short-term contracts, although total numbers of scientific staff differed little from the time of Leslie’s appointment as Director. In 1985, the newly created Agriculture and Food Research Council (AFRC) completed a comprehensive review of its research aims and management in the light of recent scientific advances in the biological sciences, changes in land use and the environmental impact of existing farming methods. This review recommended that the many different AFRC institutes and research stations, including Rothamsted Experimental Station, be rationalized administratively into eight new institutes.
Driving crop research for agricultural sustainability: Institute of Arable Crops Research, 1986–1988

With the implementation of the AFRC’s recommendations, Leslie became the inaugural Director of Research for the new Institute of Arable Crops Research (IACR), formed by the amalgamation of Rothamsted Experimental Station (Hertfordshire), Long Ashton Research Station (Somerset), Broom’s Barn Experimental Station (Suffolk) and the Unit of Insect Neurophysiology and Pharmacology (Cambridge) into one administrative unit with staff transfers between units and closure of the Letcombe Laboratory and the Weed Research Organisation. The remit of the IACR was to undertake strategic and applied research into the quality, efficient production and marketability of major field crops while conserving the rural environment by reducing pollution from agrichemicals and farming practices. This covered a wide range of disciplines, including soil management, crop nutrition and genetics, plant physiology and metabolism, disease resistance, pest control and agronomy in its widest sense. Leslie also retained directorship of Rothamsted Experimental Station, where the central IACR administration was based. However, he travelled regularly to the other IACR units to discuss research priorities and resource allocation.

Alongside overseeing the activities of Rothamsted and IACR, Leslie continued to contribute to a wide range of administrative work for external organizations. At the Royal Society, he sat on, or chaired, the International Relations Committee, Sectional Committee 8, Soiree Committee, Hooke Committee, Chinese Exchange Committee and the International Exchanges Committee. He was also a member of the Nutrition Advisory Committee of the Rank Prizes Fund (1979–2000), the Board of Trustees of the Royal Botanic Gardens at Kew (1983–1993), the Radioactive Waste Management Advisory Board of the Department of the Environment (1984–1991), advisory boards and promotions panels of the UK Research Councils (1983–1996), Chairman of the Agricultural and Veterinary Advisory Committee of the British Council (1987–1995) and Consultant Director of the Commonwealth Bureau of Soils (1973–1988). Furthermore, he was a manager of the Royal Institution from 1974 to 1977 and a scientific adviser to the Flour Milling and Baking Research Association (1974–1986), a MAFF appointment. He also continued to travel widely on behalf of these organizations and to attend conferences in connection with agricultural science.

In addition, he was in demand to advise and review plant sciences research at institutes and universities worldwide. During the period of his directorships, Leslie visited more than 25 countries worldwide, several multiple times, to promote British science and agricultural research more specifically. Given the benefits he felt that he had personally gained from international travel, he lobbied hard for organizations such as the Royal Society and British Council to create fellowship and travel grants to allow UK and foreign scientists to work abroad to learn new techniques and establish international collaborations. The number of foreign fellows and visitors to IACR stations increased dramatically from the 1980s onwards, in part due to Leslie’s advocacy of international exchanges and the excellent hospitality and training provided by the individual units.

Promoting British science globally: retirement, post 1988

After his formal retirement as Director of IACR and Rothamsted Experimental Station in 1988, Leslie was appointed to an emeritus position at Rothamsted Experimental Station as a Lawes Trust Senior Fellow for five years. He continued to play an active role in
science administration, with an emphasis on phytochemical and agricultural research. He also maintained membership of many of his existing committees and took on new projects in academia, industry and public institutions.

He joined the council of the Royal Institution and became a trustee and then Director of the Foundation and Friends of Kew Gardens (1990–1998). He was appointed Chairman of the Plant Chemistry Working Group of the International Organization for Chemical Sciences in Development, a non-governmental body fostering international collaboration between chemists in Third World and developed countries (1987–1990). He also became a scientific adviser to several international agrichemical companies, including CAB-International UK (1988–1994), BASF Agricultural Research, Germany (1988–1994), and LK Bio-research, Singapore (1993–2000). In addition, he maintained visiting professorships at the University of London and the University of Wales at Swansea, which involved teaching and external examining. These activities, together with the global growth of research in plant nitrogen metabolism, kept Leslie busy scientifically with travel and correspondence well into his seventies.

FAMILY LIFE

Leslie and Peggy enjoyed their free time together while UCL undergraduates and maintained contact after graduation. After both gained employment in London, they married in 1949. Unusually for the time, the Fowden family travelled widely, both on holiday and in association with Leslie’s work. For the Cornell fellowship, they went to New York by ocean liner and travelled along the northeastern US coast and into Canada for their holidays. The three-month Helsinki visit was made by camper van, driving 150–200 miles a day for the twelve-day journey. While there, they lived in an adult education hostel and learnt Finnish, as little English was spoken outside the laboratory. By the 1960s, family travel for Leslie’s work was more complicated because Peggy needed leave from her teaching post and their children had to go to school. Hong Kong, in particular, was an exciting place to be in 1967 with its cultural differences, rapid economic expansion and Mao’s revolution in full swing just across the border. All the travels had lasting impact and some unexpected consequences too. For instance, while in Ithaca, their London house was rented to Peter and Helen Kroger, the antiquarian book dealers cum Cold War spies, who were eventually jailed for passing naval secrets to the Russians in microdots hidden as full stops in their rare books. This association and Leslie’s Cold War visits to Eastern Bloc countries led to close scrutiny by custom officers on every US trip made by the Fowdens for the next 35 years.

Leslie and Peggy remained in Harpenden after retirement and continued to travel extensively into the early 2000s, often in association with Leslie’s work for the British Council and the Royal Society (figure 9). Throughout their lives, they loved entertaining and helping foreign visitors to adapt to British life. They hosted lively laboratory parties at home in London and summer tea parties in the large garden of the director’s house at Rothamsted. While they lived there, they invited all the foreign students and visitors who were alone for Christmas for a home-cooked meal on Boxing Day. After Peggy died in 2006, Leslie cut back on travel and entertaining because of his deteriorating Parkinson’s disease. However, he continued consulting, writing reports and reviewing scientific papers from his home until general ill health necessitated moving into a care home, where he died of heart failure at the age of 83. He is survived by his two children and four grandchildren.
Leslie Fowden

Figure 9. Leslie and Peggy tree planting on behalf of the British Council in retirement. (Online version in colour.)

**LEGACY**

Leslie published over 190 scientific papers and reviews and edited eight books. He was knighted by Her Majesty the Queen for his services as Director of Rothamsted Experimental Station in 1982. In addition to Fellowship of the Royal Society, he was elected as a Foreign Member of the Deutsche Akademie der Naturforscher Leopoldina, the Lenin All-Union Academy of Agricultural Sciences of the USSR, the Academy of Agricultural Sciences of the German Democratic Republic and the Russian Academy of Agricultural Sciences. He received many other awards and honours, including an Honorary DSc from the University of Westminster, Fellowship of the Institute of Biology and honorary membership
of both the American Society of Plant Physiologists and the Phytochemical Society of Europe.

Through his discoveries, Leslie created the new research field of plant nitrogen metabolism which still remains an active, vibrant discipline today (Xu et al. 2012; Oldroyd & Leyser 2020). He was in the vanguard of those promoting quantitative, multidisciplinary approaches to more traditional, observational areas of biology and biochemistry. In his own research, he pioneered the application of physico-chemical principles to botany to establish phytochemistry as an exact science. He championed international collaborations as a means of education and intellectual debate, not only to advance scientific research but also to foster cultural understanding between nations more broadly. Through the 1970s and 1980s, he was the voice of agricultural research in the UK, contributing to government policy and liaising between researchers, funding bodies and agrichemical industries in raising the profile of plant biochemistry and molecular biology as important research areas for solving world hunger. He believed learning was life-long and retained a questioning, razor sharp mind right to the end of his life. Probably because of the plant metaphors, he liked to quote Joseph Henry (1797–1878), the first Secretary of the Smithsonian Institution, who said ‘the seeds of great discoveries are constantly floating around us but they only take root in minds well prepared to receive them’ (56).

HONOURS, DEGREES AND AWARDS

1945  BSc (first class honours) Chemistry, University College, University of London
1948  PhD Physical Organic Chemistry, University College, University of London
1964  Fellow of the Royal Society
1966  Fellow of University College, University of London
1971  Fellow of Deutsche Akademie der Naturforsher Leopoldina
1978  Foreign Member of Lenin All-Union Academy of Agricultural Sciences of the USSR (until 1992)
1981  Corresponding Member of the American Society of Plant Physiologists
1982  Knighthood awarded by the Queen
1986  Foreign Member of the Academy of Agricultural Sciences of the German Democratic Republic (Academy dissolved 1991)
1986  Honorary Member of the Phytochemical Society of Europe
1989  Lawes Trust Senior Fellow, Rothamsted Experimental Station
1991  Foreign Member of the Russian Academy of Agricultural Sciences
1992  DSc (honorary), University of Westminster

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Author profiles

Professor Abigail Fowden
Abby Fowden is Leslie Fowden’s daughter and Professor of Perinatal Physiology in the Department of Physiology, Development and Neuroscience at the University of Cambridge and a professorial fellow at Girton College, Cambridge. She obtained a first class degree in physiology and a PhD from the University of Cambridge. She immediately joined the staff of the Department of Physiology there as a demonstrator, progressing to University Lecturer and Reader before being promoted to a personal chair in 2002. She was awarded the ScD degree in 2001. From 2015 to 2019, she was Head of the School of the Biological Sciences. Her research focuses on the factors controlling feto-placental development and aims to determine how experiences during early life alter the risk of developing adult-onset degenerative diseases.

Professor John Anderson
John Anderson received his BAgrSc and PhD from the University of Melbourne and was a postdoctoral research fellow in Leslie Fowden’s laboratory in the Department of Botany and Microbiology at University College London from 1966 until 1969. He joined the Department of Botany at La Trobe University in Australia in 1970, where he attained the position of Reader. He was awarded the David Syme Science Research Prize by the University of Melbourne in 1979 for his research on light-coupled assimilation of inorganic nitrogen and sulfur in chloroplasts. His research interests at La Trobe focused on the light-coupled metabolic activities of chloroplasts, the metabolism, distribution and redistribution of sulfur in plants and selenium metabolism. He retired in 2001 and lives in Warrandyte, Australia.

Professor Peter Lea
Peter Lea is an Emeritus Professor at Lancaster University. He received his BSc, PhD and DSc from the University of Liverpool. He was a postdoctoral research fellow in the laboratory of Leslie Fowden in the Department of Botany and Microbiology at University College London from 1970 until 1973, when he moved with Leslie to Rothamsted Experimental Station. He spent 12 years in the Biochemistry Department there and then moved to Lancaster University, where he was Professor of Biology for over 30 years. His main research interests have been in the pathways and mechanisms by which plants are able to take up nitrogen and convert it into amino acids and protein.
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