BIOGRAPHICAL MEMOIRS

Patricia Hannah Clarke. 29 July 1919 — 28 January 2010

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PATRICIA HANNAH CLARKE

29 July 1919 — 28 January 2010
Patricia Hannah Clarke was a distinguished British biochemist and microbiologist who won an international reputation for her work on microbial evolution. After completing the Natural Sciences Tripos at the University of Cambridge at the beginning of World War II, she chose to work for the Armaments Research Department, before moving into microbiological research on bacterial toxoids. She was appointed to an assistant lectureship in biochemistry at University College London in 1953, eventually becoming Professor of Microbial Biochemistry in 1974. Her pioneering work on the directed evolution of bacterial metabolic capability led to her election to Fellowship of the Royal Society in 1976. Patricia gave dedicated service to the scientific community through her many years of committee work with the Royal Society, the Biochemical Society and the Society for General Microbiology. She was a passionate advocate of the importance of equal opportunities for women in education and scientific careers.

**Early life**

Pat Clarke (née Green), the elder of two daughters of David and Daisy Green, was born in the market and coalmining town of Pontypridd in South Wales. Her paternal grandfather, George Green, had moved from the steel industry in Merthyr to establish a business as a metal merchant in Pontypridd. Daisy Willoughby hailed from a naval family in Eastbourne, East Sussex, and worked as a dressmaker and tailor in Cardiff before her marriage. Pat and her younger sister, Diana, attended the local Coedpenmaen Primary School and made good use of the swimming pool in the town park and the public library. The swimming pool was apparently the centre of social life for youngsters in the town and it was there that Pat first met Geraint Evans, the subsequently renowned operatic bass-baritone.

In 1930, Pat went as a boarder on a Foundation scholarship to Howells School, Llandaff, where she eventually became Head Girl. In addition to her studies she enjoyed frequent visits...
to the National Museum of Wales, particularly appreciating the paintings, and was active in writing and acting in plays. Her leanings were towards science, especially chemistry, and she stayed at school for an additional year to work towards the Cambridge entrance examinations. In 1937 she obtained a place to read Natural Sciences at Girton College, Cambridge, supported by College and County scholarships.

CAMBRIDGE, 1937–40

Patricia Clarke enjoyed herself as an undergraduate in Cambridge, considering herself ‘lucky to be there’ and ‘spoiled’ by the college support system. For Part I of the Natural Sciences Tripos she read chemistry, botany and invertebrate zoology, the latter combined with an introduction to the relatively new discipline of biochemistry. Part II exclusively involved biochemistry, in the department headed by Nobel laureate and former President of the Royal Society, Sir Frederick Gowland Hopkins FRS. The departmental staff also included such giants of the emerging discipline as Joseph and Dorothy Needham, Malcolm Dixon, N. W. (Bill) Pirie and Marjory Stephenson, while Ernest Gale, Donald D. Woods and R. M. (Dick) Synge were in the department as graduate students or postdoctoral researchers. (All those mentioned were elected as Fellows of the Royal Society during their careers. Richard Millington Synge shared the 1952 Nobel Prize in Chemistry with Archer Martin for their discovery of partition chromatography at the University of Leeds.) Among the dozen students in the Part II biochemistry class was Fred Sanger, whom Patricia described as ‘a quiet student’.

The late 1930s were turbulent times in Europe, of course. As a youngster growing up in South Wales, Patricia had lived through the General Strike of 1926, was used to seeing ‘unemployed miners everywhere’, and had encountered Basque refugees from the Spanish Civil War. She described her fellow undergraduates as belonging to ‘a generation of students very much aware of the dangers of fascism in Europe and the tragedy of the Spanish Civil War’. Her political views were further developed at the Cambridge University Socialist Club.

Her three-day practical component of the final examinations in the early summer of 1940 was interspersed with radio transmissions on the retreat from Normandy in Operation Dynamo.

THE WAR YEARS

While at Cambridge University, Patricia started her lifelong partnership with Michael Clarke, who had originally intended to read Classics at Cambridge but had transferred to study English. The widespread uncertainty and anxiety about the future at the beginning of the war prompted decisive action. Patricia and Michael married in June 1940. Michael volunteered to join the Tank Corps and was called up in the September of that year. Pat had arranged to undertake postgraduate research with Dorothy Needham, working on aspects of ATP metabolism, but decided to decline this opportunity in favour of trying to make a contribution to the war effort. She obtained a post with the Armaments Research Department, working in laboratories based at University College, Swansea. After about a year there she was transferred to the Woolwich Arsenal headquarters in London, with the remit of devising the analytical specifications for a new explosive.
After a year or so working on armaments, Mrs Clarke started to seek employment more closely related to her knowledge and training. Through her membership of the Committee of the Association of Scientific Workers she came into contact with B. C. J. G. Knight, the distinguished bacteriologist, who was working at the Wellcome Laboratories, Beckenham, on bacterial toxoids as immunogens against pathogenic anaerobic bacteria that cause severe infections of war wounds. Knight needed an assistant and offered the post to Clarke after a brief interview. Knight was a stimulating mentor and colleague, training Clarke in his fastidious microbiological techniques and passing on his deep knowledge of anaerobic bacteria. Clarke’s first published paper, on the toxins of *Clostridium oedematins* (1)*, described results from this work. Knight was also instrumental in arranging for Clarke to visit the Institut Pasteur while she was attending the International Congress of Women in Paris in 1945. Knight provided letters of introduction to his prewar friend André Lwoff (ForMemRS 1958), a heroic figure to Pat because of his activities in the French resistance movement as much as for his world-class science. (Lwoff won the 1965 Nobel Prize in Physiology or Medicine, with his colleagues Jacques Monod and François Jacob.)

At the end of the war Michael Clarke returned from his experiences as a Tank Commander in the Western Desert (where he was wounded outside Tobruk), in India and in Palestine and then started to work in the film industry. Patricia stayed at home for a while to concentrate on family life and bring up two sons, Francis, born in 1947, and David, born in 1949.

**THE NATIONAL COLLECTION OF TYPE CULTURES, 1951–53**

In 1951 Patricia Clarke received an unexpected letter from Samuel Cowan, Curator of the National Collection of Type Cultures, expressing his disapproval of her being the only British member of the International Committee for the Nomenclature of the Pathogenic Clostridia when she no longer worked on such organisms. She replied to express her ignorance of such a committee’s existence and of her continuing interest in pathogens. Cowan, remorseful at his misunderstanding, offered Clarke a part-time job in which she could choose her own hours, helping him to write the catalogue for the National Collection at Colindale.

She took the post and set to work on the catalogue, but soon began to have her own ideas about how some of the tests to identify bacteria might be improved. In particular, she advocated the use of washed suspensions for biochemical characterization, and experimented with this approach with Cowan’s support. A joint paper demonstrating the potential contribution of the methodology soon followed (2), leading to a series of publications on the use of biochemical activities in the classification of microorganisms.

In September 1954, Clarke was invited to present a review paper on the methods for determining the biochemical activities of microorganisms as applied to classification, as part of a general review of the principles of microbial classification by the Society for General Microbiology. In reviewing the topic she made a strong plea for the importance of agreed standardization of methods used in classification, as well as ‘a few tentative suggestions for possible developments’. Clarke’s contribution was published as part of the series of papers on microbial classification in *Journal for General Microbiology* (3).

* Numbers in this form refer to the bibliography at the end of the text.
In 1953, after responding to an advertisement in The Times, Patricia Clarke was appointed to a full-time, annually renewable assistant lectureship in the Department of Biochemistry, University College London. She had bypassed the normal PhD and postdoctoral route to a junior academic position on the strength of her publication record and the potential applicability of her research. She had no teaching experience but teamed up with Eric Shooter, a newly appointed lecturer and protein biochemist, to hone their skills through ‘private’ practice tutorials. (Shooter was elected a Fellow of the Royal Society in 1988 for his work at Stanford University, California, on nerve growth factor.) The head of department at University College was Ernest Baldwin, who had been Pat’s Part I tutor at Cambridge.

Clarke’s research interests began to coalesce around ways in which bacteria could adapt to their environments. The concept of induced enzyme synthesis had been established and was greatly clarified by the studies of Melvin Cohn, Monod and others at the Institut Pasteur on ‘gratuitous induction’ using non-substrate inducing compounds.

The focus on the highly aerobic and biochemically versatile pseudomonads originated in an extension of the observation by Kogut & Podoski (1953) that cell-free extracts of *Pseudomonas fluorescens* would oxidize intermediates of the tricarboxylic acid (TCA) cycle (also known as the Krebs cycle), whereas intact cell suspensions could only do so after a lag period. Working with Pauline Meadow, a Beit Memorial Fellow, Clarke made similar observations with *Pseudomonas aeruginosa* and showed that chloramphenicol inhibited the cells’ ability to gain oxidative capacity but did not affect the enzyme activities in the cell-free extracts (4). They interpreted their observations as showing the existence of inducible permeases required to facilitate the entry of exogenous TCA intermediates to the bacterial cells.

The next important strategic decision was the choice of regulatory system to study. Greatly influenced by the way in which Monod and colleagues at the Institut Pasteur had used analogues of lactose to study the regulation of β-galactosidase in *Escherichia coli*, Clarke sought a substrate that could readily be chemically modified.

She was aware from data of den Dooren de Jong, published in Marjory Stephenson’s treatise *Bacterial metabolism* (Stephenson 1949), that *Ps. aeruginosa* could utilize acetamide as a source of carbon and nitrogen. The homologues of acetamide, formamide, propionamide, butyramide and so on were readily available, and substituents could readily be added to the amide nitrogen. Clarke’s PhD student, Michael Kelly, was able to show that the acetamidase of *Ps. aeruginosa* was strongly inducible and that its substrate specificity was different from the inducer profile (5). He was also able to identify compounds that specifically inhibited the amidase and others that blocked the induction of amidase synthesis (see table 1).

Mutants producing the amidase constitutively were isolated by selection for growth on medium containing formamide, a non-inducing weak substrate for the enzyme, as the source of nitrogen, and with succinate, an effective catabolite repressor, as the carbon source (6). This selection gave rise both to fully constitutive mutants and to mutants that had become inducible by formamide. Genetic transfer with the generalized transducing phage F116, performed by PhD student Ashley Skinner, showed that a gene containing both types of regulatory mutation was closely linked to the amidase structural gene (6).

Working with her technician, Renée Tata, Clarke also devised a direct selection for amidase-negative mutants. Fluoroacetamide, a substrate for the amidase, is hydrolysed to fluoroacetate, an inhibitor of the aconitase reaction in the TCA cycle. Amidase-negative
Patricia Hannah Clarke

Table 1. Amides as substrates, inducers and inhibitors of induction of the aliphatic amidase of *Ps. aeruginosa* 8602A. (Data selected from a more comprehensive table presented in (5).)

<table>
<thead>
<tr>
<th>amide</th>
<th>formula</th>
<th>substrate</th>
<th>inducer</th>
<th>enzyme inhibitor</th>
<th>induction inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>formamide</td>
<td>HCONH₂</td>
<td>+</td>
<td>−</td>
<td>.</td>
<td>+</td>
</tr>
<tr>
<td>acetamide</td>
<td>CH₃CONH₂</td>
<td>+++</td>
<td>++</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>propionamide</td>
<td>CH₃CH₂CONH₂</td>
<td>+++</td>
<td>++</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>butyramide</td>
<td>CH₃CH₂CH₂CONH₂</td>
<td>trace</td>
<td>−</td>
<td>.</td>
<td>++*</td>
</tr>
<tr>
<td>valeramide</td>
<td>CH₃(CH₂)₃CONH₂</td>
<td>−</td>
<td>−</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>N-acetylacetamide</td>
<td>CH₃CONHCOCH₃</td>
<td>−</td>
<td>+++</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>N-phenylacetamide</td>
<td>CH₃CONH₆H₅</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>glycine amide</td>
<td>CH₃NH₂CONH₂</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
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* The information that butyramide is a powerful inhibitor of induction derives from (9).

Mutants are thus resistant to fluoroacetamide in the presence of an alternative carbon source such as pyruvate (11).

The ability to select for mutants capable of utilizing different amides as carbon or nitrogen sources allowed the Clarke group to direct the evolution of *Pseudomonas* strains with novel biochemical capabilities. Starting with a constitutive mutant expressing high levels of the amidase, they were able to select mutants capable of growth on butyramide as the carbon source (7). The amidase produced by the mutant strain showed altered electrophoretic mobility and substrate specificity. The substrate specificity of the amidase was altered further by seeking derivatives of the butyramide-utilizing strain that could utilize valeramide as carbon source. In a separate study they were also able to isolate mutants that could utilize acetonilide (*N*-phenylacetamide) as sole carbon source. A PhD student, Paul Brown, showed that the enzyme capable of hydrolysing acetonilide carried a replacement of a threonine residue by isoleucine at position 283 (9). This was the first demonstration that a single-site mutation in a structural gene could result in an enzyme with altered substrate specificity. A later student, Alastair Paterson, found that replacement of a serine residue by phenylalanine at position 7 resulted in an amidase that catalysed the hydrolysis of butyramide (14).

Direct selection for growth using different amides as sources of carbon or nitrogen proved fruitful, and further papers describing the evolution of *Ps. aeruginosa* derivatives with altered amidase activities followed (8, 10, 12) (see figure 1). The substrate range could be extended in a series of discrete genetic steps, often leading to the complete loss of the original acetamidase activity. It was also apparent that there were often different genetic routes to achieving a particular phenotype. For example, formamide-utilizing strains could be either constitutive or formamide-inducible; butyramide utilizers could have altered amidase enzymes or be resistant to repression by butyramide.

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</tr>
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Among derivatives selected for growth on butyramide were some that had become butyramide-inducible. Thus, in a series of manipulations, a strain had been derived in which an enzyme with a novel substrate specificity was inducible by its new substrate (18).

Patricia Clarke was elected to Fellowship of the Royal Society in 1976, largely on the basis of her seminal contribution to our understanding of directed bacterial evolution. She was awarded the Leeuwenhoek Lectureship by the Society in 1979, her lecture being entitled ‘Experiments in microbial evolution: new enzymes, new metabolic activities’ (15).

A postdoctoral colleague in Pat Clarke’s group, Robert Drew, visited my laboratory in Edinburgh in 1977 to attempt to isolate molecular clones of the \textit{Ps. aeruginosa} amidase genes. The genes were successfully isolated using a vector based on bacteriophage lambda and screening for plaques that could stimulate the growth of surrounding \textit{Escherichia coli} cells, with acetamide as sole nitrogen source (16). The nucleotide sequence of the amidase structural gene, \textit{amiE}, was determined (19) and published alongside the amino acid sequence independently determined in Richard Ambler’s laboratory in Edinburgh. The isolation of temperature-sensitive mutants of \textit{Ps. aeruginosa} that were constitutive for amidase synthesis at 28°C but amidase negative at 41°C suggested that the regulator gene, \textit{amiR}, encoded a protein that acted positively in controlling amidase synthesis (13). Studies with recombinant plasmids carrying the various amidase genes supported this idea. In the presence of inducing amides, the \textit{amiR} product acted \textit{in trans} to potentiate the expression of \textit{amiE} (20).

The full complexity and elegance of the amidase regulatory system was not revealed until after Pat Clarke’s retirement in 1984. Collaboration between Robert Drew and Laurence Pearl’s laboratory at University College London revealed three genes in the \textit{ami} cluster: the structural gene, \textit{amiE}, and two regulatory genes, \textit{amiC} and \textit{amiR}. The \textit{amiC} gene encodes the amide-binding protein, which under non-inducing conditions forms a complex with the product of \textit{amiR}. The \textit{amiR} product is an RNA-binding anti-terminator protein that interacts with the nascent RNA transcribed from upstream of \textit{amiE} and prematurely terminated by complex RNA secondary structure, the ‘termination loop’. In the AmiR–AmiC complex the anti-termination function of the AmiR protein is silenced, but binding of an inducer amide to AmiC liberates AmiR from the complex and allows it to function to potentiate ‘readthrough transcription’ of the \textit{amiE} gene (Wilson \textit{et al.}, 1996; O’Hara \textit{et al.}, 1999).

Figure 1. The evolution of a family of mutant enzymes in \textit{Ps. aeruginosa}. Wild-type strain PAC1 grows on acetamide as carbon and nitrogen source. Mutants C11, CB4 and L10 are constitutive mutants producing wild-type amidase. Mutant B6 produces an amidase with altered substrate specificity that allows growth on butyramide. The V9 enzyme has a further substitution that allows the host strain to grow on valeramide. The PhF1, PhB3, PhV1, PhV2 and PhA1 mutants all grow on phenylacetamide. The PhA1 mutant was derived from the LAm1 strain, which has an inactive amidase. (Data from (17).)
Patricia Clarke taught microbial biochemistry to the final-year undergraduates in the biochemistry BSc programme at University College. She also contributed to the biochemistry MSc degree, started in the 1950s, which was effective in training postgraduates from other disciplines at a time when courses in biochemistry were relatively rare. She was also influential in the development of a novel MSc programme in biochemical engineering, designed to allow graduates in either biology or engineering to participate. She encouraged her former PhD student, Malcolm Lilly, to develop his interest in industrial-scale microbiology. This proved to be a very successful development. In collaboration with his colleague Peter Dunnill, Lilly devised the process used in the industrial production of semi-synthetic penicillins. He became the first Professor of Biochemical Engineering in the UK and was elected a Fellow of the Royal Society in 1991.

Clarke was promoted from her assistant lectureship to a lectureship in 1956, and then to a readership in 1966 before being appointed Professor of Microbial Biochemistry in 1974. Her election as a Fellow of the Royal Society followed in 1976. She was a member of the Council of the Royal Society from 1981 to 1982 and chaired its oldest standing committee, the Library Committee. She served as Vice-President of the Royal Society from 1981 to 1982.

Although Clarke officially retired from her professorship at University College in 1984, she continued her research, holding a Leverhulme Emeritus Fellowship until 1986. She then took up the Royal Society Kan Tong Po Professorship at the Chinese University of Hong Kong for six months, when her husband, Michael, was able to accompany her. Professor Clarke produced a detailed report on the provision for biochemistry and molecular biology for the university’s Vice-Chancellor, and was gratified to be able to see significant development of the relevant facilities on a subsequent visit.

**COMMITTEE WORK**

Patricia Clarke was a strong supporter of the Biochemical Society and the Society for General Microbiology (SGM) for their roles in scientific exchange, education and fostering a ‘community of scholars’. In addition to her work for the Royal Society, she was a member of Council of the SGM from 1960 to 1970 and of the Council of the Biochemical Society from 1978 to 1981. She served as General Secretary of the SGM from 1965 to 1970. In 1974, to stimulate interest in microbiology in schools, Patricia Clarke managed the production of a booklet, *Careers in microbiology*, which was published by the SGM and distributed to schools throughout the country. She also relished her role on the British Library Advisory Committee from 1983 to 1986.

Clarke was acutely aware of the dearth of women in science and of the threat that this represents to modern society. At the time of her graduation in 1940, women could not be members of the University of Cambridge or be awarded a BA degree. They had to settle instead for the status of ‘Titular BA’. When she was appointed to her assistant lectureship at University College in 1953, the college’s professorial dining club did not admit female professors, and the Natural Science Society excluded women.

She was one of six female members of the Committee of Women in Science and Technology commissioned in 1993 by William Waldegrave, the Conservative Secretary of State for Public Service and Science. The committee’s report, entitled *The rising tide*, was published by the Cabinet Office in February 1994. It drew attention to three problematic areas that adversely affected the recruitment and retention of women in scientific careers. Education of schoolgirls
Employers, including both industry and universities, were criticized for their singular lack of good practice in ensuring equal opportunities for women employees and the absence of a constructive approach to maternity leave. The media were also encouraged to help raise the public profile of women in science through appropriate reporting and programme-making.

Government responded to the report in July 1994 with partial support, accepting and implementing the call for the setting up of a Development Unit in the Office of Science and Technology, dedicated to exploring the issues raised, but rejecting the recommendation that the costs of childcare should be offset against tax.

**Concluding Remarks**

Several years before Patricia’s official retirement from University College in 1984, she and Michael replaced the family home in North London by a flat in Bloomsbury and a house in Cirencester, where they spent most weekends. They moved in 1990 from the ‘roomy Georgian house with a large garden’ to a smaller, more modern house within the Roman walls of Cirencester. Their younger son, David, an architect with a special interest in energy conservation, redesigned and extended the new home.

Patricia continued as Biological Editor of the journal *Science progress* until 1993, when she passed it on to Robin Rowbury, a former colleague in the Botany Department at University College London.
University College. With her experience and interest in education, she continued to contribute to activities in and around Cirencester. She was a council member at Bath University, where her microbiologist friend Rod Quayle FRS was Vice-Chancellor, and at Cheltenham Ladies’ College. She was also a governor of Wye College and of Deer Park School, Cirencester. She made use of her connections at the University of Bath and elsewhere to arrange small extracurricular research projects for the Deer Park science students. These proved very successful in raising the students’ appreciation of empirical research and in increasing the numbers of students attending school science clubs; the projects became an annual event.

Patricia Clarke was awarded honorary DSc degrees by the University of Kent in 1988 and the Council for National Academic Awards in 1990 (figure 2). She took great pleasure in the fact that her degrees were conferred in such grandiose locations as Canterbury Cathedral and St James’s Palace.

In her retirement Professor Clarke remained on the left of British politics and did not hesitate to share her views in correspondence with members of Her Majesty’s Government. She reproached Margaret Thatcher for her decision to allow the US Air Force to use British bases for attacks on Libya; Kenneth Clarke, Minister for Education and Science, for his constant revision of the national curriculum for schools; and Michael Heseltine for his plans to close coal mines. She was a strong supporter of comprehensive education and told Prime Minister John Major, after reports of his disparagement of the system, that he was badly misinformed about the schools attended by the large majority of children in this country.

Patricia Clarke was a dedicated gardener and a member of the Royal Horticultural Society. She was a founder member of the Cirencester Science and Technology Society and a member of the Cotswold Canal trust and the Cirencester Civic Society. With her husband, Michael, she enjoyed walking (figure 3) and visiting medieval monasteries in France, Wales and the north of England.
Michael Clarke died in 2005, and Patricia in 2010. They are survived by their sons, Francis, recently retired from a readership in mathematics at Swansea University, and David, an architect in London, and by a grandson, Oliver.

HONOURS AND DISTINCTIONS

1976  Elected Fellow of the Royal Society
1979  Leeuwenhoek Lecturer, the Royal Society
1981  A. J. Kluvyer Lecturer, Dutch Society for Microbiology
       Marjory Stephenson Memorial Lecturer, Society for General Microbiology
1981–82  Vice-President of the Royal Society
1982  Elected to membership of European Molecular Biology Organization
1986  Elected Fellow of the International Institute of Biotechnology
       Royal Society Kan Tong Po Professor, Chinese University of Hong Kong
1988  Bernal Lectureship, Birkbeck College, London
       Honorary doctorate, University of Kent
1990  Honorary doctorate, Council for National Academic Awards
1996  Elected Honorary Fellow of University College London
1997  Elected Honorary Member of the Society for General Microbiology

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The frontispiece photograph was taken in 2005 by Godfrey Argent and is reproduced with permission.

REFERENCES TO OTHER AUTHORS


BIBLIOGRAPHY

The following publications are those referred to directly in the text. A full bibliography is available as electronic supplementary material at http://dx.doi.org/10.1098/rsbm.2015.0012 or via http://rsbm.royalsocietypublishing.org.

Patricia Hannah Clarke


