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Elected FRS 1982

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Noreen Murray was one of the architects of the recombinant DNA revolution that transformed the study of biology from the early 1970s. Her particular prowess for genetic manipulation of bacteria and their phage was critical in developing the bacteriophage lambda vectors that were a vital part of the early genetic engineering toolbox. Her skill as a microbial geneticist had earlier become apparent through her work on genetic recombination and complementation in the fungus \textit{Neurospora}, especially as a postdoctoral researcher at Stanford where her work brought her to the attention of some of the giants of early molecular biology. Back in the UK, first at Cambridge and then, for the bulk of her career, at Edinburgh, she produced a remarkable body of work focused on uncovering the mechanisms and biology of restriction enzymes, and their adaptation as tools underpinning modern biological research and the rise of the biotechnology industry. Much of this work was done in collaboration with her husband Ken Murray FRS, whose biographical memoir accompanies this one. Together they were known not only for the quality of their research but also for their vast generosity both on a personal level and on a larger canvas through their philanthropy.

EARLY LIFE

Noreen Elizabeth Murray (\textit{née} Parker) was born on 26 February 1935 in the village of Read near Burnley in Lancashire, the second child (figure 1) of a local headmaster, John Parker, and his wife, Lilian Grace Parker (\textit{née} Sutcliffe). Both branches of Noreen’s family were from Lancashire, her maternal and paternal grandfathers having both worked in the cotton mills as...
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’tacklers’, the overseers who supervised looms operated by 25 weavers. Despite having left school at the age of 12, her maternal grandfather was committed to self-improvement—learning languages, writing poetry and becoming a skilled draughtsman; throughout her life, Noreen treasured notebooks filled with his writings and drawings. Her paternal grandfather rose to become a ‘boss’ (a manager, not an owner) at the mill, enabling Noreen’s father, John, to attend grammar school at Accrington and then St John’s training college at York. After a relatively short spell as a schoolteacher, John became headmaster of the local school at Read before taking up a similar position at the larger school in Bolton-le-Sands in 1940.

Only five years old when they left, Noreen remembered little of Read beyond the noise of clogs on the pavement as the workers walked to the mill early each morning; collecting fresh milk daily in a jug from the adjacent farm; and attending matches at the nearby cricket ground where she had the unforgettable thrill of seeing the great West Indian player—and, later, first black peer—Learie Constantine. But it was in Bolton-le-Sands that Noreen spent the bulk of her happy childhood, in a house looking out over Morecambe Bay and across to the hills of the Lake District beyond.

Noreen was a self-confessed tomboy, and life in Bolton-le-Sands was enriched by numerous outdoor activities: frequent bicycle rides—ranging as far as the Lake District, some 20 miles distant—long walks, gardening (a lifelong passion), swimming in the bay, rowing on Lake Windermere and in the canal at the bottom of the family’s garden, and—favourite of all—climbing trees. Climbing was also practised on a large rock that the local children called
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‘Jumbo’ on the shore near the house. Her father—a powerfully set, rugby-playing man—was a strict disciplinarian, but also fair and companionable. For example, although he instilled in Noreen a lasting commitment to strict punctuality, he also fostered her enthusiasm for gardening and built her a seat in a tree overlooking the canal from which she could observe the fish below. Known locally as ‘Pop’ Parker, he was fondly remembered by former pupils. Many years later, when Noreen received an honorary degree from Lancaster University, she met the Mayor of that city and discovered that he, too, had grown up in Bolton-le-Sands and been a pupil at ‘Pop’ Parker’s school, memories of which he recalled cheerfully.

Noreen’s mother dedicated herself to looking after the children. As was common at that time, and especially during World War II, which was then in progress, she was an expert cook and preserver of produce from their garden and other local sources. Her skill in sewing and knitting also allowed her to make many of Noreen’s clothes, or adapt those of her older brother Neil for her use.

Neil was three years Noreen’s senior and a keen naturalist. Indeed, it was he who first awakened Noreen’s interest in genetics (figure 2). Noreen had won a scholarship to Lancaster Girls’ Grammar School when she was still only 10 years old, and was put in the top stream among girls a year ahead of her. With the benefit of excellent teachers, she prospered. By the fifth year, she had to choose between Latin or physics and chemistry (biology was offered only to students in the third stream). She chose physics and chemistry, and her ambition was to be a Domestic Science teacher until her brother, revising for his higher School Certificate (A-level) exams, taught her Mendel’s laws, an experience that inspired her, aged 15 years, to switch her allegiance from domestic to biological science.

Her lack of Latin precluded an Oxbridge application, and only during the sixth year did she take a maths O-level (at the time necessary for an application to any science degree outside the University of Hull). She won a London Intercollegiate Scholarship for entry to King’s College, London, where she arrived in 1953 to read for a BSc in botany. Among her classmates on the course that year was John Ellis (FRS 1983). Noreen graduated in 1956 with an upper second-class degree, which rather bothered her, and she kept the note sent to her by the head
of department, Professor T. A. Bennet-Clark FRS, which read: ‘Congratulations. A IIi but you should have done better.’ She had been thrown by questions on the university exam papers (which had to be taken in addition to those set by the college). These turned out to be on topics not covered in her courses at King’s, and included one on bacterial genetics which she could answer only on the basis of what she had gleaned from an article by J. B. S. Haldane FRS in the popular magazine New Biology (to which she had, as with Mendel’s laws, been introduced by her brother).

**BIRMINGHAM AND *NEUROSPORA***

Despite the disappointment of her 2.i, she had nevertheless already been offered a PhD place at Birmingham University in the laboratory of David Catcheside FRS, himself a former graduate of Botany from King’s. Catcheside had recently returned from the University of Adelaide to set up a new department at Birmingham. Although called Microbiology, the forward-looking department he assembled brought together geneticists, biochemists and even a physical chemist interested in DNA. A few years later, it might well have been called a department of molecular biology.

Catcheside encouraged his students to be independent—to devise and plan their own experiments—but was at the same time happy to share his knowledge and insights. Noreen took on a research project designed to find out whether genes involved in a given biochemical pathway in a eukaryote were linked in the manner then just being described in the operons of bacteria. For this she chose the fungus *Neurospora*. At Catcheside’s suggestion, she focused on the genes involved in methionine biosynthesis and proceeded to isolate many mutants defective in this pathway, and to sort the genes that she found into complementation groups. But mapping the genes revealed no clustering, even between complementation groups on the same chromosome. Further work on one locus, *me-2*, showed interallelic complementation and provided an insight into recombination within a gene, showing in particular that gene conversion was influenced by the position of a mutation within the locus (1, 2)*.

During her first year as a graduate student, Noreen was often invited to the Catchesides’ home when an interesting geneticist was visiting (Herschel Roman and George Beadle (ForMemRS 1960), for example). She would help Catcheside’s wife, Kathleen, and meet the eminent visitor. But this practice fell victim to Catcheside’s disapproval when Noreen became engaged to a fellow graduate student, Kenneth Murray (FRS 1979), who was then working with Arthur Peacocke, the DNA chemist in the department. (Peacocke was later to become the Reverend Cannon Peacocke, Master of Pusey Hall in Oxford, and proponent of the view that no conflict existed between evolution and Christianity, as expounded in his essay ‘Evolution: the disguised friend of faith?’) Catcheside explained to Noreen that if she were to marry, her career would come second to that of her husband. His dictum caused Noreen some distress and severely limited her subsequent interactions with both Catcheside and his wife. Later in her career she came to understand the significance of Catcheside’s reaction, but also knew that he ‘forgave her’: years afterwards he supported her election to the Royal Society; and even during her final year as a graduate student, when Ken secured a postdoctoral position at Stanford University, Catcheside wrote to David Perkins, the Stanford *Neurospora* geneticist,

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* Numbers in this form refer to the bibliography at the end of the text.
to ask whether he could accommodate Noreen in his laboratory so that she could continue her research project. Perkins complied, and even offered funding—a minimal top-up to Ken’s salary for the first year, and her own stipend thereafter. And so in late 1959 Ken and Noreen set off, travelling by boat to New York, and thence by train across the continent to California, taking up their postdoctoral positions at Stanford in January 1960.

**STANFORD: A WHOLE NEW WORLD**

During five exhilarating years at Stanford, Noreen continued her successful studies on *Neurospora*, publishing a further three papers (3–5). Like those published during her graduate studies with Catcheside, these were all single-author papers: both Catcheside and Perkins felt their contributions insufficient to justify co-authorship. Nowadays, in the era of relentless quantitative assessment, it is hard to imagine such a state of affairs, and even in the early 1960s it was far from the norm. But it attests to the level of independence that Noreen brought to her projects, in both their conception and their execution.

Beyond this research success, Noreen’s time at Stanford was even more influential because it was here that she was introduced to bacterial and phage genetics, the field in which her future career lay. She heard many inspiring lectures (including Sydney Brenner (FRS 1965) presenting the phage experiments that he and Francis Crick FRS had carried out to define the general nature of the genetic code, before that beautiful work was published), attended courses given by the acclaimed Stanford-based prokaryotic geneticists Charles Yanofsky (ForMemRS 1965) and Dale Kaiser, and took part in the Yanofsky laboratory journal club. It was at one of these journal clubs that Naomi Franklin presented the work of Daisy Dussoix and Werner Arber that began to expose the mechanistic basis of the phenomenon of restriction and modification that became so central to Noreen’s later career and to the evolution of recombinant DNA technologies. Dussoix and Arber had shown that restriction—the decrease in plating efficiency of a phage on one strain after it had been propagated on another—worked at the level of DNA degradation in the absence of strain-specific protection, protection that a few years later was shown to be due to DNA methylation (Dussoix & Arber 1962; Arber 1965).

While at Stanford, Noreen was invited to California Institute of Technology to give her first scientific seminar, in front of a daunting crowd that included Max Delbrück (ForMemRS 1967), Ed Lewis (ForMemRS 1989), George Beadle, Norm Horowitz and Sterling Emerson. Also while at Stanford she met Frank Stahl (figure 3), who invited her to Oregon to give a talk on her work on polarized gene conversion. Stahl became a lifelong friend and influential supporter. Although they worked very hard, Ken and Noreen also enjoyed life in California, especially escaping to the mountains; they took particular delight in visits to Yosemite.

**CAMBRIDGE AND THE FIRST PHAGE EXPERIMENTS**

Ken and Noreen returned to the UK only in 1964 when Ken was offered a position in the laboratory of Fred Sanger FRS at the Medical Research Council (MRC) Laboratory of Molecular Biology (LMB) at Cambridge. Noreen received a fellowship allowing her to continue work in another *Neurospora* laboratory—that of Harold Whitehouse, in Cambridge University’s Botany Department. After Stanford, life in Cambridge had its challenges:
facilities made available to Noreen were vastly inferior to those she had become accustomed to at Stanford, and as her Birmingham PhD was not recognized by Cambridge University she was expected to work for a Cambridge degree. Thus, in her sixth postdoctoral year, she appeared in the photograph of Cambridge PhD students. On the plus side, Frank Stahl was by then on sabbatical leave at LMB, and he was happy to have Noreen do some experiments with him. As Stahl has recently written (Stahl 2013):

Then, late one afternoon, Noreen Murray, an acquaintance with a background in fungal genetics, appeared in my lab and asked if there was anything going on that she might help with. She wanted to take part time off from her work in the botany department if I had anything for her. Did I! The search for co-adapted genes would use (over and over) all the elementary moves of phage genetic analysis, making it an ideal project for a beginner, especially for one familiar with sterile technique. Noreen signed on once I convinced her that her lack of experience would be more of an asset than a problem.

Noreen relished the experience, to the extent even of overcoming her anxiety about working in a laboratory to which she had no formal connection—a discomfort that led her to hide beneath the bench whenever Sydney Brenner came into the room. The experiments that she and Stahl completed at this time on mapping genes on the circular T4 genome were her first with phage and marked the start of her transition from fungal to bacterial systems. They also resulted in a pair of papers, published with Stahl in 1966, which established her as a bona fide phage geneticist (6, 7). The first of these papers presented evidence that the clustering of genes of related function within the phage genome might be driven by adaptive constraints (à la R. A. Fisher) rather than regulatory constraints (as the recent operon model suggested). Thus,
clustering might ensure that recombination events between phages during co-infection would be more likely to produce viable progeny than if those genes were not clustered and so more susceptible to reassortment by recombination events. Stahl asked Francis Crick and Sydney Brenner for comments on the manuscript before he submitted it for publication. In reply, Crick jokingly wrote that he thought the work ‘is nearer theology than science. In fact I think you would have made an excellent Jesuit’ but concluded: ‘Are you nevertheless permitted to publish? Certainly. But I would suggest the Journal of Theological Biology. Sydney’s lips are sealed. We enjoyed having you here, awake or asleep.’ (Stahl had regularly slept through performances at the Aldwych.)

Looking now at a reprint of that paper, two features characteristic of Stahl stand out: a humorous footnote appended to Noreen’s name gives her affiliation as ‘On loan from the Botany School’; and in the middle of the circular genetic map of phage T4, Stahl stamped ‘US Get Out Of Vietnam’ on every copy he sent out.

The experience, so influential in Noreen’s life, was also special to Stahl, as he noted in the recent memoir of his year at LMB (Stahl 2013):

The entire, memorable experience was topped up by the opportunity to work with Noreen years before she was honoured for her contributions to phage-based genetic engineering. Unforgettably, on my sabbatical leave at LMB I had the pleasure of teaching Noreen Murray (1935–2011) the ABC of phage genetics using Dick Epstein’s (1929–2011) amazing amber mutants. How blessedly lucky can a guy be? Serendipity indeed!

**EDINBURGH AND THE MRC UNIT**

Ken was due to take up a position as a lecturer at the new University of York in October 1965. However, neither his laboratory there nor even the library was ready and, after Ken and Noreen were involved in a car accident just a few weeks before their planned move, Ken requested to postpone their relocation for three months. When his request was curtly denied—see the memoir of Ken Murray (Brammar & Gratzer 2014)—Sanger provided sanctuary in his laboratory and they remained in Cambridge until, in 1967, Ken was appointed a Senior Lecturer at the University of Edinburgh, in the new Department of Molecular Biology.

The situation at Edinburgh was in many ways ideal for Ken and Noreen. As well as the department itself, under the leadership of Martin Pollock FRS, there was soon to be an MRC Unit of Bacterial Genetics headed by Bill Hayes FRS, which relocated from the Hammersmith Hospital in London in 1968. Noreen wrote to Bill Hayes who, after an interview, offered her a position in his Edinburgh-bound Unit; her time working with phage had paid off.

Pollock had also previously been employed by the MRC (at the National Institute for Medical Research, Mill Hill) and had moved with some colleagues to Edinburgh in 1965. Generous MRC funding was critical in combining Hayes’s unit, with its expertise in microbial genetics, with Pollock’s biochemists to create the first Department of Molecular Biology in the country. Michael (later Lord) Swann FRS, himself an eminent cell biologist, and at the time Principal of Edinburgh University, was the other key figure in driving the formation of this exciting new department.

Noreen moved to Edinburgh in January 1968, ahead of the arrival of Bill Hayes’s Unit, and at first had no bench to work on, just a desk she shared with Bill Brammar’s technician. (Bill Brammar was a member of the new department and would later collaborate closely with
Noreen.) In July the new building, subsequently called the Darwin Building, was completed, providing three floors for molecular biology. Noreen had a tiny room on the eighth floor, while Ken’s laboratory was on the sixth floor. Initially she continued her *Neurospora* work—the fine-structure analysis of genes and the mechanisms of genetic recombination, in particular the study of polarized gene conversion. A decade of these studies had led her to the idea that genetic exchange might be preferentially initiated at certain sites on the chromosome, perhaps at specific sequences found at the ends of genes. She realized that to take this analysis to a deeper mechanistic level—to approach a molecular understanding of what was going on—she would need to move into systems more amenable to that sort of study, bacteria or phage. So during the early part of 1968 she was already familiarizing herself with other systems, even as she continued her *Neurospora* work. She decided that site-specific recombination in phage lambda, or restriction enzymes, might provide propitious systems in which to investigate how specific sites on DNA are recognized.

**RESTRICTION ENZYMES**

The first restriction enzyme (EcoK) was purified at Harvard by Matt Meselson (ForMemRS 1984) and Bob Yuan, a feat published in *Nature* (Meselson & Yuan 1968) in a paper that Noreen always claimed was one of the most impressive she ever read. This breakthrough opened up the possibility that Noreen might combine her genetic manipulations with Ken’s biochemical prowess to analyse how these enzymes act on phage genomes. Towards the end of his time in Sanger’s laboratory, Ken had started to deduce short DNA sequences at the ends of DNA molecules (he had used the lambda genome) by end-labelling. So the plan was for Noreen to genetically manipulate lambda to generate a series of phage genomes each with just a single recognition site for EcoK, each at a different location. The purified phage genomes could then be cut by EcoK, and polynucleotide kinase used to add $^{32}$P phosphate to the 5′ terminal nucleotides. The sequence of a few nucleotides at those ends could then be determined with the technique that Ken had developed in Sanger’s laboratory. This would hopefully reveal the precise sequence recognized by EcoK.

The approach was a good one, but the Murrays were unlucky in their choice of the enzyme EcoK. This is a Type I restriction enzyme, not one of the Type II enzymes that later became so well known for their role in recombinant DNA manipulations. Type II enzymes recognize specific DNA sites (‘target sites’) and cut at a defined place within those sequences. Although Type I enzymes also recognize specific DNA sequences, they cut, not within those target sites, but apparently randomly, some distance away. Thus there was no sequence similarity between the ends of DNA molecules generated by EcoK digestion.

The collaborative studies were greatly facilitated when Noreen moved from her rather isolated room on the eighth floor down to the sixth floor, in response to the arrival of Frank Stahl, who, together with his wife, Mary, came to Edinburgh for a sabbatical year in 1969. Noreen shared an office with Stahl, and her bench and facilities were contiguous with those in Ken’s laboratory, at which Frank and Mary were working.

Daisy Dussoix, the student in Werner Arber’s laboratory involved in early dissection of restriction mechanism as mentioned above, was by now at University of California at San Francisco in the laboratory of Herb Boyer. There she was involved in attempts to purify a plasmid-encoded (and, as it turned out, Type II) enzyme, EcoRI. Encouraged by discussions
with her, Noreen and Ken turned their attention to that class of enzyme. They picked a different plasmid-borne system, *Eco*RII, and determined that this—like *Eco*RI—cut DNA into discrete fragments. Noreen and Ken (with his postdoctoral researcher Cynthia Biggar) were able to work out its target sequence in 1972. Not long afterwards, Hamilton Smith sent them the *Haemophilus influenzae* strain in which he had identified a restriction enzyme (*Hind*II), using phage T7 as a substrate. In purifying the enzyme, Ken instead used lambda DNA; in that way he discovered there were in fact two enzymes present in the strain, and soon worked out the target sequence of the second enzyme, *Hind*III (which, fortunately for Smith, did not occur in the T7 genome) (Old et al. 1975).

### THE DAWN OF RECOMBINANT DNA

In September 1972 there was a meeting of the European Molecular Biology Organization (EMBO) in Switzerland. This event was significant in several ways, not least because of an unscheduled extra session, chaired by Norton Zinder, to discuss the possibility that biohazards might attend recombining DNA molecules from different organisms. This was well before such concerns were raised in the famous ‘Berg letter’ to *Science* (Berg et al. 1974) and the subsequent well-documented Asilomar meeting, but it seems to have been largely overlooked. On the purely scientific front, Noreen spoke about her work manipulating the *EcoK* sites in lambda, and she and Ken presented the *Eco*RII target sequence (and possibly preliminary data on *Hind*III as well). Herb Boyer and Howard Goodman reported their results on *Eco*RI, indicating that they had identified its target site, but the data were not at that time quite complete; the sequence was published later that year (Hedgpeth et al. 1972). Boyer and Goodman were also engaged in attempts to find the target sequence of *Eco*RII and asked Ken to hold back on publishing his results until they were ready to submit theirs at the same time. Ken agreed, though this led to a six-month delay in publication (Boyer et al. 1973).

Also at this fateful meeting, two other findings from Stanford were reported in an abstract. One, the finding, later published by Lobban & Kaiser (1973), that poly(A-T) tails could be attached to the ends of DNA molecules to create self-complementary ‘sticky ends’, thus allowing molecules to be joined. The second—even more exciting in Noreen’s view—was the result from Ron Davis and Janet Mertz that *Eco*RI cleaved DNA to generate fragments with 5′ single-stranded overhangs of four nucleotides that were complementary to one another and could be joined by DNA ligase. This allowed different molecules cut with *Eco*RI to be joined efficiently in new combinations (Mertz & Davis 1972).

At about this time, Bernard Allet, at Cold Spring Harbor Laboratory, used the recently invented gel separation and ethidium bromide staining system to show that *Eco*RI cut the lambda genome into six fragments, revealing that it bore five sites for that enzyme. But he was not at the EMBO meeting, and so Noreen discovered this fact only when it was published in January the following year (Allet et al. 1973). She then immediately realized that manipulation of those *Eco*RI sites, in the way that she had already done for *Eco*K, would generate lambda phage able to carry foreign DNA generated by digestion with *Eco*RI. This would enable the power of transducing phages—naturally occurring recombinant phages carrying parts of the bacterial genome long used by bacterial geneticists—to be extended to the analysis of DNA from any source.

However, at this time, life in Edinburgh became less secure. Threats of closure fell upon the MRC Unit, triggered in part by the desire of its director, Bill Hayes, to accept an attractive
post-retirement position in Australia. The threats came despite a piece entitled ‘Escherichia at Edinburgh’ that was published in Nature New Biology (anonymously, but possibly with Werner Arber’s input) in March 1972, praising the work of the department, including what Ken and Noreen were doing with restriction enzymes (described at the time as a way to study protein–DNA interactions rather than to generate recombinant DNA molecules) (Anon. 1972). There was also an MRC report that extolled the work going on in Edinburgh and recommended that the Unit be kept alive after Hayes’s retirement, if on a smaller scale. However, the MRC subsequently set up a subcommittee review that recommended closure on Hayes’s retirement.

Noreen felt the stress. She was one of six members of the department without tenure who faced the axe. To evade the oppressive atmosphere caused by this uncertainty over the future, she escaped back to Stanford for a few months and there took up her Neurospora work again. This, she later came to believe, was a mistake. The task of eliminating the EcoRI sites from lambda she left in Edinburgh in the hands of a new technician, who, lacking phage-handling experience, struggled to make headway. When Noreen returned some months later (in September 1973), it took her only three weeks to create phages with single and double EcoRI sites—derivatives that could serve as receptors for foreign DNA—the first lambda vectors. Another regret was the decision not to mention her plans for EcoRI when she gave a seminar during her stay at Stanford on the manipulation of EcoK sites in lambda. This, she felt, would have established a public precedent for her idea, which was soon taken up by others.

That autumn, Ken created their first recombinant molecules using these new lambda vectors, but the paper describing this success was not published (or even submitted) until the following year (9). The delay was of course largely because of Noreen’s flight to Stanford, but also her insistence, as a geneticist, that she map each of the EcoRI sites accurately within the genome before they published the paper. This was not critical to their main findings and unfortunately took some time. The significance of these delays lies in the fact that their cloning paper appeared in 1974, whereas Boyer and Cohen’s paper describing cloning in plasmid vectors came out in 1973 (Cohen et al. 1973).

The future of the MRC staff was clarified in the autumn of 1973. Although the Unit was to close, Noreen and several other members were granted MRC tenure. Noreen believed that her case was bolstered by strong supporting letters from Frank Stahl and John Fincham FRS. Tenure did not immediately guarantee that they could stay in Edinburgh (they could have been moved to an MRC Unit elsewhere), but within a year that tenure was transferred to the university department and so at last their security in Edinburgh was assured. One consequence of this was that in April 1975 Noreen was at last able to submit her first grant application, entitled ‘The generation of transducing phages by in vitro recombination and their amplification of gene products’. This was funded after very favourable review. Noreen subsequently remembered that even Sydney Brenner had been very supportive—although she would also wryly observe just how long it had taken her to reach this level of independence.

Despite the continued success of her research and her commitment to teaching, her rank in the department rose rather slowly. When she was first nominated as a candidate for Fellowship of the Royal Society she was still just a Senior Lecturer. On a visit to Edinburgh the following year, John Fincham suggested she should get a promotion. This duly happened, and she became a Reader in 1978. But even though she was elected to the Royal Society in 1982 she was appointed professor only six years later, in 1988. Not being a professor meant she was not able to make long-distance phone calls from her office, a restriction that caused her
some inconvenience (not to say embarrassment) when she became President of the Genetical Society, particularly during negotiations with Cold Spring Harbor Laboratory over investment in the journal *Genes & Development*. She had to resort to using Ken’s phone. (Her predecessor as President—David (now Sir David) Hopwood FRS—had been mortified to discover he could not introduce her as ‘Professor Murray’ when she took over.)

Noreen liked to tell this story more as a positive reflection on the Royal Society than as a negative one on the university. Indeed, she felt that the Royal Society was less gender-biased than people, and the media, at times maintained. Rather, she believed strongly that it did—as it should—reward people for their science irrespective of gender.

**OVEREXPRESSION OF CLONED GENE PRODUCTS**

By 1975 Noreen had created both insertion vectors (able to incorporate additional DNA) and replacement vectors (containing regions that could be replaced by foreign DNA). Replacement vectors had the virtue that they could accommodate larger DNA fragments, because there is a limit to how much DNA the lambda heads can accommodate (figure 4). These vectors could accept DNA fragments generated by either *EcoRI* or *HindIII* (10).

A particularly neat trick applied to the insertion vectors. Insertion was at a site within the lambda *cI* gene, which encodes lambda repressor, and so recombinant phage (containing insertions) could not form lysogens. As a result, the recombinant phage could readily be discriminated from empty vectors because, when plated on a bacterial lawn, recombinants produced...
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clear plaques, whereas the empty vector formed turbid plaques (11). This discrimination was later enhanced by the use of Hfl (high frequency of lysogeny) bacterial host strains. When grown on a lawn of these cells, cl+ phages (for example vector) always formed lysogens, and so produced no visible plaque at all; only recombinant phages, unable to form lysogens, grew lytically and produced plaques.

The next few years were very exciting for Noreen. She collaborated not only with Ken but also with Bill Brammar, with whom she by now shared an office. Brammar’s student Ann Moir was working with classical λtrp transducing phage, examining (by assaying the products of the trpD and E genes) expression from the lambda P_L promoter. This started them thinking about how one might not just clone genes, but also overexpress their products. Noreen and Bill also generated libraries of Escherichia coli DNA in lambda vectors and identified clones of various genes by complementing mutant host cells lacking that function.

Edinburgh quickly became a Mecca for recombinant DNA technology. In those days very few people had direct access to the protocols and reagents required to clone genes. Two features of the department at Edinburgh fostered its role in the dissemination of recombinant DNA techniques. First, many researchers were taken in and taught the lore, including John Atkins, Jean Beggs (FRS 1998) and Alan Hall (FRS 1999). Another local colleague, Ed (now Sir Edwin) Southern (FRS 1983), benefited from the new technologies introduced by Ken and Noreen; these were critical to his developing, in 1975, Southern blotting, a powerful technique that added to Edinburgh’s reputation as a centre for recombinant DNA (Southern 1975). Second, in working out how to express genes cloned in lambda vectors, Noreen realized it would be useful if they experimented using genes whose products were needed for recombinant DNA techniques, thereby ensuring their plentiful supply. Thus, together with another visitor to the laboratory, Geoff Wilson, she cloned the gene encoding phage T4 ligase, the enzyme used to join recombinant DNA molecules, and, later, polynucleotide kinase, which is used in DNA end-labelling (12, 16). In addition, in response to a request from Bill Kelley (in Pittsburgh, Pennsylvania), she screened her E. coli libraries for a clone encoding DNA polymerase. She was in luck: the entire polA gene was within a small HindIII fragment and thus present as a clone in her library. This clone became the source from which the Klenow fragment was produced (13).

High-level production of T4 ligase was achieved by using a recombinant lambda prophage harbouring the gene in a region of the genome expressed from the late promoter P_R upon induction; for polA, expression was driven from one of the early promoters, P_L, during lytic growth (just as with the trp genes in the earlier experiments). By overexpressing these genes, their products could much more easily be purified in large quantities. Indeed, Noreen gave the T4 ligase clone to the pharmaceutical firm Boehringer, who used it to produce commercial ligase for years. (A characteristic tale: in the late 1980s Boehringer discovered that their ligase strain had died, and sheepishly asked whether Noreen could replace it. Of course she could; her stocks were always carefully preserved. As reward for this kindness the company offered her a choice of laboratory equipment. When those present in her laboratory picked from the list a gel-dryer, she replied, ‘Oh I can’t ask for that, it’s the most expensive item on the list!’)

Ken and Noreen did not patent any of these constructs, although it was suggested that they might have tried to. However, Noreen had talked publicly about the EcoRI vectors at an EMBO meeting in Ghent in 1974, and the UK patent office therefore decided not to take the matter further.
The discovery of the restriction enzyme Sau3A enhanced the quality of DNA libraries. This enzyme recognizes target sequences only four nucleotides in length, but cuts them in such a way that they generate sticky ends compatible with those generated by another enzyme, BamHI, which recognizes a six-nucleotide target sequence. An enzyme that recognizes a target site of six nucleotides (as EcoRI and HindIII also do) will cut on average once in every 4096 base pairs (bp). In contrast, an enzyme that has a target site of four nucleotides will cut on average every 256 bp. By choosing conditions in which the enzyme only partly digests the donor DNA—that is, it cuts only a subset of its sites in any given molecule—Sau3A can generate a set of overlapping fragments that can then be cloned into a vector designed with an appropriate BamHI site. The benefit of this is that even if a gene of interest has a site for Sau3A within its coding region, a clone containing the entire gene can still be present in the library (figure 5).

So there arose a demand for a lambda vector with a suitable BamHI site. But there was a problem: of the five BamHI sites found in lambda, one lies within an essential gene and so could not be removed by genetic deletion (which is how Noreen had typically removed other restriction sites). As a solution, she took advantage of the recently developed system for packaging lambda DNA in vitro. The method for assembling lambda head proteins in vitro and packaging the phage DNA was originally devised by Dale Kaiser. This was further developed for packaging recombinant phage genomes by Ken and Barbara Hohn (ForMemRS 2008), with the help of participants in the 1976 EMBO course on recombinant DNA—see below (Hohn & Murray 1977). Until then, recombinant lambda genomes had been introduced into host cells by transformation, just as plasmid vectors had been. The efficiency of this process was low; packaging lambda DNA in viral coat proteins and using these to infect host cells was 100 times more efficient. This increased efficiency was critical.

To eliminate the troublesome BamHI site, Noreen first generated a lambda carrying just that one BamHI site in its genome. She then grew up the stock of phage, purified the DNA and incubated it with BamHI. This treatment eliminated all genomes except for the rare cases in which the phage had picked up a spontaneous mutation that eliminated the BamHI site. When
the mixture was packaged in vitro and used to infect a host cell, the phage that emerged had indeed lost the BamHI site (Klein & Murray 1979).

Unfortunately for Noreen, despite making this critical step, she was not able to finish the construction of the first BamHI vector. Instead, the mutant phage resistant to BamHI was taken on by Sydney Brenner, who completed the job at LMB (Karn et al. 1980). For Noreen, the project was interrupted by another stint abroad. Ken had been invited to spend a few years at the new European Molecular Biology Laboratory (EMBL) in Heidelberg, and moved there in the autumn of 1979, with Noreen following in early 1980 after she had fulfilled her teaching commitments for the year at Edinburgh. This move, while highly beneficial in many ways, was also—like her return to Stanford in 1973—rather disruptive for Noreen, who, having just taken advantage of her first grant (1976–79) and having two graduate students and her first postdoctoral researcher, would now have to curtail the development of her laboratory at Edinburgh for a few years. However, she had excellent technical assistance at EMBL and it was a productive time. In collaboration with Hans Lehrach’s laboratory, she created a series of new lambda vectors—the so-called EMBL vectors—carrying polylinkers bearing sites for EcoRI, HindIII and BamHI, among others. These, which included replacement vectors (figure 6), were Noreen’s most widely used cloning vectors, and the paper describing them was her most highly cited (14).

A RETURN TO TYPE I RESTRICTION AND MODIFICATION SYSTEMS

While at EMBL, Noreen also returned to Type I restriction–modification (R–M) systems, and these remained the focus of her research after her return to Edinburgh in late 1982, and for the rest of her career (26).

These large, multi-subunit enzymes can both modify (methylate) and restrict (cleave) DNA carrying appropriate target sites. Each enzyme includes a specificity (S) subunit responsible for recognizing that enzyme’s specific DNA target sequence, R subunits for cleavage and M subunits for modification. We earlier noted that Type I enzymes do not cut DNA within their target sequences, but nevertheless initiate this action by first binding to those sites. The target sites are bipartite—that is, they comprise two defined regions separated by a non-specific linker. For example, EcoK recognizes the site 5′-AAC(N₆)GTCC-3′. Type I enzymes are grouped into families, with extensive sequence homology between members of the same family.

While still at Heidelberg, with the help of her technician Jill Gough, Noreen sequenced the genes encoding the S subunits of three members of the EcoK family, each with a different target sequence specificity. Comparing the different S genes revealed two regions of homology—100 nucleotides in the middle of the gene, and 250 at the end—and two non-conserved regions each of about 500 nucleotides, one at the beginning of the gene, and the other between
the two conserved regions. This led to the proposal that each variable region encoded a domain that recognized one part of the bipartite target sequence (15).

This was demonstrated in experiments begun in Heidelberg with another technician, Francis Fuller-Pace, and continued later in Edinburgh by Fuller-Pace, who was by then a graduate student, and by other students who followed. These studies showed that re assorting domains between different S subunits within a family produced enzymes recognizing novel, hybrid (and predictable) target sites. Moreover, specificity subunits from different families (which typically show no homology with those from the EcoK family) do share strong homology in their variable regions when those enzymes recognize the same target sequence (17–19).

Noreen’s laboratory also sequenced the R and M subunits of Type I R–M systems. There followed extensive mutational analysis and structural studies that revealed how the subunits interact with each other and with DNA, and identified regions associated with the various enzymatic activities, including ATPase and DNA cleavage (20–23). The structural studies finally produced a model for the entire complex—a feat achieved in 2011, soon after Noreen’s death, by David Dryden, a former postdoctoral researcher who now has his own laboratory at Edinburgh. The work was published in a paper dedicated to her memory (Kennaway et al. 2012).

In the last phase of her work on Type I R–M systems, Noreen—together with her penultimate graduate student, Sveta Makovets—uncovered the unexpected and striking fact that cells protect themselves against restriction, not only through methylation of their target sites but also by ClpXP-mediated proteolysis of the restriction subunits of the enzyme after it has bound to its site and initiated DNA translocation (24, 25).

**The first recombinant DNA courses**

As already mentioned, Ken and Noreen contributed to the dissemination of recombinant DNA technology by taking in those desiring to learn and by helping to make the reagents more readily (and cheaply) available. They were also involved in the first formal courses offered in this technology. The very first such course was organized by Werner Arber (figure 7) under the auspices of EMBO and held in Basel in 1976. Ken and Noreen acted as instructors, as did Ed Southern, David Glover, Barbara Hohn and others. Among the students who took the course were Walter Gehring (ForMemRS 1997), Bernard Dujon and Martina Couterier. The course was repeated at Basel for the next three years before moving to EMBL, Heidelberg, in 1980, where Ken and Noreen were by then based. One of the students who took the course in the first year at EMBL was Paul (now Sir Paul) Nurse (FRS 1989; PRS 2010–), along with Chris Leaver (FRS 1986), Marilyn Monk and Peter Jackson. In his comments on the occasion of EMBO’s 40th anniversary in 2004, Nurse recalled the huge influence that the recombinant DNA course had on his career (Nurse 2004, p. 132; 2014):

> EMBO has been very important to my scientific activities in a number of ways …. But the key role that EMBO played at a very crucial stage in my research career was a practical course held at EMBL around 1980/81.

This course was organized by Noreen and Ken Murray, who I believe were spending some months in Heidelberg at the time. The course was designed to train participants in the basic procedures of gene cloning—how to construct and bulk up plasmid and phage vectors, to generate recombinant DNA molecules, to screen for inserts, to produce proteins in bacteria and so on: all
common place now, but rather unusual then and certainly very exciting. As is often the case in practical courses, the work was intense and exhausting but was also enormously productive. We, the students, got lots of hands-on experience and also exposure to some of the great molecular geneticists of the time, who came and gave visiting lectures.

My transition to molecular genetics was made vastly easier by this fine course and I am grateful to both EMBO and our inspirational teachers, Noreen and Ken Murray. I still remember it with affection and respect over 20 years later—thank you Noreen and thank you Ken!

NOREEN AS A COLLEAGUE

We would like to convey something of what it was like to work with Noreen. One of us (A.G.) was a graduate student in her laboratory from 1985 to 1989 and stayed in close touch with her afterwards. In Noreen’s laboratory, he worked on Type I restriction enzymes, genetically characterizing their DNA recognition domains and investigating how new specificities arise. J.B. knew Noreen for longer, since her arrival as a postdoctoral researcher to learn recombinant DNA techniques in the mid 1970s, and later as a colleague on the staff of the Department of Molecular Biology at Edinburgh, and as a close friend and neighbour. Inspired by Noreen’s success cloning genes in bacteria, she, together with John Atkins, cloned the 2 micron plasmid (the name refers to its circumference of 2 μm) from *Saccharomyces cerevisiae*, which she then used to develop the first yeast–*E. coli* (hybrid) shuttle system and an efficient method for cloning DNA sequences in budding yeast cells.

Noreen had only 17 graduate students in her career. This was partly because she never wanted her laboratory to get too large, but also because she was not allowed to supervise a
student until rather late in her career: her first student completed her thesis in 1975, close to Noreen’s 40th birthday. She did help supervise a few earlier students, most notably Jeremy Brockes (FRS 1994), who arrived in 1969 and spent his first year learning bacterial and phage genetics with Noreen before returning to biochemistry with Ken, his official supervisor.

Noreen and Ken had no children, but Noreen thought of her students and postdoctoral researchers as her family and she earned their admiration and affection. To those in her research group, Noreen was a wonderful supervisor. Because she still worked in the laboratory every day (figure 8) one could learn directly from her—and as she was a virtuoso in the genetic manipulation of bacteria and phages, this was a huge bonus as well as a great pleasure. She was always available to chat about science or pretty much anything else. One could spend long hours in her cosy office beside her bench, talking about people, ideas, experiments and the intellectual history of molecular biology.

Noreen was remarkably conscientious and meticulous. This was reflected in many ways, none more so than in how she dealt with requests for bacterial and phage strains. She had an extensive collection of many hundreds of each, predominantly constructed by her, but including those from other masters in the field as well. Her collection was catalogued in little hardback notebooks. The broken spines were sellotaped and the oldest books had yellowing pages. All genotypes were annotated—sometimes impenetrably to others—in her small, spidery hand.

From the 1970s onwards, requests for *E. coli* and lambda strains arrived almost daily. Before sending a strain to anyone, Noreen would get the stock out and grow it up, pick a colony or plaque, and do whatever genetic tests were needed to confirm that it was indeed exactly the strain it was supposed to be. Some of these tests could be fairly involved and tricky, and she did them all herself—there was no dedicated technician to take care of this business.
There were also requests for entirely new strains, constructed by her from scratch to provide the ideal genetic background for specific experiments. Such bespoke strains were in great demand because her skills were held in such high regard. To watch her pick out just the right plaque or colony was a treat; she had an instinct, built on experience and careful observation, that made it seem almost mystical at times. While a postdoctoral researcher in Edinburgh, J.B. screened thousands of recombinant phage clones, searching for one encoding the \textit{EcoK} restriction subunit. Noreen, who would often say ‘show me the plate’, looked at the results, tested a dozen or so that looked interesting and found one. Everyone would trust any strain Noreen made, and nothing would have mortified her more than sending out a strain that was not as she had described it.

She was also very generous and supportive. Perhaps following the example set by her own PhD supervisor, David Catcheside, Noreen made sure that young colleagues met interesting and influential scientists when they visited, often at dinner in her home. Among others we met in this way were Sydney Brenner, Alan Campbell, Frank Stahl, Jim Watson (ForMemRS 1981), Paul Nurse and the legendary local geneticist Lotte Auerbach FRS.

This level of generosity and friendship endured after one left Edinburgh. Noreen always stayed in touch, shared news of Edinburgh and liked to hear about one’s own adventures. She visited A.G. in Boston, London, Lancaster and Cold Spring Harbor. While visiting A.G. when he was a postdoctoral researcher in Mark Ptashne’s laboratory, Ken and Noreen sat in on one of Ptashne’s undergraduate lectures. This, as Ptashne told the students, was rather nerve-wracking for him as ‘those two sitting there are Ken and Noreen Murray, and they actually know a lot more about lambda than I ever did!’

On another occasion, while A.G. was a lecturer at Lancaster University, Noreen came to stay and the two toured round the places of her childhood—including Bolten-le-Sands, the village where she grew up. Seeing Jumbo—the rock so often climbed as a child on the shore of Morcambe Bay—her tomboyish enthusiasm resurfaced; she was confident she could still scale it, and was truly frustrated to discover she could no longer get quite to the top.

**Honours and Committee Work**

We have touched on some of the problems experienced by Noreen as a married woman in science, and these issues vexed her. Needless to say, they did not prevent her from achieving outstanding success and earning many honours, including the Gabor Medal of the Royal Society, the Royal Medal of the Royal Society of Edinburgh and six honorary degrees. In her collaborations with Ken (figure 9), the importance of her contribution was always evident. Her skills perfectly complemented Ken’s, she being the geneticist and he the biochemist in their projects.

As well as serving as President of the Genetical Society from 1987 to 1990, she later took on other important committee work, much of it for the Royal Society, where she served on Council, as a Vice-President from 2002 to 2004 and, in 1998, chaired the Working Party on Genetically Modified Organisms. The latter produced the report on the controversial experiments conducted by Dr Arpad Pusztai. In addition to much other committee work, she served from 2005 to 2009 on the Science and Technology Honours Committee and between 2002 and 2007 on the Fellowship Committee for the Royal Commission for the Exhibition of 1851.
From 1990 until her death, Noreen also served as a Trustee of the Darwin Trust of Edinburgh. This trust was established by Ken and Noreen in 1984 with money from royalties that Ken received for the hepatitis B vaccine that he developed for Biogen (see Brammar & Gratzer 2014).

**LIFE OUTSIDE SCIENCE**

After science, Noreen’s great love was gardening, a manifestation of her continued interest in botany and an activity she found very relaxing. She rejoiced in spending a sunny evening or weekend in the garden of their final home on Mortonhall Road in Edinburgh, which was magnificent and maintained to an exceptionally high standard (figure 10). As in many other aspects of life, she rejected new technology, pushing a manual lawnmower well into her seventies. She could often be found on her knees pulling weeds from the highly manicured lawn. Her gardening boots stood proudly outside the entrance to the house (figure 11).

Noreen and Ken were generous and delightful hosts. They frequently invited friends and colleagues to their home for dinner, when an exquisite meal and fine wines could be expected. Noreen liked high-quality ingredients, cooked simply. Favourites were venison or halibut, with roast vegetables. Many guests requested recipes, which Noreen would write out meticulously by
hand with tips for variations. They were also generous with invitations for dinner at restaurants or, more often latterly, at the Edinburgh New Club, where they regularly dined themselves.

Noreen and Ken could often be spotted in art galleries and were discriminating collectors. Their home was richly furnished and well endowed with work by artists including Renoir, Anne Redpath, L. S. Lowry, Duncan Grant, Augustus John, John Singer Sargent and contemporary artists such as Victoria Crowe, who became a personal friend.

Noreen was also a keen follower of rugby. Her father had introduced her to the game, and she kept on her office wall a caricature of him playing. As a student in London she attended international matches at Twickenham, and continued in later life to watch games during the annual Six Nations tournament on television—one of the very few times that she watched television at all.

As already indicated, Noreen had an aversion to technology. Although she and Ken eventually bought mobile phones, they never used them. The shop obligingly set up the phones so that Noreen had Ken’s number on her list of contacts and Ken had Noreen’s. But there was a mix-up: Noreen’s phone listed her own number under Ken’s name and vice versa. Three years later it was one of us who discovered the mistake. They had apparently never used them to call each other, let alone anyone else!

Noreen was also reluctant to use a computer. She did learn to read emails on a computer set up for this purpose in her office, but she always wrote a reply by hand and passed it to Ken’s secretary for emailing. It was therefore unfortunate that, when she developed a form of motor
neurone disease in 2010 and her speech deteriorated, she felt unable to use texting or other electronic means to facilitate communication. However, she confronted this affliction with courage and dignity. By the beginning of 2011 she could no longer speak but she continued to come into her office to deal with correspondence and she maintained a lively involvement in discussions by jotting in little notebooks that she carried everywhere. Noreen was fit and energetic until this illness developed, and then she seemed more concerned for the welfare of those around her than for herself. Noreen passed away on 12 May 2011, with Ken at her side. She is remembered with huge affection and admiration by so many, and is greatly missed. Ken died at home less than two years after Noreen, and their passing feels like the end of an era.

**AWARDS AND HONOURS**

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<tr>
<th>Year</th>
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<tr>
<td>1980</td>
<td>Elected to EMBO</td>
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<td>1982</td>
<td>Fellow of the Royal Society</td>
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<td>1987–90</td>
<td>President of Genetical Society of Great Britain</td>
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<td>1989</td>
<td>Fellow of the Royal Society of Edinburgh</td>
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<td>1989</td>
<td>Royal Society Gabor Medal</td>
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We thank Walter Gratzer, David Finnegan and Millie Masters for helpful suggestions, Frank Stahl for letting us quote from his letters in the Archives of the Cold Spring Harbor Laboratory, and Frank Stahl and Hugh Huxley FRS for permission to quote from Stahl’s LMB memoir. We also thank Carrie Cowan for help with figures.

The frontispiece photograph was taken in 1985 by Godfrey Argent and is reproduced with permission.

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