Professor Richard Penry Ambler (1933–2013)

Richard Ambler, one of the most skilled practitioners of the techniques of protein sequence determination developed by his PhD supervisor, Fred Sanger, died after a short illness in December 2013 – within a few weeks of the passing of Sanger himself. He will be missed by many across the globe for his intellect, his constructive support, the infectiousness of his wide-ranging interests and, perhaps above all, his ready sometimes anarchic wit, and usually poker-face.

In his research, Richard employed protein sequencing to cast light on evolutionary relationships between organisms, an approach that is now known as 'molecular taxonomy'. He maintained that sequence accuracy was essential if evolutionary conclusions were to be drawn. He concentrated almost exclusively on microbial sequences, and his studies helped to establish[1], not without controversy, the very great importance in these organisms of horizontal (Richard used the term 'lateral') gene transfer, identified through non-congruence of evolutionary trees for multiple genes, in contrast with the predominantly vertical inheritance seen in higher organisms. After the concept of horizontal gene transfer was finally accepted, he wrote in 2007, "I think that the soldiers who worked away at the sequencing of bacterial cytochromes can now say that we have won the war – even if (in 1998) the World thought we had lost the battle."

Richard was born in Bexleyheath on 26 May 1933. In 1940, the family moved to Poona (now Puna), in India, where Richard spent much of his childhood before returning to boarding school at Haileybury in Hertfordshire, UK. National Service in the Royal Signals followed before, in 1954, he entered Pembroke College, Cambridge, UK, to study Natural Sciences. He remained in Cambridge as a postgraduate student in the Department of Biochemistry, and obtained his PhD with a thesis entitled *Structural Studies on Bacterial Proteins* in 1961. There then followed postdoctoral research in the MRC Laboratory of Molecular Biology, including a year spent in La Jolla, CA, USA, with Martin Kamen.

In 1965, the Principal of Edinburgh University, Michael Swann, having failed to persuade biochemists in the Medical School to introduce molecular biology into their department, asked Martin Pollock to create the (first UK) Department of Molecular Biology in the Faculty of Science, at the King's Buildings campus. Richard was recruited to the founding staff of the department to provide protein chemistry expertise, and he remained at Edinburgh for the rest of his life. In 1984, he became Head of Department, and played a key role in the reorganization of the University's diverse and dispersed biology departments into the Division of Biological Sciences – part of which became the Institute of Cell and Molecular Biology, of which he was Head from 1990 to 1993. He was elected a member of the European Molecular Biology Organization in 1985 and was promoted to a personal chair in protein chemistry in 1987.

Richard's career was devoted to answering questions about the evolution of bacteria with the aid of amino acid sequence information: in 1963, he published the first such sequence of a bacterial protein, that of *Pseudomonas* cytochrome c_{551}. Martin Pollock's research centred on penicillin resistance in bacteria, and this became a central theme of work in the new department. Much of the resistance is due to the production of an enzyme, penicillinase or β-lactamase, which destroys the antibiotic. Resistance is seen in very diverse bacteria, and Richard asked whether the enzymes responsible for this had a common origin or had arisen independently in response to the antibiotic. By 1978, the amino acid sequences that he and his colleagues had determined showed that, whereas the most widely distributed penicillinases (the class A enzymes in his classification scheme[2]) had a common origin, other enzymes had originated independently.

Richard applied similar amino acid sequence-based methods to investigate the origins of chloroplasts and mitochondria. He showed that there is close sequence similarity between the cytochromes and copper proteins from photosynthetic bacteria and the equivalent proteins of chloroplasts, and between the sequences of some bacterial cytochromes and those of mitochondria. These studies suggested that organisms evolved both by mutation and selection of their genomes and by the acquisition of genes that had evolved in separate organisms. Such horizontal gene transfer can occur at very high frequency for functions such as antibiotic resistance, as his studies of β-lactamases had shown.

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The use of sequence information to answer evolutionary questions is now routine. Today, these sequences are derived from cheaper, faster, fully automated nucleic acid sequencing. Initially, there were at least formal doubts about the accuracy of DNA sequencing. Richard played a key role in 1978 in validating one of the first published nucleic sequences, and thus symbolically marking the beginning of the transition to the current era of molecular biology. The first complete genetic unit to be sequenced in Walter Gilbert's Harvard laboratory was a bacterial plasmid. This contained the gene which codes for a β-lactamase, whose protein sequence was nearing completion in Richard's laboratory. He supplied these data, in a sealed envelope, to Jeremy Knowles, also at Harvard, who kept them under seal until Gilbert and Sutcliffe considered they had the DNA sequence solved. The DNA-derived and Ambler-sequenced results were compared at a meeting over a cup of tea in Knowles's study. Both groups were satisfied with the outcome[3,4].

Richard continued to do bench work essentially every day of his working life. This was always directed to protein sequencing, but he was also always prepared to take time and care to give reliable and helpful advice on all aspects of protein chemistry to colleagues with other areas of expertise. Students, postdocs and colleagues will remember chatting to him in the lab as he painstakingly prepared amino acid hydrolyses, paper electrophoretograms or typed out overlapping peptide sequences. They will also remember his careful teaching of matters protein chemical, his suggestions always insightful, of what to do when something had not worked and his poker-face telling of total fabrications to see whether or not you were on your toes.

He was unusually aware of the importance of collaboration and a multidisciplinary approach to solving the important problems of molecular biology. To this end, he frequently provided the impulse to bring new techniques – including, at various periods, biomolecular X-ray crystallography and NMR, nucleic acid synthesis and proteomics – to the King's Buildings campus. For the same purposes, he was principally responsible for the creation of the Scottish Protein Structure Group. This met about three times a year to provide a forum for methods, results and gossip to be shared, originally among the protein sequencing academics in every Scottish university – and, later, as crystal structures began to emerge, those working on any aspect of protein structure. The group's activities eventually ended with the 103rd meeting in 2011.

Richard had a wide range of non-scientific interests – he referred to them as his "non-Philistine activities" – particularly archaeology, and was a Fellow of the Society of Antiquaries of Scotland. He could always be relied upon to provide an accurate answer, backed up by an appropriate reference book, to all questions no matter how esoteric. His house was often frequented by visitors from around the world mixing his scientific and family life in a very welcome way. His companionship, common sense and mischievous wit will be missed by his colleagues and family alike.

Richard met his first wife, Pat, while they were both science undergraduates at Cambridge. They had two daughters, but this marriage ended in divorce. Some years later, in 1994, he married Sue Hewlett: she sadly died in 2003, but Richard is now survived by two daughters, four stepdaughters and seven grandchildren. ■

Lindsay Sawyer and **Andrew Coulson**
(University of Edinburgh, UK)

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