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RICHARD NELSON PERHAM

27th April 1937 – 14th February 2015

Elected FRS 1984

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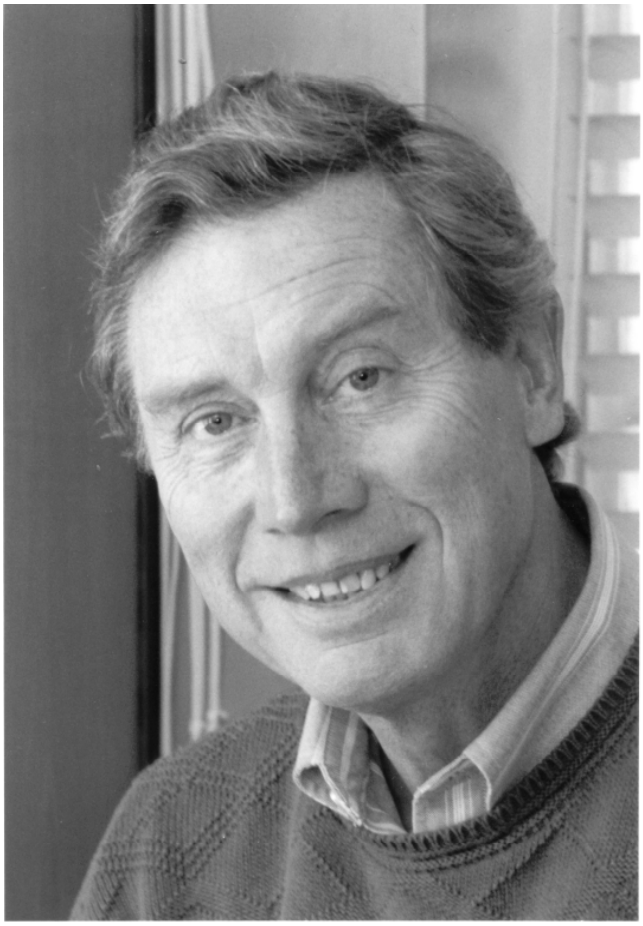
SUMMARY

Richard Nelson Perham, FRS, FMedSci, FRSA, was a British Professor of Structural Biochemistry. He undertook his academic career at the University of Cambridge, holding positions as Lecturer, Reader, Chair and Head of the Department of Biochemistry, as well as Master of St John's College. Perham published close to 300 scientific papers on protein structure and function, with a focus on mechanistic enzymology, particularly how large multienzyme complexes and flavin-containing enzymes work. He is most renowned for determining how reactive intermediates are transferred between enzyme active sites, for alterations of coenzyme and substrate specificity by his pioneering use of protein engineering and for developing protein display methodologies. Married to Nancy Lane-Perham and with their two children, Perham enjoyed a full and active life in Cambridge and St John's College. He was a keen participator and supporter of sport and enjoyed art, literature, theatre and music. Perham was a vocal and active champion of equal opportunity in education. His legacy to science is a greater understanding of how enzymes work. His legacy to scientists is as a role model of how to attain the highest levels of achievement whilst maintaining a sense of personal modesty and keen support for others.



PREAMBLE

Richard Nelson Perham was known to his colleagues as 'RNP'. He had a full and varied career. We have done our best to capture his life and achievements in this biography by talking to his friends and colleagues who lived, worked and knew him, many for much longer than we did. RNP gave us some notes he had made himself as a prelude to this biography when he knew his time left with us was limited. The text below is taken from these notes and the many conversations, shared memories and photographs that RNP's friends have kindly shared with us. What unites us all is the memory of RNP's mantra 'Onwards and Upwards'. And it is in that vein of 'Onwards and Upwards' that the words below, we hope, will tell of a man who achieved so much and gave in equal measure.

FAMILY BACKGROUND AND EARLY LIFE

Richard Nelson Perham was born on 27th April 1937 at 3, St Paul's Close, Hounslow West, Middlesex. His father Cyril Richard (born 1904) was a carriage painter who worked on the London Underground in the maintenance department. His mother, Helen (née Thornton, born 1906), was head of the front of house staff (usherettes and so on) at the Kensington Odeon cinema. During his childhood, Richard lived at the family home in Hounslow, then a rural community, a far cry from the Heathrow Airport concrete hinterland it is now. One of Richard's earliest memories was of the flickering red skies and rumblings to the east as London suffered the blitz. On such nights when the sirens sounded the family went down into the Anderson shelter dug in their small back garden. Another of Richard's memories was watching the vapour trails of fighter planes and, towards the end of war, listening to the drone of the V1 bomb as it coasted in from the east and waiting for its sudden cessation, followed shortly by a massive explosion as it crashed nearby. The V2 they never heard until the big bang. Meanwhile, life went on as normally as possible in such circumstances.

SCHOOL DAYS

Richard started school in 1942 at the local primary, Martindale Road School, in Hounslow West. He remembered two teachers who took a particular interest in him: Miss Mizen and Miss Troth. It was these two teachers who started Richard's academic career, by recognising his talent, and encouraging him to take the 11^{+}-scholarship and the Latymer Upper School entrance examination. He passed both and embarked on seven happy years (1948-1955) at Latymer Upper School. At Latymer Upper Richard's love of sport and science was born. He formed a life-long bond with the school, holding positions of governor of the Latymer Foundation from 1991 to 2010 and Chairman of Governors from 2005-2010. Latymer shaped Richard's strongly held view that all with ability and promise should have the opportunity to experience the very best education, regardless of family connections or financial means. It was in this vein that Richard left a legacy to the school to permanently endow a free place to a deserving and talented pupil.

When Richard was 11 his father died and it was left to Richard's mother to keep the family home going. She avidly supported Richard's education: they read books together (Shakespeare, encyclopaedias, the total works of Charles Dickens) and, when money allowed, visits to the cinema, or to the theatre in the West End. It was from his mother that Richard inherited his lifelong interest in the performing arts. When Richard was 15, his mother married Mathew Gray, a local bachelor who had served 22 years in the Royal Navy (a service in which Richard was later to serve himself).

Richard thought Latymer Upper School was 'intellectual heaven'. The Headmaster, Mr Fred Wilkinson, a graduate of Sidney Sussex College, Cambridge and veteran of the First World War, insisted on a liberal outlook and a wide curriculum. Richard thrived at the school, excelling at languages and sciences in equal measure, and it was there that he learned to row eights on the river Thames, a second passion that he upheld throughout his life. Latymer School's liberal outlook and broad curriculum inspired Richard as an academic and as a budding scientist. The inclusion of the arts and sport were added bonuses which Richard enjoyed for the rest of his life.

In the sixth form Richard pursued A-levels in pure and applied maths, physics and chemistry. He was influenced again by outstanding teachers: Messrs Howard in maths, Abbott in physics and Moody in chemistry. Bernard Moody was especially important. At the time Moody was in his first teaching job after graduating from St John's College, Cambridge, and he introduced his charges to physical science of a high order, including Linus Pauling's *Nature of the Chemical Bond* – a work a bit beyond the capacity of the boys, but a magnet to those who saw in it a whole new world of physics and chemistry beyond the normal curriculum.

After completing his A-levels in 1955, in which he was awarded a State Scholarship in maths and physics, Richard was encouraged by Moody to try for entry to the University of Cambridge. Coming from a family in which none of its members had attended university, this was both an exciting and daunting prospect. It required staying on an extra term at Latymer Upper to take the Cambridge Entrance Scholarship examinations. But which College? Here Moody's influence was decisive: St John's it had to be. This was Richard's introduction to St John's College, a place which was to prove so significant for the rest of his life.

A DELAY IN A CAMBRIDGE CAREER - LIFE IN THE ROYAL NAVY

In the Scholarship examinations of December 1955, Richard was awarded an Exhibition in Natural Sciences and was all set for him to matriculate at St John's College the following year. However, this was the era of compulsory National Service and, after discussion with his future tutor at St John's (Mr Edward Miller), Richard was advised against applying for deferment, but instead he should 'get his military service out of the way'. Richard chose the Royal Navy, inspired by the Navy tradition in his mother's family. Richard was summoned to the Victoria Barracks in Portsmouth for aptitude tests and sent to the Signals Branch to work in cryptography and radio warfare. Richard enjoyed Navy life relatively unthreatened by military issues. However, in the late summer of 1956 the Suez War erupted and Russia invaded Hungary. As a consequence, Richard was promoted from rating, to Upper Yardman and then Officer, hurried through his courses and despatched in an RAF Hastings aircraft from a small airfield in East Anglia (now Stansted Airport) to Malta. There he joined a Daring Class destroyer, *HMS Defender* (Figure 1), for the last part of the Suez operation. Always a good linguist, Richard learnt Russian and was his ship's intelligence officer, decrypting Russian navy signals. After the Suez crisis was over Richard was expecting to return to the UK, but *Defender* was diverted to Cyprus to take part in the war against the Greek Cypriot nationalist guerrilla organisation, EOKA, which was then raging, delaying yet again his academic studies at Cambridge. These were important times, as they initiated Richard's lifelong love of Cyprus and prompted his decision to buy a house there later in his life.

Perhaps as a prophecy to his future successful academic career, Richard was also Ship's Schoolmaster (an ancient office introduced by Lord Nelson) and he arranged classes in various subjects for the ship's company, including lessons in applied mathematics for a couple of the junior officers. In all, Richard spent over a year in the Mediterranean Fleet, enjoying *Defender*'s visits to 'show the flag' in Naples and Marseilles, and time in the naval bases in Malta and Gibraltar. In Valletta he met another coder, Leslie Iversen, FRS, who was going up to Trinity College, Cambridge and read Part II Biochemistry in the same year as Richard. Richard later thought that National Service had been "very good for him" – "a formative experience as it was a great equaliser". It widened his knowledge of the world, taught him self-sufficiency, helped him to get on with people from any walk of life, and illustrated the importance of working together. This experience remained with him throughout his life in science, as did his photo of *HMS Defender*. All who visited Richard in his laboratory in the Department of Biochemistry at Cambridge will remember the photograph of the ship (reproduced in Figure 1) which took pride of place on his desk throughout his career.

Figure 1. The Daring Class destroyer, *HMS Defender*, on which Richard served. This photograph stood on Richard's desk in the Department of Biochemistry in Cambridge throughout his career.

AN ACADEMIC CAREER IN CAMBRIDGE - STARTING AT LAST

After deferring his entrance to Cambridge for two years to fulfil the requirements of national service, Richard finally matriculated at St John's College in October 1958 where he read Natural Sciences. Richard's first inclination was to specialize in physics or chemistry, but his Tutor, Reverend Alan Welford (a Lecturer in Experimental Psychology), persuaded him to take a biological subject. 'Try physiology or biochemistry', he was advised. One taste of biochemistry and Richard was hooked. These were halcyon days for Biochemistry in Cambridge - the 3D-structure of DNA had been solved in 1953 by the James Watson, ForMemRS and Francis Crick, FRS; the first amino acid sequence of a protein, insulin, had been determined by Fred Sanger, FRS in 1955, and the first three-dimensional structure of proteins: myoglobin was solved by John Kendrew, FRS, in 1958 and haemoglobin by Max Perutz, FRS in 1959. A new world was opening up in biomolecular science.

Richard spent the whole of his academic career in the Department of Biochemistry at Cambridge: after his PhD (in the Laboratory of Molecular Biology (LMB)), he became University Demonstrator in Biochemistry (1964-1969), University Lecturer (1969-1977), Reader in Biochemistry of Macromolecular Structures (1977-1989), Professor of Structural Biochemistry (1989-2004), Head of Biochemistry (1985-1996) and Emeritus Professor from 2004 until his death in 2015. He always found inspiration, he said, 'walking down these streets that Newton and Darwin walked down, in this place where so much has happened' (Nature, 2005). During his time as Head of Department, Richard piloted the introduction of the 4-year Part III course in Biochemistry and led the fund-raising campaign that enabled the construction of a new building for Biochemistry. The building was formally opened by Fred Sanger, FRS in 1997 and it gave Richard great pleasure to see it named after

his lifelong friend and PhD mentor (and a double Nobel Laureate, prized for developing protein and DNA sequencing) (Figure 2). Richard was also the founding Chair of the Cambridge Centre for Molecular Recognition (1988-1993), an inter-departmental and multi-disciplinary grouping that aimed to bring about much closer cooperation between Chemistry and the Biological Science departments.

Figure 2. Richard (right) with his PhD supervisor Dr Fred Sanger, FRS, in the Department of Biochemistry, University of Cambridge (photo

Going back to the beginnings of his career; Richard again remembered inspirational teachers in St John's College: Ken Budden, FRS for physics, Don Northcote, FRS for biochemistry, F B Kipping for organic chemistry and W G Palmer for physical chemistry. Inspiration in his University lecturers came from Tom Faber and W H Fowler in the Cavendish; Sam Perry, FRS, Ken McQuillen, Ernest Gale, FRS, in Biochemistry and H C Longuet-Higgins, FRS in Chemistry. Bowled over by the lectures given to the part II students by Dr Fred Sanger, FRS (Nobel Laureate 1958) on the chemical structure of insulin and its determination, Richard approached Sanger and asked him if he could become a graduate student under his supervision. He was subsequently interviewed for a PhD studentship by Max Perutz, the chairman-designate of the new MRC Laboratory of Molecular Biology (LMB) which would be opening in 1962, and offered a position dependent on graduating with a First Class Degree. In June 1961 Richard achieved that feat, and in late September of the same year he joined Fred Sanger's group taking up a PhD studentship as a Medical Research Council Scholar and Slater studentship in the Department of Biochemistry. Notably, Richard was the first graduate student recruited to the about-to-open MRC LMB. His career in research had begun.

Fred Sanger put Richard to work under the immediate supervision of Dr J Ieuan Harris with the challenge of determining the structure and mechanism of action of the enzyme glyceraldehyde 3-phosphate dehydrogenase (GAPDH). This was Richard's first encounter with mechanistic enzymology and, prophetically, involved an enzyme in glycolysis – the metabolic process by which energy in the form of ATP is obtained by the oxidation of glucose. There was evidence that the action of GAPDH involved a thiol group, but it was unclear whether this group was provided by a cysteine residue in the enzyme itself or was provided by a peptide cofactor such as glutathione. It was a puzzle, and one Richard was keen to solve - after all he had been trained as a cryptographer in the Royal Navy! It soon became apparent that glutathione was not involved, and by the use of ^{14}C-labelled iodoacetic acid as an inhibitor, Richard and Ieuan were able to identify the key cysteine residue in the protein (1, 2). More sequencing followed, and by the mid-1960s the Perham-Harris team held the record for determining the longest amino acid sequence (over 330 residues) of a protein. Published in the journal *Nature* in 1968 (4), this paper is today still one of Richard's most highly cited works.

In September 1962, Richard married a Hounslow girl he had been seeing for some years. Sadly it soon became apparent that life as the wife of a young aspiring academic did not suit her and by January 1964 the marriage was over. This was a bitter blow and Richard never spoke of it again. This personal setback coincided with the annual competition for the election of Research Fellows of St John's College. Richard successfully applied and was awarded the Henry Humphreys Prize for the best application in the sciences. After a brief five months living with Clive Dalton, with whom Richard shared a lifelong love of vintage cars, Richard moved into College. This marked the beginning of Richard's 57-year long devotion to the cause and well-being of St John's.

Figure 3. The St John's College May Ball Committee 1969. Richard was President of the May Ball Committee that year. Richard and Nancy Lane-Perham are 8th and 7th from the right. Other members of the committee that year included several of Richard's tutees, who became his lifelong friends, including Derek Lyon, Captain of the Cambridge rugby side and later a distinguished businessman and the (now) Lord Browne of Madingley, (now) Lord Hennessy of Lympsfield and (now) Sir Richard Aikens, PC.

From 1967-1977 Richard was tutor for lawyers, geographers, economists and historians at St John's. He was much-liked, as a wise elder 'brother' to his pupils and undergraduate friends, but loving to join in the fun, whether at Eagles desserts, the Committee dining club, in the College bar or the May Ball committee (Figure 4). One of his early pupils at St John's was (the later) Professor Dan Reinstein, a distinguished eye surgeon and jazz saxophonist. Professor Reinstein recalled that "everyone regarded Richard as the 'coolest' don in college". Richard rose through the ranks in his 57 years at St John's – from undergraduate (1958-1961), post-graduate (1961-1964), Fellow (1964-2004), President (1983-1987) and Master (2004-2007) (Figure 4). All who knew Richard were keenly aware of his passion for St John's - its academic brilliance, sport, College life, and its history, which

included an encyclopaedic knowledge of every portrait in the Great Hall. Another of Richard's contributions to the college was to instigate a "Fellows' Boat" in the college boat club in 1970. That boat did not win its oars, but Richard again rowed and did win his oar in the 1973 Fellows' boat, coxed by Dr Mervyn King, later Governor of the Bank of England, but known then as "Merve the Swerve". Richard thereafter rowed in, coached, or supported numerous Fellows' Boats, with no interruptions, even when Master. Above all, however, Richard believed that the College should help those who came from modest backgrounds so they could enjoy the best of educations, as he had been lucky enough to experience himself via Latymer Upper and St John's. In that vein, Richard was also an early advocate of the admission of women to St John's, smoothing the path of that not-so-easy decision, for some, which finally came to pass in 1983. Richard was also a great fund-raiser for his college – "not a grand college, but a great one", he said. His four years as Master of St John's were marked by major refurbishment projects and, in an enormous cycle of fund-raising in 2011, Richard spearheaded a campaign which generated £50 million for the college's 500th anniversary. He also inaugurated, and was first President of, the Beaufort Society, an association of Johnians who have pledged to remember the College in their will.

Figure 4.Richard and Nancy Perham in *ca*. 2004 in the garden of the Master's Lodge at St John's College, Cambridge.

BACK TO SCIENCE – DISCOVERIES IN MECHANISTIC ENZYMOLOGY

In 1965 with his PhD completed, Richard was appointed as University Demonstrator in the Department of Biochemistry in Cambridge and awarded a Helen Hay Whitney Fellowship to study in the Department of Molecular Biophysics at Yale University with Professor Frederic Richards, famed for solving the crystal structure of ribonuclease S in 1967 and for defining the concept of the solvent accessible surface. This was to prove another epochal moment in his life. For there, Richard commenced his studies of tobacco mosaic virus (TMV) and began his career-long passion in understanding the chemistry of higher order macromolecular structures. Richard's work on TMV revealed the importance of charge-charge interactions between protein subunits in the self-assembly of the TMV capsids (30) and he elucidated the mechanism by which protein-DNA charge interactions are used to govern the assembly of these filamentous bacteriophage virions (30). He also demonstrated the orientation of the RNA (5'→3') within the rod-like TMV structure (13, 15, 16) and the mechanism of capsid (coat) disassembly which begins at the 5'-end *in vitro* (20, 21).

Equally significant, it was in Yale, over the shared use of an electron microscope, that Richard met Nancy Lane, an ebullient Canadian, and a brilliant microscopist. Nancy and Richard had many interests in common, including science and art. Two years later, Richard returned to Cambridge and was elected to a teaching Fellowship and Tutorship at St John's. A year later, Nancy Lane arrived in Cambridge, having been appointed a Scientific Officer of the Agricultural Research Council working on insect neurophysiology in the Department of Zoology. She and Richard married in Halifax, Nova

Scotia, in December 1969 and went on to enjoy 46 happy years of life together, including the births of their two children Temple (in 1970) and Quentin (in 1973). They were enthusiastic and avid hosts, sharing their home with friends, colleagues, collaborators and group members for many memorable dinners, barbecues and parties. Following Richard's passion for literature of all kinds, Temple went on to read Classics at Lady Margaret Hall, Oxford and now lives in California with her husband, Barney Schauble, and their two children, Isabella and Tristan. Quentin, who suffers from cerebral palsy, was always included in family activities.

Following his time in Yale and as a University Demonstrator, Richard was appointed to a Lectureship in the Department of Biochemistry in Cambridge in 1969. There he developed a number of important techniques in protein chemistry, including reversible citraconylation of amino groups (3), amidination of lysine residues (23, 28), hybridization of native and chemically modified subunits in oligomeric enzymes to study subunit interactions (12), and reversible chemical cross-linking to probe the quaternary structure of protein complexes (14, 27). These methods were widely used in the 1970s to interrogate protein structure and function, until the development of site-directed mutagenesis in the 1980s which rapidly replaced the 'old-fashioned' and much less specific methods of chemical modification. Ironically, following the advent of mass spectrometry for protein sequencing (Wilm *et* al, 1996; Abersold & Mann, 2003; Taouatas *et al*, 2008) these 'old-fashioned' methods are enjoying a resurgence of popularity, with researchers worldwide needing to re-discover the tricks of chemical modification developed by Richard and his colleagues more than 40 years ago (3, 5, 6, 8, 11, 14, 28).

As well as developing chemical methods for protein modification, Richard was also involved at that time in trying to establish the chemical structure of the active site of Class I aldolases, an enzyme that functions upstream of GAPDH in glycolysis that he had sequenced 11 years previously for his PhD work (22). At the same time, the group discovered the existence of Class I aldolases in prokaryotes, overturning the notion that this class of aldolases are only found in eukaryotes (9, 17).

A major theme of Richard's research career, and the subject for which he is probably best known, is his work on multienzyme complexes, which he began in 1970. His choice of a subject was the

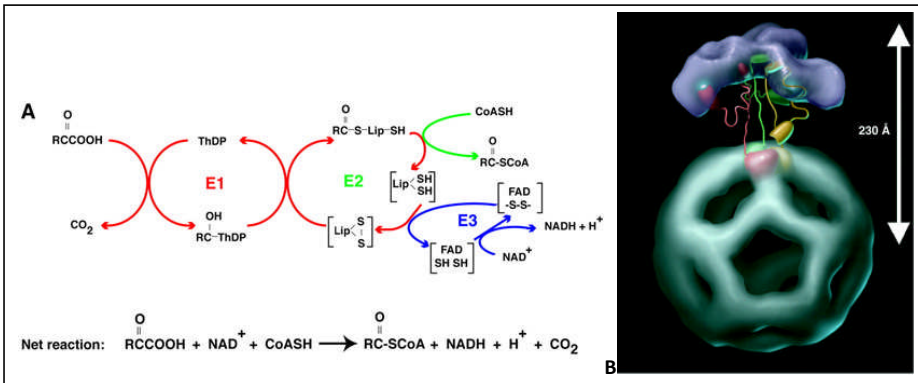


Figure 5. (A) Schematic diagram of the reaction mechanism of a 2-oxo acid dehydrogenase multi enzyme complex and (B) the structure of the pyruvate dehydrogenase multienzyme complex reveals a remarkable molecular machine. From (57), with permission.

'swinging arms' of the 2-oxo acid dehydrogenase complexes discovered in the 1950s and 1960s by Dr Lester Reed in the Chemistry Department at the University of Texas at Austin, USA (Reed, 1974). These enzymes are giant assemblies (*ca*. 3 to 9 MDa complexes, similar in size to a ribosome) of multiple copies of three different enzymes – a 2-oxo acid decarboxylase (E1), a dihydrolipoyl-acytransferase (E2) and a dihydrolipoamide dehydrogenase (E3). These complexes catalyse a four step mechanism to oxidatively decarboxylate the substrate and rely on the involvement of five coenzymes or cofactors (thiamine pyrophosphate, lipoic acid, FAD, NAD and Coenzyme A) (Figure 5A).

Among many research highlights from Richard's 40 years of innovative experiments on these enormous molecules, are a) establishing the nature of an intrachain disulphide bridge that participates in the highly unusual catalytic mechanism of the dihydrolipoyl dehydrogenase (E3) component (7, 10); b) discovering the multiple lipoyl groups and the intramolecular transacylation reactions between them in the acyltransferase (E2) core that underpin the system of active site coupling (18, 19, 26); c) pioneering (with Professor Gordon Roberts, then at the National Institute for Medical Research (NIMR), London) the use of ^{1}H-NMR spectroscopy to identify conformational flexibility of the inter-domain linker regions in the E2 subunit (25); d) using site-directed mutagenesis to introduce residues (histidines) with identifiable ^{1}H-NMR signals into putative conformationally flexible regions of a polypeptide chain to locate dynamic segments (32); e) working out the elaborate domain-and-linker structure of the E2 subunit and the location of the lipoyl-lysine swinging arms (24, 29, 31, 36); and f) discovering that the specificity of the interaction of the lipoyl domain with the E1 component is the molecular basis of an elegant system of substrate activation and channelling (34, 37). Richard was a passionate believer that a full molecular understanding of these fascinating molecular machines could only be fully achieved by determination of their molecular structures. He was one of the first to use the approach, now termed 'integrative structural biology', in which a wide variety of techniques are combined to determine a molecular structure. Working with Dr Wim Hol, Seattle, USA, Drs Ben Luisi, Ernest Laue, and Bill Broadhurst, Cambridge, Dr Richard Henderson FRS (LMB, Cambridge) (Nobel Laureate, 2017) and latterly Dr Sriram Subramaniam (National Institute of Health (NIH), USA) over a period of years, Richard solved the solution NMR structures of a number of lipoyl domains (43, 47, 53) and peripheral subunit binding-domains (40, 44, 60) of different 2-oxo acid dehydrogenase complexes; and the X-ray crystal structure of the E2 catalytic core (50). He then integrated the results to solve the structures of different protein sub-complexes and those of interacting domains (46, 59). Finally, with his collaborators he used cryo-electron microscopy, to solve the structures of the E1-E2 (57) and E2-E3 complexes (61), allowing a model of the complete giant E1-E2-E3 multienzyme complex to be built (Figure 5B) (57, 61). This amazing structure showed a remarkable architecture in which the E1 and E3 components are peripherally distributed in a shell around the E2 acetyl transferase core (Figure 5B). This allowed the overall mechanism for the enzyme complex to be formulated. It begins with a newly discovered 'proton wire' in the thiamin-dependent E1 component (59). Movement (Brownian motion) of the lipoyl domains to peripheral E1 components to undergo reductive acylation, combined with visits of the acylated lipoyl domain to the E2 acyl transferase active sites in the inner core, then allows acyl transfer to CoA. Finally, another outward movement of the lipoyl domains allows oxidation by the peripheral E3 subunits. This tour-de-force was the culmination of over 40 years of diverse and multi-disciplinary work on 2-oxo acid dehydrogenases and revealed these complexes as the first fully worked-out example of a catalytic machine that can achieve a 4-step catalytic reaction.

This amazing dynamic and beautifully choreographed enzyme complex turned out not to be a one-off. In the course of his work Richard also demonstrated that these ideas extend to other systems with swinging arms, notably the biotin-dependent carboxylases and fatty acid synthases (49, 51). This was confirmed by elegant structural work by others on both systems (Jitrapakdee & Wallace, 1999; Witkowski *et al.*, 1999), as reviewed in Richard's article in *Annual Review of Biochemistry* in 2000 (54). Other examples of Richard's landmark discoveries, both citation classics, were the first rational redesign of the coenzyme specificity of dihydrolipoyl dehydrogenase from the 2-oxo acid dehydrogenase complex (from NAD(H) to NADP(H)) (42) and by a similar switch, but from NADP(H) to NAD(H), in the related enzyme, glutathione reductase (38). Other significant, and also highly cited works, describe the switch of the kinetic mechanism of glutathione reductase (from the native Ping-Pong to ordered sequential (33)) and the introduction of cooperativity into the enzyme mechanism by selective mutation of amino acid sidechains remote from the active site (41). His manuscripts were based on innovative research and were beautifully penned and elegantly illustrated.

OTHER COMMITMENTS - EDITING, COMMITTEES AND THE COMMERCIALISATION OF BASIC SCIENCE

Richard's research interests were wide and varied. He listed them as 'proteins, their chemistry and interactions, and the mechanisms and pathways of biomolecular assembly; the mechanisms and assembly of enzymes and multienzyme complexes; the principles of molecular recognition at protein subunit interfaces in self-assembly, and macromolecular scaffolds; the assembly of helical viruses; multiple display of foreign peptides on bacteriophage virions and icosahedral virus-like particles; the immunological properties of displayed peptides; the structure of protein epitopes, and vaccine design'. In all these topics, Richard made significant and lasting impacts.

Richard was also enterprising and had an entrepreneurial streak. Building on his discoveries on the assembly of TMV (30), Richard extended his interests to include the filamentous bacteriophages, and showed that the single-stranded DNA is packaged end-to-end by exactly matching charges on the elongated DNA with the C-terminal ends of the coat proteins (35). These studies led to the invention of a methodology of displaying foreign peptides on the surface of the phage, by using protein engineering to insert the desired protein sequence into the N-terminal region of the P8 major coat protein (39). The displayed peptides turned out to be highly immunogenic and capable of eliciting specific antibodies (both T-helper and cytotoxic T-cells) of potential commercial importance (45). He also showed that the individual peptide epitopes adopt what appear to be their natural conformations on the surface of the virion (in collaboration with Dr Stan Opella, University of California, San Diego), using solid-state NMR spectroscopy (48, 56). Armed with his experience of cubic point group symmetry learned from his

Figure 6: A love of practical science, despite a busy career. Richard Perham in his laboratory with then PhD student David Rowitch (now Professor and Head of the Department of Paediatrics, University of Cambridge) checking the DNA sequencing gel of filamentous bacteriophage – *ca.* 1985.

studies of the 2-oxo acid dehydrogenase complexes, Richard then re-invented the icosahedral core of these assemblies to generate an alternative molecular scaffold on which to display foreign proteins (55). By contrast with the much smaller filamentous bacteriophage, these custom-designed assembles were able to accommodate protein insertions of essentially unrestricted size, whilst exhibiting virtually identical immunological properties (52, 58). Building on these advances and their so-called CamPhage technology which he patented (PCT/GB1991/001785 'Engineered bacteriophages and vaccines containing them'), Richard set up a company in 1992 with Judith Greenwood and Anne Willis, his group members with whom the original discoveries had been made. The company, named Cambridge Bacteriophage Technologies Ltd., was later sold (in 1996) to Peptide Therapeutics who used it extensively to generate gene8 libraries to isolate peptide epitopes and to raise antibodies. This brought significant financial returns to the Department of Biochemistry and the University of Cambridge.

Despite being so committed, Richard loved being in the laboratory, working with his students and postdoctoral fellows to enjoy the latest discovery or to help to unpick a problem (Figure 6). Interviewed by the journal, Nature (Nature, 2005), he commented "I always remind them (his group members) that they work with me, not for me. They'll make their own mistakes, and that's part of the learning process. It's crucial", he added, "for group leaders to learn from their students too."

Alongside his full and active career, Richard became Editor-in-Chief of the European Journal of Biochemistry (EJB) in 1998, now renamed the FEBS Journal. Even when he was travelling, postcards would arrive at the EJB/FEBS J. office from all corners of the globe. Vanessa Wilkinson who worked with Richard on the journal in Cambridge from 1999 comments that "Journal editing was paper-based in those days and Richard was frequently there, with fountain pen poised, to sign all decision letters and to discuss many other matters". His handling of rebuttal letters, we are told, was particularly impressive: Richard would send a perfectly crafted, detailed letter to authors, kindly but firmly reiterating the decision of rejection. Richard stepped down as Editor-in Chief of FEBS Journal in 2013, leaving the journal in a buoyant state and having turned it around completely in his 15 years at the helm. Richard's scientific achievements were matched with his strong commitment to serving the scientific community, not only as a senior academic at the University of Cambridge, but also in his membership of numerous national and international committees.

LATER YEARS

Richard made lifelong friends with those he met and he enjoyed lasting collaborations nationally and internationally with many, including career-long collaborators in Yale, Naples, Heidelberg and Washington, USA. From his Italian post-doc, Bruno Forcina, who worked with Richard from 1971-1973 and then became lifelong family friend, Richard developed a love of all things Italian, became a dab hand at cooking excellent spaghetti, and was often heard giving a cheery 'ciao' on parting.

The award of a prestigious Fogarty International Scholarship from 1990-1993 allowed Richard to make many trips to the NIH, where he worked, amongst others, with his long-standing collaborator Ettore Appella whom he had first met in Cambridge in 1964. Together they worked on a number of proteins over their 27-year-long partnership on peptides, their modification and display. Another facet of Richard's love of travel was that he took every opportunity to explore the world, usually with Nancy accompanying him. A sabbatical in 1972 with Professor Ted Thompson (coincidentally

Fred Sanger's first PhD student) at the University of New South Wales provided Richard, Nancy and a then one-year-old Temple the opportunity to visit Iran, India, Thailand, Singapore and Hong Kong *en route* to Australia.

Even in 'retirement' Richard continued in his passions for St John's, for art, travel, literature and for Biochemistry. With Nancy he bought a house in Cyprus: a haven with lemons growing in the garden and a study set up to inspire reading and composition. With the late Dame Professor Louise Johnson, FRS (Oxford) and Professors Wolfgang Baumeister (Martinsried, Germany) and Alasdair Steven (NIH, USA), Richard had been preparing and co-authoring for several years a major new textbook entitled "*Molecular Biology of Assemblies and Machines*" for advanced undergraduates, graduate students and scientists more generally (62). This 852 page epic describes current structural and functional knowledge of every macromolecular machine in the cell. This was not a task for the faint hearted and one that needed an encyclopaedic knowledge of Biochemistry. While he had greatly looked forward to seeing this mammoth effort in print, Richard died before it was completed (as had Louise Johnson just 30 months before). Thanks to the remaining two co-authors the book finally went to print in 2016.

Figure 7: Happy in his garden with friends. Richard enjoying his 72nd birthday at Barton Road, Cambridge.

Figure 8: Richard and Nancy Perham relaxed at home in their Barton Road garden in 2013. The photo was taken by Loanne Metcalfe from New Zealand, Nancy's childhood friend and also a biochemist.

In retirement Richard continued to hone his skills and interests in horticulture, taking enormous pride in his garden at Barton Road (Figures 7 and 8). He also amassed an impressive collection of antique clocks during his lifetime, which he maintained and wound himself. He was a dab hand at making orange and lemon marmalade, chutney, crab-apple jelly and plum jam, using produce from their gardens in Barton Road and Cyprus. Richard was also a talented landscape photographer, and he and Nancy gave calendars to friends with photographs taken on their travels (Figure 9). He was also a collector of modern art and of antique furniture and, when younger, vintage cars. He and Nancy were keen theatre and opera-goers, and Richard enthusiastically accompanied Nancy to the many plays, musicals and other dramatic events that she attended whilst serving as a judge for the

annual Olivier Awards. In his retirement Richard and Nancy continued to enjoy life to the full: visiting their daughter Temple in California, attending FEBS congress meetings without fail, whichever country it took them to, visiting their house in Cyprus (good for writing and reminiscing about naval days), and attending as many concerts, plays and operas as they could fit in.

Figure 9: One of the calendars the Perhams sent out to their numerous friends and colleagues, with photographs they had taken on their many trips overseas. Poignantly Richard died just 6 weeks into 2015.

A LIFE CUT TOO SHORT

Richard was diagnosed with cancer at New Year 2015 and died on St Valentine's Day just a few weeks later. He is survived by his wife, Nancy, their children Quentin and Temple, son-in-law Barney and grandchildren Isabella and Tristan. He left us with a profoundly greater knowledge about how enzymes function; more than 200 Perham-trained scientists who today are spread across the continents of the world, and an even greater number of Johnians who knew Richard as teacher, tutor, mentor, Master and friend.

HONOURS AND AWARDS

1965	PhD at the MRC Laboratory of Molecular Biology, University of Cambridge
1965-1966	Helen Hay Whitney Fellow in Molecular Biophysics, Yale University, USA
1967	Society of Sigma Xi, USA
1971	EMBO fellowship, Max Planck Institute for Medical Research, Heidelberg, Germany
1972	Drapers Visiting Professor, University of New South Wales, Australia
1976	ScD (Doctor of Science), University of Cambridge
1983	Member of the European Molecular Biology Organization (EMBO)
1984	Fellow of the Royal Society (FRS)
1984	CIBA Prize and Medal, Biochemical Society, UK
1986	Royal Institution for Great Britain member
1988	Fellow of the Royal Society of Arts (FRSA)
1989-1992	Fogarty International Scholar in Residence, NIH, USA
1992	Member of Academia Europaea
1993	Max Planck Research Prize
1998	Novartis Medal and Prize Biochemical Society
2000	Silver Medal Italian Biochemical Society
2005	Fellow of the Academy of Medical Sciences (FMedSci)
2005	Honorary Fellow, Darwin College, Cambridge
2008	Edman Prize International Association of Protein Structure and Proteomics (IAPSAP)

with Dr Ettore Appella
2011 Diplôme d'Honneur Federation of European Biochemical Societies

ACKNOWLEDGEMENTS

We wish to thank all who kindly contributed material that helped to create this memoir, including the many individuals who kindly provided photos, memories and stories about Richard's life and his many adventures and achievements. We especially thank Nancy Lane-Perham for her help in preparing this memoir, Temple Schauble for collecting the notes that formed the foundations of the memoir from her father before his death, and Sir Richard Aikens PC who provided insights into Richard's life in College which were published in *The Eagle* (Aikens, 2015). We are grateful, also, to Vanessa Wilkinson and her colleagues at FEBS J for memories of Richard as an Editor-in-Chief. We thank St John's College for sharing their information about Richard and his contributions to St John's. Thanks also to Professor Nicholas McCave, University of Cambridge, Peter Winter, Headmaster of Latymer Upper, 2002 – 2012, Dr Colin Diggory, Headmaster of Latymer Upper in 1991 – 2002, other Perham-ites from the RNP lab, and the many friends and colleagues of Richard's for sharing their personal stories and photos with us. Finally, we thank Helen McAllister for helping us to collate the information from Richard's friends and colleagues and for proof reading this article.

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FIGURE LEGENDS

Figure 1. The Daring Class destroyer, *HMS Defender*, on which Richard served. This photograph stood on Richard's desk in the Department of Biochemistry in Cambridge throughout his career.

Figure 2. Richard (right) with his PhD supervisor Dr Fred Sanger, FRS in the Department of Biochemistry, University of Cambridge (photo taken *ca.* 1962).

Figure 3. The St John's College May Ball Committee 1969. Richard was President of the May Ball Committee that year. Richard and Nancy Lane-Perham are 8th and 7th from the right. Other members of the committee that year included several of Richard's tutees, who became his lifelong friends, including Derek Lyon, Captain of the Cambridge rugby side and later a distinguished businessman and the (now) Lord Browne of Madingley, Lord Hennessy of Lympsfield and Sir Richard Aikens, PC.

Figure 4. Richard and Nancy Perham in *ca*. 2004 in the garden of the Master's Lodge at St John's College, Cambridge.

Figure 5. (A) Schematic diagram of the reaction mechanism of a 2-oxo acid dehydrogenase multi enzyme complex and (B) the structure of the pyruvate dehydrogenase multienzyme complex reveals a remarkable molecular machine. From (57), with permission.

Figure 6: A love of practical science, despite a busy career. Richard Perham in his laboratory with then PhD student David Rowitch (now Professor and Head of the Department of Paediatrics, University of Cambridge) checking the DNA sequencing gel of filamentous bacteriophage - *ca*. 1985.

Figure 7: Happy in his garden with friends. Richard enjoying his 72nd birthday at Barton Road.

Figure 8: Richard and Nancy Perham relaxed at home in their Barton Road garden in 2013. The photo was taken by Loanne Metcalfe from New Zealand, Nancy's childhood friend and also a biochemist.

Figure 9: One of the calendars the Perhams sent out to their numerous friends and colleagues, with photographs they had taken on their many trips overseas. Poignantly Richard died just 6 weeks into 2015.

SHORT BIOGRAPHY OF THE AUTHORS

Professor Alan Berry (AB) and Professor Sheena E. Radford, FMedSci, FRS (SER) were both Perham-ites. SER undertook her PhD in the RNP laboratory in the Department of Biochemistry in Cambridge from 1984-1987, followed by postdoctoral fellowships, including a Royal Society University Research Fellowship at the University of Oxford. She joined the University of Leeds in

Professor Alan Berry was a postdoc and Royal Society URF in the RNP laboratory from 1985-1994.

Professor Sheena E. Radford, FMedSci, FRS, was a PhD student in the RNP laboratory from 1984-1987.

1995 as lecturer and has remained there ever since. She is currently Astbury Professor of Biophysics and Director of the Astbury Centre for Structural Molecular Biology. Alan Berry joined the RNP lab as a post-doctoral researcher in 1985, holding a Royal Society University Research Fellowship in Cambridge until he left to take up a lectureship at the University of Leeds in 1994. SER and AB were privileged to enjoy a lifelong friendship with Richard and Nancy Perham, enjoying many fruitful scientific discussions, but also good food, good wine and excellent, always educational and enjoyable company. It was a particular pleasure that both Richard and Nancy were able to attend the celebrations of SER's election to the Royal Society hosted by the University of Leeds in November 2014, just a few months before Richard's death.

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