BIOGRAPHICAL MEMOIRS

Robert Joseph Paton Williams MBE. 25 February 1926 —– 21 March 2015

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Elected FRS 1972

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Robert J. P. Williams was a pioneer in advancing our understanding of the roles of chemical elements, especially the metals, in biology and in biological evolution. During the first half of his career of more than 60 years at Oxford University he studied the thermodynamic stabilities of transition-metal complexes with organic ligands, their redox properties, magnetism and colour, to understand their biological function. In parallel he collaborated with biologists and biophysicists, for example with Bert Vallee, studying zinc in proteins. Williams was the first to describe how proton gradients could be used to drive the formation of the universal biological fuel, ATP (adenosine triphosphate), a fundamental step in biological energetics. From the late 1960s he studied many proteins that use metal ions for catalysis, for electron transfer and cellular regulation. A leading figure in the establishment of the Oxford Enzyme Group, Williams developed high-field nuclear magnetic resonance (NMR) to study the mobility and dynamics of many protein structures, leading to a deeper understanding of protein function. He held the Royal Society Napier Research Professorship from 1974 until his retirement in 1991. Subsequently he published several books setting out his understanding of the roles of metal ions in biology, and their wider significance in evolution. Bob Williams's deep insights across many disciplines made him a charismatic teacher. His lateral style of thinking never failed to inspire. His legacy lies in the successful careers of his many students and collaborators worldwide and the vigour of the new discipline of bioinorganic chemistry that he helped to establish.

Early life and education

Robert Joseph Paton Williams was born in Wallasey, Cheshire, to Ernest Ivor Williams, a customs and excise officer at Liverpool, and Alice Williams (*née* Roberts), a milliner. Both

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sides of the family were involved in the use of steam to drive engines both at sea and on the railways. His father was a veteran of World War I, an experience that deeply changed him. Bob, as he was always known, was the second child of four, Greta being the first, Gerald the third and Kathleen the last.

From 1931 to 1937 Bob attended St George's School in Wallasey. In his early teens, and his last year at primary school, he suffered from diphtheria and was unable to go to school for six months. As a consequence he failed to win a place at the local school, Wallasey Grammar. Fortunately his parents could afford to pay the fees to allow him to attend the grammar school. There he began to show his academic potential. But he was also fond of sport—so much so that, at the age of 15 years, after taking his School Certificate, he dropped chemistry in favour of cricket! His father insisted that he take up the subject again. In addition to chemistry he studied physics and pure and applied mathematics for his Higher School Certificate. Mr Livesey, the chemistry teacher, was a man of wide general knowledge and enthusiasm. He was a Cambridge graduate who had become a schoolmaster after losing his post with a metallurgical company in the 1930s. An intellectual and interesting teacher, he was insistent that his pupils learn the subject in depth and detail. Mr Eggleshaw, the mathematics teacher, was also highly influential on the young Williams. He, too, was a Cambridge graduate, an all-round sportsman who had been in the cross-country running team at Cambridge. He had a wide interest in science, music and poetry and supplied his pupils with books to read on science subjects such as James Jeans on the Universe and even quantum theory. Some of the teaching, especially from Mr Eggleshaw, took place while pupils were fire-watching from the school rooftops during the German bombing raids over Liverpool in World War II. Those nights between 8 p.m. and midnight became an extension of Bob Williams's education and contributed to the development of an insatiable curiosity that was to last throughout his life.

In addition to fire-watching, schoolboys were encouraged to work during the school holidays in agricultural and forestry camps to help the war effort. There Bob learnt that certain chemicals were applied to growing crops, lime to control soil pH, and potassium phosphate. Indeed, agriculturalists already knew that various trace elements were required, such as boron for plants and cobalt licks for sheep. It occurred to him that such elements must be an essential part of biological systems. He had already read Darwin's *Voyage of the Beagle*, one of the few books owned by his father. This stimulated in him an ambition to understand the chemistry of life although, ironically, at school he was not permitted to study biology. Importantly, it led him to the proposition, rather precociously for a teenager, that if Darwin was correct, the best of all chemistry for life had already been discovered. It posed many questions: How many of the chemical elements did life depend on? What was their particular chemistry? What were their biological roles? The search for answers was to preoccupy Bob Williams for the rest of his scientific life.

Towards the end of his schooling, Bob was encouraged by the school to apply to Cambridge and Oxford. Having failed to win a place at Cambridge he travelled to Oxford to take the Scholarship Entrance Examination in December 1943. Thus he sat his first Oxford examination in the Hall of Wadham College, where he was later to become a fellow for more than 50 years. In January 1944 he learnt that he had been awarded a major scholarship, a Postmastership, at Merton College. Because he had no Latin qualification he had to pass a national examination in Latin to secure entry to Oxford. Although having less than six months to learn Latin from scratch, a challenging task, he nevertheless succeeded. Thus Bob Williams went up to Merton College in October 1944. Within six months he had forgotten all his Latin.

Oxford University

Undergraduate and postgraduate studies

Bob Williams's time at Oxford started somewhat inauspiciously. His sense of deprivation in his first term living in a large cold room in Merton College was increased by the prevailing food rationing and by college regulations. But these discomforts were little compared with his dismay at the tutorial system. The war had deprived Oxford of many of its younger teaching fellows. Thus his first chemistry tutor, although a kindly, well-meaning older man, seemed to know little of the revolution in scientific outlook after about 1920. Tutorial topics of the first term were dull, mere descriptions of laboratory facts not leading to any principles. There was little to discuss in tutorials.

At the end of his first term Bob seriously considered leaving Oxford and moving to Liverpool University, a place where he had friends. But he resolved to return to Oxford, determined to change things. He plucked up courage to request a change of tutor, explaining that he wanted to know the basic nature of chemical systems in modern times. The next term his new, younger tutors taught him the disciplines of thermodynamics and wave mechanics, how to think about colour and magnetism, about structure, chemical combination and reaction rates. Slowly he began to grasp chemistry.

The following extract from Bob's own writing describes vividly, after his initial negative impressions of Oxford, how he came to feel about the place in which he was to spend the rest of his life and to which he became devoted:

> I was intellectually awake and had become emotionally aware and alive as I had been when I was eighteen. I punted, often alone, on the River Cherwell; I cycled deep into the country, again often alone; I discovered Wytham Hill; I went to lectures on history, poetry and on Art. My spirits lifted. My overwhelming desire was now to show that I could succeed at Oxford. I became a very independent, dedicated spirit and I began to love the place. The idea that anything other than science, for example politics or administration, could be a way forward for me meant nothing then and means rather little now. I wanted to understand, not to manipulate. I wanted to find a satisfying relationship between living and dead objects—both were chemistry. The world in action was, and is, a somewhat shabby affair often in science as well as in everything else, but knowledge is not spoilt by that.

From 1946 onwards Oxford was changed further as demobilized servicemen who had started courses anything up to seven years earlier returned in numbers to Merton. The college became, instead of a continuation of public school life, a lively place of study. Although they studied seriously, the students rebelled against the rules. Suddenly undergraduates were allowed in pubs, and girls came into college. Many of these ex-servicemen had a more direct interest in the future, whereas those directly out of school had little thought for a career.

After sitting final examination papers at the end of three years, Bob Williams was given to understand that he could expect a first-class honours degree provided that he performed an outstanding fourth and final year, the Part II. This was a research year with a short thesis. He still wished to study chemical elements in biological systems but had little idea how to begin. His tutor for part of his third year was an analytical chemist, Dr Harry M. N. H. Irving, whose laboratory interest was organic reagents that could select metal ions from solution as coloured complexes in order to determine the concentrations of those metal ions in water. This topic attracted Bob. He saw in this work a possible parallel with the selective uptake of metal ions by organisms. To work with Irving was something of a risk, however, because the latter did
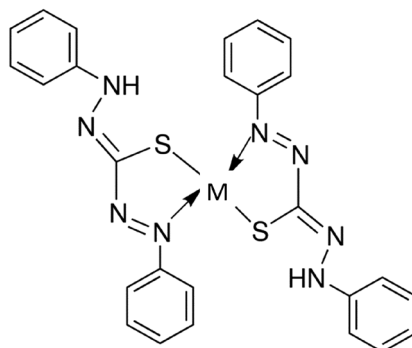
Figure 1. Metal dithizone complex, in which M can be a divalent metal ion such as the second half
of the first transition-metal series Mn(II), Fe(II), Co(II), Ni(II), Cu(II) or Zn(II).

not then have a distinguished career and had few, if any, publications. The particular work that Irving proposed to Bob was to find a way to analyse for traces of zinc in water solutions by using dithizone (figure 1), an organic molecule with two sulfur atoms that would bind zinc ions.

Bob found that the experiments were slow and laborious, involving shaking by hand for 1–30 minutes in a separating funnel containing a chloroform solution of the organic reagent, green dithizone. This reagent extracted from water a zinc dithizone complex that was red. Each experiment had to be repeated many times, because the reagent dithizone was not very stable. So Bob devised a shaking machine to enable him to leave the laboratory to play hockey while waiting for equilibrium to be established. Eventually, he was able to derive expressions for the extraction process involving the metal–ligand equilibrium constant, the acid dissociation constant of the ligand and the partition coefficient between water and chloroform. This was a considerable achievement. He could now select the best conditions for analysis. Further questions then arose: Was the reagent selective for zinc? What other metal ions lying in the same region of the Periodic Table could bind to dithizone? Bob therefore tested manganese(II), iron(II), cobalt(II), nickel(II) and copper(II). Within six months of starting work, by Easter 1948, he had established an order of the selectivity of the binding of the organic reagent dithizone for the metal ions thus:

$$Mg^{2+} < Mn^{2+} < Fe^{2+} < Co^{2+} < Ni^{2+} < Zn^{2+} < Cu^{2+} .$$
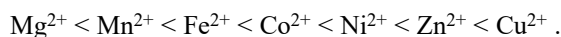
By chance Bob then came across elegant work carried out between 1940 and 1944 in Copenhagen by Jannick Bjerrum on the stability constants of ammonia and ethylenediamine complexes with metal ions in water and was immediately struck that the order of stabilities was the same as he had found, although Bjerrum himself had not noted it (Schäffer 1994). He convinced Irving that they should urgently submit a paper. It was published in *Nature* in 1948 (1)*. This won Bob a first-class honours degree and made something of a reputation for himself as well as for Irving. This order of stability was to become widely known as the Irving–Williams series and today can be found in every inorganic textbook.

Bob recounted an amusing anecdote from that initial year of research. In the front row of his first research seminar presenting his work on the Irving–Williams series sat the world-

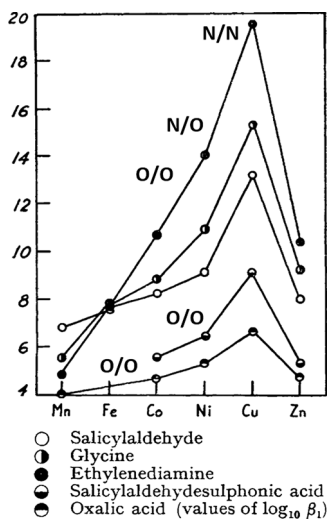* Numbers in this form refer to the bibliography at the end of the text.

Figure 2. Irving–Williams series of thermodynamic stabilities ($\log_{10} \beta_1$) of divalent transition-metal complexes with various ligands that differ in the nature of the non-metal atoms that ligate the metal ions. (Adapted from (3), with permission of the Royal Society of Chemistry.)

famous American chemist, Dr Linus Pauling (ForMemRS 1948), a hero of Bob's, who was visiting Oxford as the Eastman Professor. Throughout his talk, Bob was frequently interrupted by Pauling until eventually he told Dr Pauling that if he persisted in interrupting his talk he would not be able to continue. Pauling then listened as Bob explained that Pauling's view of complex ion stability did not fit Bob's data. After the lecture, Pauling complained to Irving that Bob had been rude to him. On learning that Bob was still an undergraduate, Pauling immediately apologized to him. This anecdote reveals that Bob, even as a young man, had remarkable self-assurance and determination.

Supported by a Harmsworth Scholarship at Merton, for a further two years Bob continued studies with Irving on the stability of complexes of transition metals, obtaining his DPhil degree in 1950. The main aim during the doctorate was further experimentation to demonstrate the generality of the Irving–Williams series (figure 2). However, before beginning his DPhil work, during the summer of 1948 Bob visited Denmark and Sweden with the help of a Merton College travel grant. In Copenhagen he finally met Jannick Bjerrum and his father Niels, one of the great names of Danish science. He greatly enjoyed the free exchange of views about science. He learned from the Bjerrums how to use glass electrodes to measure H^+ ions released when organic acids complex with metal ions. During his subsequent doctoral work, a major experimental task was to make glass electrodes and to devise a meter to measure H^+ concentrations. This allowed him to confirm that the order he had previously found was general, but with one or two exceptions of special significance. In the case of Fe(II) ions, certain strong-field ligands changed the magnetic character of the iron and increased its stability many fold. This was an early observation of the chemical significance of changes in the electronic spin states of transition-metal ions. Later his knowledge of the function of glass electrodes in which a gradient of protons across a thin (glass) membrane is driven by an electric field was to inform his discussion with Peter Mitchell (FRS 1974) about chemiosmosis. His doctoral work was included in a lengthy paper published in 1953 (3).

Figure 3. Bob Williams in the laboratory of Professor Tiselius during his research fellowship in Sweden in 1950. (Reproduced with kind permission of the family of R. J. P. Williams.)

Research fellowship

During the trip to Sweden between his Part II year and his doctoral studies, Bob visited the laboratory at Uppsala University of Professor Arne Tiselius (ForMemRS 1957), the well-known biochemist and Nobel laureate, and also met Professor Stig Claeson. Both were involved in the development of chromatographic techniques for protein separation. Bob was impressed with laboratory facilities compared with those at Oxford. He therefore returned to work in these laboratories in 1950, after his DPhil degree, with the support of a Rotary International Fellowship, to learn about protein purification (figure 3). Within the first three months he had devised a new method for the separation of molecules using a form of chromatography called gradient elution analysis (2). The method is widely used to this day in most biochemical and many chemical laboratories.

While in Sweden, Bob collected together his ideas for a review entitled 'Metal ions in biological systems'. *Chemical Society Reviews* refused to publish it because it did not contain new experimental material. However, it was published in the journal *Biological Reviews* in 1953 (4). Because many biologists but few chemists read it, several were to contact Bob, some eventually becoming collaborators and he their chemical mentor.

College fellowship and university lectureship

Towards the end of his stay in Sweden, and at the invitation of his friend Courtney Phillips, a newly elected chemistry fellow at Merton College, Oxford, Bob won a Junior Research Fellowship at Merton. He held the fellowship at Merton followed by an additional year as a lecturer at the college, and a junior demonstratorship in the Chemistry Laboratory from 1951 to 1954. Out of the blue, in 1954, Sir Cyril Hinshelwood FRS, then Oxford Professor of Chemistry, asked to see Bob. Hinshelwood was a powerful and forbidding figure, President of the Royal Society and sometime head of the Classical Society. He told Bob that three

colleges—Christ Church, Pembroke and Wadham—needed a tutor in chemistry. Each one, Bob was told, will invite you to dine. Come back again in two weeks to give me your decision. Thus in 1955 Bob Williams joined Wadham College as its only chemistry tutor. He was to remain there for the rest of his life.

Research, 1951–65

The work on the stability of metal-ion complexes continued in the Irving group, which was strengthened greatly by two outstanding students, Hazel and Francis Rossotti. Together the group systematized a great deal of analytical practice in inorganic chemistry. By his own admission Bob was not a dextrous experimentalist; rather, his strength lay in bringing together apparently disparate facts and drawing out interesting correlations. In 1953 he and Irving published a paper (3) setting out a comprehensive account of the stabilities of complexes formed between organic ligands and ions of the first series of transition elements from Mn to Zn. This work confirmed that the *sequence* was independent of the chemical nature of the ligand, although it did reveal the importance of ligand denticity. The paper also discussed the electronic factors controlling the stability of metal ions underlying this sequence in terms of Pauling's theory of ionic and covalent bonds using hybridization of d, p and s orbitals. It concluded that the interaction cannot be purely electrostatic but must involve increasing covalence along the series.

At the same time a different explanation was provided by L. E. Orgel (FRS 1962), a Fellow of Magdalen College, Oxford, in a seminal paper entitled 'The effects of crystal fields on the properties of transition metal ions' (Orgel 1952). This paper introduced the chemical world to the ideas of crystal field theory first developed by two physicists (Schlapp & Penney 1932). They had shown how, in a crystal lattice, the symmetry of the local electrostatic field, provided by a set of negative ligands, split the energies of the d orbitals of a positively charged transition-metal ion. Orgel developed this idea, describing how the symmetry of the surrounding electric field from the ligands leads to a stabilization of certain d orbitals and hence can account for the increase in the heats of hydration along the series from Mn^{2+} to Zn^{2+}. In his paper Orgel did not refer to the Irving–Williams series of metal-ion complex stability published in 1948 (1). Williams later admitted that, until Orgel explained this theory, he could not understand the physics well enough to apply it. Nevertheless, a lively debate continued over the next few years between Williams and the crystal field adherents, including Orgel and J. S. Griffiths, about the relative contributions to the stabilities from symmetry effects and covalence (Jørgensen *et al*. 1958).

From 1956 until the mid 1960s, Bob Williams carried out research in the Inorganic Chemistry Laboratory with groups of Part II and DPhil students as well as research fellows. The research was focused on the chemical properties of transition-metal complex ions then known to have roles in the capture of biological energy mainly through the transfer of electrons. Electron transfer depends on a change in oxidation state of a metal ion, so key properties include the relative stability of oxidation states in a given environment, measured by the redox potentials. With students J. Tomkinson (6) and B. James (12) Bob analysed oxidation–reduction potentials of Fe(III) and Fe(II) and of Cu(II) and Cu(I), two metals of biological importance. They showed how the covalency, size and charge of metal ions affect redox potentials. Potentials could also be controlled by the use of different donor atoms

of organic ligands or by changing the stereochemistry around the metal ions. Thus it was possible to generate a sequence of redox potentials of metal-ion complexes from high to low, matching the potentials from O_2/H_2O (+0.8 V) to H_2/H_2O (−0.45 V) used in biological cells. An additional important feature of the Fe(III)/Fe(II) complexes was the effect of a change in electron spin state that would become crucial to understanding the functions of haemoglobin and cytochromes (13).

Little was understood of the mechanism of electron transfer between metal centres in organic matrices including proteins, a process essential to respiration. So Williams began investigating electron conduction in solid matrices between metal ions and their complexes. Paul Braterman and Beverly Phipps, his first students in this area, studied the electrical conductivity of the pigment Prussian blue, a compound of iron cyanides containing two oxidation states, Fe(II) and Fe(III), a mixed-valence compound (15). They recognized that the intense colour arose in part from optical electron transitions from the Fe(II) to Fe(III) ions, so-called intervalence transitions. Hence a growing interest in the assignment of the optical spectra of transition-metal complexes led to a seminal review of the optical spectra of haemoproteins, revealing key connections between the haem absorption spectra and the electronic spin states of Fe ions (16). The paramagnetism of haemoglobin that depended on the state of oxygenation of the haems, first described by Pauling & Coryell (1936), could now be read out from its absorption spectrum. This was later to prove crucial to understanding haem–haem cooperativity in haemoglobin (16). Peter Day (FRS 1986), a Part II then DPhil student, followed Braterman, measuring photo-induced conductivity in metal phthalocyanines and investigated the origin of colour in mixed-valence Cu(I) and Cu(II) complexes (21). Day was later to build a distinguished career, independently of Bob, in the field of mixed-valence and magnetic materials.

It had been known since the 1930s that molybdenum was essential to healthy plant growth. Bob started to explore molybdenum chemistry with student Phillip Mitchell (14) using the thiocyanate ion, SCN^-, known as an ambidentate ligand, to probe binding to a metal ion through either the sulfur or the nitrogen atom. Mitchell used infrared spectroscopy to distinguish between the two modes of binding.

Vitamin B_{12} and cobalt

Vitamin B_{12}, the anti-pernicious-anaemia factor, became available for chemical study in the 1950s from large-scale bacterial cultures. With a team in Oxford, Dorothy Crowfoot Hodgkin FRS determined the molecular structure by crystallography in 1956 with material obtained from Dr Lester Smith of the Glaxo drug company (Dodson 2002).

This revealed one of the most complex structures of any of the vitamins, with several unusual chemical features. It contained a cobalt ion in the centre of a novel tetrapyrrole ring (known as corrin) that lacked one methine bridge, causing the ring to pucker. This cofactor was responsible for the red colour of the vitamin. But quite unexpected was the presence of a direct cobalt–carbon bond between the 5′ carbon of the sugar component of the 5′-deoxyadenosyl moiety (the sugar part) and the cobalt ion in the coenzyme form of vitamin B_{12} (figure 4). Bob Williams, working in the same building as Dorothy Hodgkin, became intrigued by the chemistry of this new cobalt complex. He was initially sceptical of Dorothy's evidence for a stable cobalt–carbon bond, given that all the metal-alkyls then known, such as Grignard reagents, were immediately hydrolysed on contact with water. He saw both the importance of studying the reactivity of the cobalt ion in B_{12} and the potential
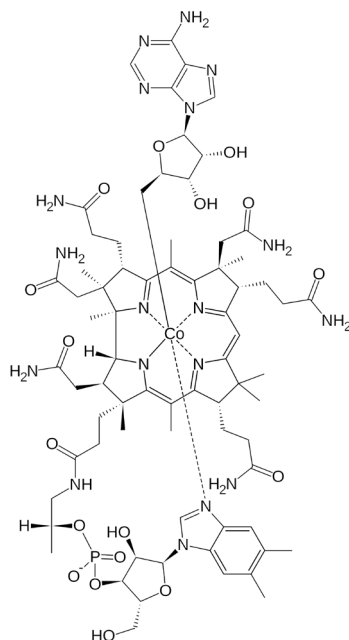
Figure 4. Structure of the coenzyme of vitamin B_{12} showing the direct bond between the central cobalt ion (Co) and the alkyl group ($-CH_2-$) of the sugar moiety. (Taken from https://commons.wikimedia.org/w/index. php?curid=2034238.)

for using optical and other spectroscopic methods. Over the years between 1961 and 1973 Bob published some 26 papers, mostly in *Journal of the Chemical Society*, on the chemistry of B_{12}; he had a strong team of co-workers led by J. M. Pratt, who obtained his DPhil in 1963, and H. A. O. Hill (FRS 1990), a research fellow from Queen's University Belfast, trained in organic chemistry.

The group analysed a wide range of the chemical properties of the vitamin, described in a comprehensive monograph by Pratt (1972). Studies included ligand substitution reactions at the cobalt site, and characterization of the cobalt ion redox states Co(I), Co(II) and Co(III). The latter were prepared by Hill, using coulometry (22). The complexes were also characterized by NMR and electron paramagnetic resonance (EPR) spectroscopies, introducing these powerful analytical techniques into the Inorganic Chemistry Laboratory (24). The group showed that vitamin B_{12} will bind and transfer the methyl group ($-CH_3$) to other metals including mercury and platinum (25). Methyl mercury ion, [CH_3-Hg^+], produced in bacteria by transfer of the methyl group from B_{12} to polluting Hg, caused poisoning in the Japanese fishing community of Minimata as it was passed up the food chain to people via fish. Studies of a dioldehydratase, a B_{12}-containing enzyme, in collaboration with M. A. Foster in an early application of EPR spectroscopy, detected radical intermediates produced during turnover implying the *homolytic* fission of the Co–C bond (27). Hill's introduction of electrochemical techniques to prepare defined oxidation states of B_{12} led to the development of methods for obtaining the direct interaction between redox proteins and a graphite electrode. From this work came a handheld electrochemical sensor of glucose concentrations in a finger-prick of blood, allowing diabetics easily to monitor blood-sugar levels quantitatively.

Early biological work

Zinc and Bert Vallee

Alongside his research at the Inorganic Chemistry Laboratory on the chemistry of transition-metal ions, Bob Williams began to study their roles in biology through correspondence, and collaboration, with biologists. He had neither the experimental expertise himself nor access to laboratories appropriately equipped for work on proteins. This work proceeded largely unknown to his research group working in the Inorganic Chemistry Laboratory. After publication of his seminal 1953 review (4) he was contacted by Bert Vallee, a medical doctor at Harvard, who was analysing the zinc content of various biological cells with the use of the colorimetric reagent dithizone, which Bob himself had studied with Irving. Vallee had observed that red cells from blood contained a relatively high concentration of iron, owing to the presence of haemoglobin, but a very low concentration of zinc, whereas white cells had little iron but surprisingly large quantities of zinc. He wondered whether the observation had wider significance, because zinc was not then known to be of importance in biology. Vallee visited Bob in Oxford in 1955 just after he had analysed the enzyme carboxypeptidase, a major hydrolytic enzyme in pancreatic digestive juices. Hans Neurath, who had first isolated the enzyme, claimed that it contained magnesium. Vallee discovered that without zinc the enzyme was catalytically inactive. Until then zinc had been known in only one other enzyme, carbonic anhydrase. For some 15 years Vallee and Williams worked together, the former with expertise in cellular medical chemistry and analysis of metal content in enzymes, and the latter with knowledge of the properties of inorganic chemicals (7). They became pioneers of a new subject area. They developed methods of exploring metal binding using spectroscopic methods and binding affinities, by substituting coloured metal ions such as cobalt for colourless zinc, known as isomorphous replacement. Bob spent 1956 at Harvard Medical School devising ways of inhibiting zinc enzymes with standard organic analytical reagents such as *o*-phenanthrolines and 8-hydroxyquinolines (8, 10).

Vallee and Williams put forward, in 1968, a general concept for the reactivity of metalloproteins, proposing that the protein imposes an unusual coordination number and geometry on metal ions to induce enhanced chemical reactivity for catalytic function or rapid electron transfer (23). This was demonstrated, for example, by atypical optical absorption and EPR spectra. They called this an 'entatic state' (figure 5), derived from entasis (from the Greek ἐντείνω), meaning tension, and defined it as 'the existence in the enzyme of an area with energy closer to that of a unimolecular transition state than to that of a conventional stable molecule thereby constituting an energised poised domain'.

For example, in the electron shuttle protein plastocyanin, the copper centre exchanges between Cu(II) and Cu(I) states. Although each Cu oxidation state prefers a distinct coordination geometry—Cu(II) is normally planar, whereas copper(I) is normally tetrahedral—in the protein the Cu site is intermediate between the two, a highly distorted tetrahedron. Because the electron transfer rate depends on the reorganization energy, the fastest rate from a Cu centre occurs at an intermediate geometry that minimizes geometrical reorganization on switching oxidation state. This they considered an entatic state. Others, including H. Eyring, D. Koshland, R. Lumry and B. G. Malmström, had earlier discussed ways in which a substrate might fit into an enzyme's binding pocket, thereby lowering the activation energy of catalysis. This was called an induced fit or the 'rack' mechanism. Vallee and Williams stressed that their view presented a property of the protein or enzyme itself and did not involve a bound substrate. This led to vigorous discussion over priority. In 2000,
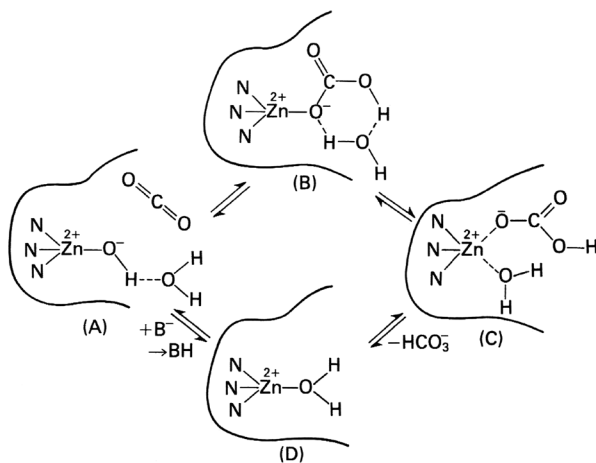
Figure 5. The use of a zinc(II) ion as a Lewis acid in the pathway of hydrolysis of carbon dioxide to give bicarbonate ion by the enzyme carbonic anhydrase. Zinc is held in an ideal coordination site or 'entatic' state. (Taken from p. 241 of (34), by permission of Oxford University Press.)

with Malmström and H. B. Gray, Bob wrote a review about the concept of the entatic state using the example of the coordination of copper in the blue redox proteins to clarify, and dispel, earlier misunderstandings (35).

Protons, ATP and Peter Mitchell

While his own laboratory was investigating electron transfer between transition-metal ions in solid complexes, Bob Williams was attending research conferences on respiration and listening to discussions about the generation of ATP, the universal biological fuel generated in chloroplasts from photons, and in mitochondria from the reduction of oxygen to water concomitant with the oxidation of sugars. The latter process, glycolysis, was known to involve phosphorylated compounds, leading to the formation of ATP. It was thought that the intermediates, precursors of ATP, were energized phosphorylated organic compounds.

Many advocates, including D. E. Green, E. C. Slater (FRS 1975), A. L. Lehninger and E. Racker, argued strongly for the existence of such phosphorylated intermediates although they were unable to identify or isolate any. However, B. Chance (ForMemRS 1981), a physicist by training, rather than searching for such intermediates, studied changes in the spectroscopic properties of mitochondria and chloroplasts during energy transduction. He found three, or possibly four, cross-over points, as he called them, during electron transfer in the spectroscopic analysis of both organelles. This observation seemed to imply that electron transfer was due to three or four chemical changes. However, Bob saw that the generation of a single intermediate, along with electron transfer, was common to all the organelle reactions. He proposed that the intermediate must be the proton and that the formation of ATP in every step entailed the migration of protons back to negative charge on organic molecules. The condensation of ADP and phosphate to ATP is driven by protons. In 1959 Bob gave the first description of this, a completely novel idea, in a chapter of the book called *The enzymes* (edited by P. D. Boyer) (9). In August 1960 he submitted a fuller version of his hypothesis, at the invitation of the editor, Professor J. F. Danielli, to the new *Journal of Theoretical Biology* (11). Williams described the way in which electron flow stimulated by light or chemistry was

converted to a proton gradient that was then used to drive ATP formation. He was confident that he had described a fundamental step in biological energetics and that he was the first to have clearly seen that energy could at some point in time and space be accumulated in a gradient of protons. He further stated that this gradient could be across a particle.

Almost immediately Williams received a letter from Dr Peter Mitchell (FRS 1974), a lecturer in Edinburgh, saying he had read Williams's articles back to 1959, and asking for an explanation of his hypothesis. An exchange of letters followed in which Williams explained several times his ideas that Mitchell then interpreted, sometimes incorrectly, and asking for further enlightenment. Only a month or two later Mitchell wrote, suddenly declaring that he had had a similar idea, one of the two forms of Williams's hypothesis. However, during his communications with Williams he did not reveal that he was writing papers or that he had in press a note containing his ideas. This note failed to acknowledge Williams's work or their mutual correspondence. Williams then discovered that Mitchell had included some of his views in an earlier conference report, again without acknowledgement. In 1978 Mitchell was awarded, on his own, the Nobel Prize in Chemistry for his theory of chemiosmosis, published in 1961, defined as ATP synthesis by means of a protein gradient across a membrane driving the condensation of phosphate to form ATP (Mitchell 1961).

These events led to an unusually protracted discussion in the literature, sharpened by the award of the Nobel prize, about the proper attribution of priority of the idea of ATP synthesis by way of proton electrochemical coupling. In the Royal Society Biographical Memoir of Peter Mitchell (Slater 1994), E. C. Slater writes: 'More surprising, however, is the lack of reference in Mitchell's 1961 paper or in subsequent reviews to an earlier proposal by Williams that H^+ ions produced by reduction of ferric iron in the cytochrome system could drive the ATPase in the direction of the synthesis of ATP.' Slater continues:

> The suggestion was first made in a review published in 1959 …. Williams elaborated his ideas in more detail in the *Journal of Theoretical Biology*, submitted on 7 August 1960 and published in January 1961. … After Williams' paper appeared, Mitchell wrote to him on 24 February asking for clarification, and this letter started an extensive correspondence (six letters from Mitchell, five from Williams, the 11 letters totalling about 7500 words [these are deposited in the Royal Society's archive]. … the exchange reads as a friendly scientific discussion, mostly concerning Williams' two already published papers, but the opening paragraph of Mitchell's letter of 19 April, written shortly after the meeting of the Biochemical Society in Oxford at which he presented the chemiosmotic theory of oxidative phosphorylation for the first time and just before submitting his article to *Nature*, introduced a new tone.

Slater concludes: 'In view of the extensive correspondence with Williams it is difficult to understand that Mitchell did not refer to his papers in his publications in 1961. Even in his Nobel Lecture, Mitchell gave no reference to Williams' 1959 or 1961 papers.' Slater opines that the 'record shows that Williams was the first to propose that protons produced by the respiratory chain could bring about the synthesis of ATP by reversal of an ATPase, although his concept of the way in which it did so differed from that of Mitchell.'

A lengthy article, published by Weber & Prebble (2006), analyses in detail the hypotheses proposed, their antecedents, and the extensive correspondence between the two parties. It also discusses the development of the dispute between them, examines the cases for priority and explores their motives. They reach the following conclusions:

> Mitchell's proposals were original (a view disputed by Williams) although it is evident that prior to the correspondence Williams had considered and rejected a proposition similar to Mitchell's

theory. However, a major cause of the dispute was the difference in disciplinary backgrounds of Mitchell, a microbial chemist and Williams, a chemist.

Despite the dissension in these lengthy debates, Williams was one of those who supported Mitchell for the 1978 Nobel Prize in Chemistry: footnote 101 in Weber & Prebble (2006) refers to a letter dated 8 January 1978 from R. J. P. Williams to the Secretary, Nobel Committee for Chemistry.

Haemoglobin and Max Perutz

In 1961, a year before receiving the Nobel Prize for solving the crystal structure of haemoglobin, Max Perutz FRS heard Bob Williams give a seminar at a conference in Lucerne, Switzerland. In that talk Bob discussed the possible mechanisms of haem–haem cooperativity in haemoglobin, proposing that when a haem moiety is oxygenated, the spin state of the central Fe(II) ion changes from high to low spin, causing the ionic radius of the Fe(II) ion to decrease. Because the hole in the centre of the haem ring is too small to accommodate the high-spin Fe(II) ion, on oxygenation the decrease in the ionic radius of the Fe(II) ion causes it to move towards the haem plane. Williams pointed out that the iron–histidine bond length would also shorten, thereby triggering protein motion and transmitting the effect to the other haem groups in the protein. In the early 1950s, studying spin-state changes in small iron chelates, Williams had seen that they could entail changes in bond lengths by at least 0.1 Å (0.01 nm) as a result of stronger binding of the low-spin Fe(II) state compared with the high-spin ion (5). This suggested to him that in proteins there would be similar change in bond lengths of Fe(II) and ligating groups on oxidation, or on binding O_2 or CO. Max and Bob met several times in both Cambridge and Oxford, when Bob gave tutorials to Max on crystal field theory and spin states. In 1970 Perutz proposed a detailed mechanism of the stereochemistry of cooperative effects in haemoglobin in which he cited R. J. P. Williams (Perutz 1970). Further details are described in the biography of Max Perutz by Georgina Ferry (Ferry 2007, pp. 219–221).

Iron–sulfur proteins

In the 1960s, with the increasing availability to biologists of EPR spectrometers, plant scientists discovered unique EPR characteristics in a brown protein isolated from spinach. No EPR signal was detectable in the oxidized form, but on addition of strong reductant and at very low sample temperatures, a strong, anisotropic EPR signal was detected centred at $g = 1.98$. Bob asked J. M. H. Thornley, an expert on EPR of metal ions in solid lattices working in the Clarendon Physics Laboratory, Oxford, for his suggestion as to the origin of this signal. Thornley proceeded to show that the signal arose from a mixed valence *pair* of high-spin ions Fe(III) with $S = \frac{5}{2}$ and Fe(II) with $S = \frac{4}{2}$ that interact anti-ferromagnetically, probably via bridging sulfur atoms, to give a resultant spin of $S = \frac{1}{2}$, consistent with the observed g values. This was the first evidence for a dimeric Fe centre in a protein and was the prototype of many family members subsequently discovered (Gibson 1966).

Cisplatin

Bob Williams had an early involvement in the discovery of the anti-tumour platinum compound cisplatin. It began with his meeting Barnett (Barney) Rosenberg, a biophysicist, in March 1963 at a conference at Stanford, California, about the bioelectrochemistry of electrons and protons. The conductivity of biological materials was at that time a means of understanding electron transfer in proteins. Soon afterwards Barney, working at Michigan

State University, East Lansing, passed high-frequency alternating currents between platinum electrodes across liquid cultures of the common gut bacterium *Escherichia coli*, to see whether the electric field would interfere with cell growth. He was inspired by seeing pictures of mitotic spindles in dividing cells that reminded him, as a physicist, of magnetic lines of force that electrical fields might disturb. The fact that the bacteria possessed no such mitotic apparatus did not deter him. The startling outcome was the observation of reversible filamentation of *E. coli* cells—that is, arrest of the cell division process—caused not directly by the electric field but by dissolution by an alternating current of some platinum from the electrodes. Barney, having no understanding of platinum chemistry, asked Bob for help in identifying the chemical state of platinum that was the causative agent of filamentation. Bob drew this intriguing problem to the attention of his student Andrew Thomson (FRS 1993), who was about to complete his DPhil studying the polarized optical spectra of crystals of platinum(II) salts. On completion of his degree in 1965, Thomson went to work with Barney. He discovered that the *cis* stereoisomers of the Pt(IV) and Pt(II) oxidation states, *cis*-[Pt(IV)(NH$_3$)$_4$Cl$_2$] and *cis*-[Pt(II)(NH$_3$)$_2$Cl$_2$], were highly effective at inhibiting cell division of *E. coli*. Barney immediately tested their efficacy on the experimental tumour sarcoma 180 in mice and showed that *cis*-[Pt(II)(NH$_3$)$_2$Cl$_2$] was highly potent in regressing the tumour. This compound, known as cisplatin, has been widely used against human cancers. It has proved particularly effective against testicular cancer, giving a 95% cure rate of a tumour that, with rising incidence, afflicts young men. (A full account of the discovery is given in Christie & Tansey (2007).) Bob Williams continued his interest in this work over several years, writing a seminal review in 1972, with Thomson and Reslova (26), setting out the chemistry significant for activity and the possible modes of binding to biomolecules, including DNA. This period of reading about cancer and chemotherapy was to stand Bob in good stead when he made his successful application in 1974 for the Royal Society Napier Research Professorship that, as part of its responsibilities, was 'to ascertain the cause of cancer, including any corresponding allied disease and the means of prevention, cure and alleviation'.

Teaching and inorganic texts

Over this period Bob Williams had been teaching undergraduate students inorganic chemistry at Wadham in face-to-face tutorials of one or two. The understanding acquired through research enabled him to begin to systematize the subject. Typically, textbooks then were highly descriptive, giving lists of chemical properties element by element. Williams strove always to find the underlying principles. Together with his friend and colleague from Merton College, Courtney Phillips, Bob undertook to write a major textbook to expound a new approach, calling it simply Inorganic Chemistry. The preface states the novel manner of its organization in the following terms: 'Broad general principles and the comparative chemistry of the elements are given pride of place over the detailed descriptive chemistry of individual compounds.' The book was developed over several years and was based on a one-year course of lectures given to Oxford undergraduates. It is said that, unusually, this lecture course retained a very high attendance throughout, and the lecturers, both of whom attended every lecture, one as observer, were rewarded with a round of applause! Two volumes were published, in 1965 and 1966, by Oxford University Press (17, 18). These books have been widely acclaimed as undoubtedly influential not only in the teaching but also in the deeper understanding of the subject. It can be seen, of course, as the exposition of the subject that

must underlie the roles of metal ions in biology. This was to be explored explicitly by Bob Williams in a series of books written later, during his retirement.

Research from 1965 onwards

A year in Harvard

The year 1965 marked a watershed in Williams's career. Up to this point he had followed two parallel threads of research. The first had been to acquire a deeper understanding of the chemistry of the metallic elements, enabling him to describe their pathways and functions in biology. Second, through collaboration with biologists he had applied his understanding of metal ion chemistry to several important biological problems. Thus his prescient realization that proton gradients could act as the carrier of free energy in respiration, his tutorials with Max Perutz on the way in which iron spin-state changes underlay haem cooperativity in haemoglobin, and his work with Vallee on zinc enzymes, all gave him the confidence that he could make progress in biology. But this way of working had become frustrating because, *inter alia*, it did not always yield the appropriate credit due to him. He must work with the proteins themselves.

During 1965–66 Bob spent a sabbatical year at Harvard Medical School. Bert Vallee had arranged a one-year Commonwealth of Massachusetts Fellowship to fund a Harvard visit. Bob took lectures in the biochemistry course for graduates reading medicine; he also read widely in the library and began a piece of research with Professor Gene Kennedy. Working with Kennedy's graduate student, Joan Lusk, on the uptake by *E. coli* of magnesium coupled to the generation of an energized proton gradient was for Bob part of his interest in proton-driven events, although the proton dependence was not followed up (19). He also worked with Warren Wacker in Vallee's laboratory. Using literature data on known levels of sodium, potassium, magnesium and calcium in blood, they published a paper in *The New England Journal of Medicine* that began for Bob a deep interest in calcium (20).

During that year at Harvard, Bob wrote to Wadham College resigning his fellowship in chemistry and requesting appointment to a fellowship in biochemistry. Wadham reluctantly agreed, but only on condition that he took a salary drop. Thus in 1966 Bob Williams became a biochemist in both teaching and research.

The Oxford Enzyme Group

From his earlier discussions with Max Perutz about haemoglobin, Bob Williams had realized that proteins must be dynamic and, indeed, might function as molecular machines. However, protein crystallography at that time gave only a static structure in the crystalline phase, not always revealing function. What of the structure in solution? Spectroscopy could provide a comparison between crystalline and solution phases and even allow the dynamics of molecular structures to be observed. The opportunity for Bob to pursue these ideas arose within the Oxford Enzyme Group, which was formally established in October 1969.

In 1966 D. C. (later Lord) Phillips (FRS 1967), who had solved the first three-dimensional structure of an enzyme, lysozyme, at the Royal Institution, London, moved to Oxford. He set up a new Laboratory of Molecular Biophysics, giving impetus to structural enzyme research at Oxford. At fortnightly dinners, Phillips brought together colleagues from several disciplines to form collaborative groups. NMR equipment, X-ray crystallography and high-speed

computation, expensive facilities, would be required for such interdisciplinary research. The Science Research Council (SRC) set up a Joint Enzyme Panel in February 1968, drawn from its Biological Sciences, Chemistry, and Chemical Engineering and Technology Committees, to examine where new enzyme research could profitably be undertaken. The panel included Sir Ewart Jones FRS as chair, D. C. Phillips and J. R. Knowles (FRS 1977), all from Oxford University. In February 1969 the panel recommended that support, 'in ways novel to the SRC', should foster research in the enzyme field, 'a highly interdisciplinary, exciting and economically important field'. In Oxford, by 1969, plans for collaborative research were already well advanced, led by R. E. (later Sir Rex) Richards FRS as chair along with D. C. Phillips, J. R. Knowles and Bob Williams, and including some dozen other participants. The three-year programme at Oxford was funded at the first meeting of the Enzyme Chemistry and Technology Committee in April 1969. The subject was the investigation of proteins and enzymes by diffraction methods and by NMR spectroscopy (Oxford Enzyme Group 1968). In the period 1970–85 the Oxford Enzyme Group became a powerful research unit that pioneered many developments in the determination of the molecular structure of proteins, especially in the rapidly developing field of NMR spectroscopy. During this period, under the leadership of Rex Richards, high-resolution Fourier-transform NMR spectroscopy increased in resolving power, with operating frequencies rising from 270 to 600 MHz. This involved collaboration with the Bruker instrument company. It also required the development of powerful magnetic fields of high uniformity generated by superconducting magnets. Oxford Instruments, the first spin-off company from that university, carried out the research and development required. Their expertise in building superconducting magnets was later to allow them to dominate the field of magnetic resonance imaging for medical diagnostics (Oxford Enzyme Group 1968).

Bob Williams applied the NMR technology to study the structures and dynamics of metalloproteins. In 1972 he was elected to the Fellowship of the Royal Society and in 1974 he was awarded the Napier Royal Society Professorship, freeing him from all teaching duties and giving him the research time required. His team developed methods to assign NMR peaks to specific residues, using the paramagnetism of endogenous metal cofactors including haem in cytochrome *c* and peroxidases and copper in cupredoxins, as well as lanthanide ions as exogenous shift and broadening reagents. Signals from aromatic residues allowed the measurement of degrees of rotational mobility on both protein surfaces and interiors, giving the first evidence of the relative motion of protein α helices. By using lysozyme as a model with pulsed NMR techniques to measure slow exchange rates, the local movements of groups and small segments were demonstrated and shown to allow the fast recognition and binding of substrate. Order–disorder transitions in response to the binding of calcium and zinc ions in calmodulin, osteocalcin and metallothionine were also studied. The motions of protein helices within domains relative to helices or sheets in other domains could act as triggers like mechanical devices. The contributions of the Williams group to our understanding of protein mobility have been summarized (30). By combining NMR and X-ray diffraction methods with theoretical approaches, views of protein structure were changed to one that incorporated dynamics ranging from conventional vibronic–rotational coupling to disordered motions characteristic of random polymers. Only the understanding of dynamics, Bob maintained, could lead to a full appreciation of function.

Over this period Bob had many outstanding collaborators, including the late Iain Campbell (FRS 1995), Raymond Dwek (FRS 1998), Chris Dobson (FRS 1996), Allen Hill (FRS 1990), Peter Sadler (FRS 2005), the late Antonio Xavier, Geoff Moore, Barry Levine, Peter Wright,

Glyn Williams, Rachel Klevit and Nigel Clayden. Early in this period Iain Campbell set about trying to solve complete protein structures in solution by NMR, but with rather limited success. Eventually procedures that allowed the complete determination of protein structures in solution were devised by the group of Kurt Wüthrich (ForMemRS 2010) working at the Eidgenössische Technische Hochschule, Zurich.

Biominerals

In the late 1970s Bob became increasingly fascinated by biological minerals. A medical condition causing him to lose balance had alerted him to the nature of tiny crystalline particles of calcium carbonate, called otoconia, present in the inner ear that sense gravity and acceleration. Bob also met Professor Derek Birchall (FRS 1982) (Kelly 1997), a visiting fellow at Wolfson College, Oxford, between 1977 and 1979. Birchall had spent his career at ICI becoming a distinguished materials scientist, an expert in alumina, silica and their colloidal and hydrated forms, inventing new cements. He drew attention to the remarkable shapes of shells as well as their mechanical properties, including tensile strength. Bob wished to understand the roles of an organic matrix in initiating crystal nucleation and regulating growth within compartments, especially biological cells. Together with two able students, Steve Mann (FRS 2003) and Carole Perry, he began a study of the biological mineralization of calcium carbonate, silica and iron oxides, among many. Initial experiments showed that it was relatively easy to precipitate and grow crystals such as silver salts inside small compartments including liposomes. Jerry Skarnulis modified an electron microscope for these studies. In addition to the spatial resolution, new developments in the technique gave the ability to track metal ions and anions by using their characteristic X-ray fluorescence (28).

Bob came across the beautiful work of the naturalist Ernst Haeckel, who by 1887 had identified and illustrated more than 150 new protozoa, *Radiolaria*, that produce highly symmetrical skeletons 0.1–0.2 mm in diameter. Bob's group investigated *Acantharia*, organisms that produce exoskeletons made of strontium sulfate spicules, and the green algae, desmids, that use barium sulfate. The exoskeleton of *Acantharia* is made of 20 spines, each a single crystal of strontium sulfate, that radiate from a single point towards the surface of a sphere (figure 6). The directions of the spines are true crystallographic planes (31).

Silicon, one of the commonest elements on Earth, is little used in animals or broad-leaved plants, but grasses use silica not only to strengthen structures but also to act as a defence against both biomechanical and biochemical predation. Williams and Perry studied the fine hairs on the leaves of stinging nettle, which are miniature tubes terminated by small balls of amorphous silica. When the hair enters the skin, the ball breaks off and a liquid poison is squirted into the body (29). With typical insight Bob reached the conclusion that plants use silica as a building material to harden their structures because the sap of a plant has an acid pH of about 5 compared with that of circulating fluids in animals, which is about 7.5. At the low pH in sap, calcium carbonates (shell) and phosphates (bone) are too soluble to precipitate, whereas the solubility of silica is independent of pH over this range.

RETIREMENT AND THE WRITING OF BOOKS

Bob retired in 1991, relinquishing his Royal Society Napier Research Professorship and ceasing laboratory-based research. He devoted himself to writing a series of major books
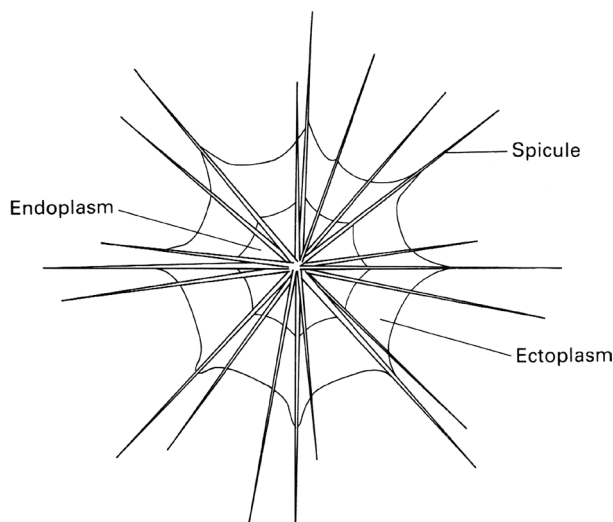
Figure 6. The skeleton of the unicellular, eukaryotic, diatom *Acantharia* consisting of 20 spicules, each a single crystal of strontium sulfate ($SrSO_4$). (Taken from p. 477 of (32), by permission of Oxford University Press.)

setting out the understanding of the roles of metal ions in biology that he had acquired over the preceding 40 years. Five were co-authored with his friend John Fraústo da Silva, who had originally proposed that they should write a book together on biological inorganic chemistry. They had met in 1955 when John studied in Oxford with Irving. John became Professor of Chemistry in Lisbon, later sending some of his finest pupils to Oxford to work with Bob. His contributions to the books were clarification, critical evaluation, and correction. Bob said he could not have written them on his own.

The aims of the first book, *The biological chemistry of the elements* (32), published in 1991, were to

> describe the functional value of the chemical elements in living organisms, free or combined with the actual biological molecules *in vivo*, the reasons for the selection of such elements, the processes of their uptake, transport and final localization in cells, the regulation of these processes and the control of their reactions in a very complex holistic system which includes the interactions with their environments.

A second, updated, edition was published in 2001.

This volume, however, did not touch upon the roles of the availability and chemistry of the elements in evolution. Three further books discussed this intriguing aspect. The first, with John Fraústo da Silva in 1996, was called *The natural selection of the chemical elements* (34), and in 2006 appeared *The chemistry of evolution: the development of our ecosystem* (36), again co-authored with John. These dealt with the principles underlying the selection of chemical elements for their functional value to a biological organism and the relationship to Darwinian selection. A discussion of the possible consequences of man's industrial mobilization of elements not hitherto exposed to biology raised the question of whether mankind is entering a new stage of natural selection.

The title of Bob's book published in 2012 with R. E. M. Rickaby, Professor of Biogeochemistry, Department of Earth Sciences, Oxford University, was *Evolution's destiny:*

co-evolving chemistry of the environment and life (37). Only recently has the Earth's geochemical record become detailed enough to be placed alongside the biological trees of evolution. The matching of timescales has led to many new insights into the chemical influences on the course of evolution. Williams and Rickaby examine the development of the chemistry of an ecosystem that took place alongside evolution as set out by Darwin, a random, competitive, selection process. The authors show that a major feature of life and its evolution is a changing availability and utilization of selected inorganic chemical elements from their environment into cells. For example, one particular problem examined is the changing role of inorganic elements in the evolution of an ecosystem. Production of oxygen, a waste product of photosynthesizing cells, relatively rapidly initiated major changes in inorganic chemistry such as the oxidation of water-soluble iron, $Fe(II)$, to insoluble oxides of iron, $Fe(III)$, making this element less available to cells. This contrasts with the increasing biological availability of potentially poisonous copper, as soluble $Cu(II)$, from insoluble $Cu(I)$, copper sulfides. This book, his last major publication, has the broad intellectual sweep typical of Bob's work. It completes his scientific journey seeking to understand questions that had intrigued him as a schoolboy.

LIFE AT WADHAM COLLEGE

Historically, Wadham College, founded in 1614, had not been particularly distinguished except for early meetings of a group that was to lay the foundations of the Royal Society. The group met at Wadham under the leadership of Bishop Wilkins, Warden of Wadham, and sometime later Bishop of Chester, who became Founding Secretary of the Royal Society at Gresham College, London. Bob Williams took up his tutorial fellowship at Wadham in 1954, when the college was led by the highly successful, bluff Warden, Sir Maurice Bowra. The college was determined to improve itself academically. Wadham then, and still today, was different from many Oxford colleges in that it recruited most of its students from grammar schools. This was a policy born of necessity, because the college was not richly endowed and therefore did not have the history of connections with public schools as did some other Oxford colleges. The opportunity for Wadham came at the end of World War II, when the government decided that higher education should be free. Hence students coming from grammar schools as well as those returning from the war provided the opportunity for Wadham to increase student recruitment and expand. Bowra's leadership and forceful personality created among the fellows an *esprit de corps* that rapidly developed the college. Bob firmly believed success to be a matter of selecting young people carefully, guiding them and giving much time and effort to teaching them. Wadham now has some 300 undergraduates, nearly all paid for by the government. The physics fellow, Tom Keeley, a close associate of Lord Lindemann FRS, was the first science fellow of the modern era. Bob initially was the only chemistry fellow. Because more help was needed from fellows capable of tutorial teaching of organic and physical chemistries as well as biochemistry, Bob raised funds, including the Tate & Lyle Bequest. This enabled Jeremy Knowles to be appointed as the first tutor in organic chemistry. Later a fellow in physical chemistry was appointed, and in 1967 Bob himself became tutor in biochemistry. Bob was always a vigorous energizer, persuading the college to expand, to appoint new fellows and research fellows, and to build new buildings. He had no need of formal positions of authority.

Figure 7. Bob making a point, 1985. (Reproduced with kind permission of
the family of R. J. P. Williams.) (Online version in colour.)

The man

Bob Williams was a brilliant scientist who developed considerably our understanding of the chemistry that underlies biology. As a teenager he had read about Darwin's theory of evolution, selection by the survival of the fittest, and realized that the chemistry of the elements themselves must also provide a critical restraint on the evolution of species. He determined to explore how this chemistry might play such a role. His quest for that biological chemistry was to underpin all the science he undertook over 65 years until the day he died. His work, carried out from his base at Oxford University, not only inspired several generations of able research students and fellows, many of whom went on to have successful careers developing the ideas seeded by Bob; he also pioneered the establishment of a new subject known, somewhat paradoxically, as bioinorganic chemistry.

Bob's way of working was unusual. He had little direct involvement in experiments himself. Bob said he actually disliked laboratories, finding them uninspiring places. He preferred to think on his own or with scientists from outside his discipline. Because the research canvas Bob had chosen was wide, he needed to gather knowledge from different areas of chemistry and biological science to find links. His students would jokingly complain about his experimental incompetence. They remarked that 'each day brings a different idea', which had to be converted into an experiment and carried out. A friend once said, 'I have never heard you lecture on the same topic twice.' This was not wholly true but Bob did move quickly from problem to problem. His great strength was to be able to assimilate knowledge widely, thereby gaining deep insights and drawing original conclusions. This method of pursuing science, in multidisciplinary research teams, has become commonplace today.

Bob was vigorous and forthright, but always open and honest, in debating and advocating his ideas (figure 7). He was not slow to challenge when he thought he saw error or

Figure 8. Jim Fraser, Tom Wess, Clive Fell and Bob Williams by Pen-Y-Gwryd, the climber's hotel at the foot of Snowdon. (Reproduced with kind permission of the family of R. J. P. Williams.) (Online version in colour.)

misunderstanding. This strongly competitive spirit sometimes led to friction with other scientists, as has been described earlier. He was often in correspondence with scientists. His ideas and teaching helped many to win accolades, some of whom did not always acknowledge their debt to him. This affronted his strong sense of justice and decent behaviour.

Throughout his career he avoided committee work, claiming he was temperamentally unsuited. He was impatient of such meetings although he did occasionally intervene, usually forcefully, when he foresaw that a bad decision was about to be made. He did make exceptions: he agreed to become President of the Chemistry Section of the British Association for the Advancement of Science in 1985–86 and President of the Dalton Division of the Royal Society of Chemistry between 1991 and 1993.

His mastery of chemistry and deep insights across disciplines made him a charismatic and inspiring teacher of undergraduates and research students. One of Bob's many successful students has said, 'Bob's style of lateral thinking, both as tutor and as research supervisor, profoundly influenced my own approach to looking for novel insights.' Research lectures in many countries never failed to inspire. The books he has left illustrate those qualities.

Bob balanced his vigorous and busy life in science with a happy and supportive family life and a passion for the isolation and beauty of the countryside. Wytham Woods, on a hill just outside Oxford, became a favourite place to escape from Oxford itself. Frequently, from his undergraduate days onwards, Bob went wandering alone on the more remote trails. As a boy he was introduced to walking in north Wales by his parents. His mathematics teacher at school, Mr Eggleshaw, taught him to climb rocks in the mountains of Wales. This remained his favourite landscape for the rest of his life.

Every year in May he visited Snowdonia with three lifelong friends, Jim Fraser, Tom Wess and Clive Fell: a vicar, the export manager of a large company, and a music teacher (figure 8). They always stayed in a climber's hotel, the Pen-Y-Gwryd, at the foot of Snowdon. In the evenings after a long day tramping the hills a few drinks were shared, before putting the world to rights. Bob walked in many mountainous regions of the globe, sometimes as a side trip after attending a conference.

Figure 9. Jelly and Bob with sons, John and Tim in 1958.
(Reproduced with kind permission of the family of R. J. P. Williams)

Bob's strong sense of justice was demonstrated if he felt that a public organization was making bad decisions. He was more than willing to write to the papers to highlight nepotism or official lies. For example, during the miners' strike of the Thatcher era, he wrote to both the Coal Board and the government, trying to persuade them that they were not able to justify their decision to close the pits on logical grounds. He was also strongly committed to the local neighbourhood of north Oxford, where he lived. He cajoled Oxford City Council into converting a large area of derelict land, then used as a rubbish tip, into parkland for all members of the public. For this he received an MBE from The Queen, his proudest achievement of all.

Marriage and family

During his stay in Uppsala in 1950 as a Rotary Fellow, Bob met Jelly Büchli, from Groningen, Holland, a vivacious student studying languages. They took long cycle rides together around the countryside of Sweden and even went skiing in the far north. On one occasion when they were cycling home with some eggs in the front basket, some of the eggs fell out and broke on the road. Not wishing to waste money, Jelly leapt off her bike, scooped up the eggs, told him to open his mouth and poured the broken eggs in. Around Easter time they became engaged. Jelly was against rings and 'wasting money on rubbish', so Bob bought her a small brass curtain ring to seal their match. They were married in July 1952. Jelly soon settled into Oxford life. She read English language and literature at St Hilda's College between 1952 and 1955. However, her final exams were interrupted by the birth of their first son, Tim. He was followed two years later by John (figure 9), who became a successful museum designer. Tim qualified as a clinical psychologist and married Nicki, a family doctor. They have three children, Nuala, Kirsten and Jack.

Bob was a devoted family man, taking great pleasure in spending time with his sons and the grandchildren (figure 10). His wife and sons accompanied him to the USA for his sabbatical

Figure 10. Bob with his granddaughters. (Reproduced with kind permission
of the family of R. J. P. Williams) (Online version in colour.)

leave at Harvard in 1967. They drove to Montreal to visit Expo 67 that summer. He took them to the mountains of Wales, Cadair Idris being a particular favourite. When the grandchildren arrived, Bob found new roles including, at Christmas, as a designer and constructor of large cardboard structures in which presents were hidden. This included a 6-foot-long Christmas cracker hung over the stairs at home and a 20-foot-long cardboard Eurotunnel, which had to be negotiated to find the presents. He devised a variety of imaginative pursuits to keep them occupied on their frequent babysitting visits.

His family claim that Bob's special gifts have been passed to his descendants. The art of bodging an unattractive but effective repair is known as a 'Williams job', said to be eagerly practised even by the grandchildren. Another is the unerring ability to find boggy or wet ground on any, and every, walk even after months of drought.

When the children had left home, Bob and Jelly travelled widely together (figure 11), sometimes on side trips from a conference. Throughout their long marriage Jelly was a rock of stability for Bob from the vicissitudes of science.

Not only was Bob an inveterate letter writer in his professional life but he also left behind a letter to his family. It was first written before his heart bypass in 1995, but re-dated as each health crisis came and went.

Dearest Jelly and family,

I just want to write a few words in case I do not escape the operation. I have had a wonderful life and nobody gave more to me than you, especially Jelly but I think about Tim and John, Nicki,

Figure 11. Jelly and Bob in Kazakhstan in 1984. (Reproduced with kind permission of the family of R. J. P. Williams.) (Online version in colour.)

Nuala, Kirsten (how do you spell it) and Jack. I have no sense that I have missed out on anything. Thank you.

I leave only one instruction—do not let yourselves do anything but live as you wish for your own fulfilment. I do not want to be a shadow in the background but rather a spirit joining you in the same joys and happiness we have had together.

Bob Williams died in the John Radcliffe hospital in Oxford on 21 March 2015.

AWARDS, HONOURS AND VISITING APPOINTMENTS

Civic honour

2010   MBE

Royal Society honours

1974–91 Napier Research Professor
1979   Hughes Medal
1995   Royal Medal

Membership of foreign academies

1981   Lisbon Academy of Science
        Royal Society of Science, Liège
1984   Royal Swedish Academy of Science
1989   Czechoslovakian Academy of Science
1993   Member of Academia Europaea

Academic medals

1970	Tilden Medal, Chemical Society
1972	Keilin Medal, Biochemical Society
1979	Liversidge Medal, Royal Society of Chemistry
1980	Claire Brylants Medal, University of Louvain
1985	Sir Hans Krebs Medal, European Biochemical Society
1986	Linderstrom-Lang Medal, Copenhagen
1987	Sigillum Magnum Medal, University of Bologna
1989	Sir Frederick Gowland Hopkins Medal, Biochemical Society
1998	Heyrovsky Medal, International Union of Biochemistry
2002	Longstaff Medal, Royal Society of Chemistry

Honorary doctorates

1980	University of Liège
1985	University of Leicester
1992	University of East Anglia
1993	University of Keele
1996	University of Lisbon

Appointments

1985–86	President, Chemistry Section of British Association for the Advancement of Science
1991–93	President, Dalton Division of the Royal Society of Chemistry

Acknowledgements

Author profiles

H. A. O. Hill

Photograph by Veronika Vernier

H. Allen O. Hill studied Chemistry at Queen's University Belfast and, after his PhD with Reg Bacon, moved to Oxford, where he worked with Bob Williams. He was appointed a fellow of Queen's College, Oxford, in 1965. Hill and Williams investigated the chemistry of vitamin B_{12}, leading to a study of the enzyme dioldehydrase. Although involved in high-field NMR spectroscopy of biomolecules, Hill initiated attempts to obtain electrochemistry directly between electrodes and redox proteins. While seeking to obtain direct electrochemistry with glucose oxidase, Hill's team discovered that ferrocene was a highly effective mediator. Thus

the glucose electrode was born that became the basis of a highly successful sensor that is widely used by diabetic patients. Subsequently he explored the scanning probe microscopy of proteins on surfaces, seeking structure–function relationships. Hill was elected to the Fellowship of the Royal Society in 1990, and was awarded the Mullard Medal in 1993 (with M. J. Green and A. E. G. Cass) and the Royal Medal in 2010.

A. J. Thomson

Between 1959 and 1965 Andrew Thomson was taught chemistry at Wadham College, Oxford, by R. J. P. Williams. After his doctorate he worked with Barnett Rosenberg for two years in the Biophysics Department at Michigan State University, where he discovered a platinum complex that inhibited the cell division of *Escherichia coli*. Known as cisplatin, this compound was the first metal-based anti-tumour agent to be widely deployed; it proved especially effective against testicular cancer. Thomson spent his independent research career at the School of Chemical Sciences, University of East Anglia (UEA), Norwich, where he served as Head of School and then Dean of Science. He developed the application of magnetic circular dichroism spectroscopy, particularly at variable fields and temperatures, to probe the structures of metal centres, such as haem and iron–sulfur clusters, in large multicentred proteins. With the late Colin Greenwood from the School of Biology, UEA, he founded a highly successful inter-disciplinary unit, the Centre for Metalloprotein Spectroscopy and Biology, that attracted many young, and successful, faculty members. He was elected to the Fellowship of the Royal Society in 1993 and awarded the OBE in 2008.

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