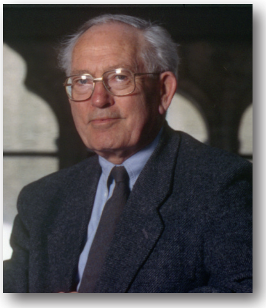
Robert Joseph Paton Williams, MBE, FRS 1926–2015



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Professor Bob Williams pioneered our understanding of the roles of metal ions in biology. When he began his research in the late 1940s, little was known of the biochemistry of the chemical elements apart from carbon, hydrogen, nitrogen, oxygen, sulfur and phosphorus plus iron as a key to the function of haemoglobin. The biological requirements, let alone functions, of metallic elements such as manganese, cobalt, nickel, zinc or molybdenum were virtually unknown. As a teenager during the war, working in agricultural camps, he became curious about the functions of elements in biology, noting that the addition of potassium phosphate and trace metals such as iron and molybdenum helped ensure healthy plant growth. Over some 65 years at Oxford University, he explored the biological roles of the elements including calcium, iron, cobalt, copper and zinc from his perspective as a chemist. His research and innovative writings led to the emergence of a new discipline, biological inorganic chemistry.

Born on 25 February 1926, Bob spent his teenage years at Wallasey Grammar School. He was encouraged to enter for Oxford University and duly won a place at Merton College to study chemistry. As an undergraduate, he undertook a research project with H.M.N. Irving using organic colorimetric reagents to quantify trace metal ions. Having measured the thermodynamic stabilities of various organic ligands for a range of metal ions he established an order of transition metal stability constants known as the Irving–Williams series, an important indicator of the ways proteins might select and interact with metals. After obtaining his doctorate in 1950, a Rotary International Fellowship took him to Sweden to work with Arne Tiselius, the Nobel laureate who devised the separation of proteins by electrophoresis. Bob himself invented a method of gradient elution chromatography for protein isolation.

During that period he wrote a seminal article 'Metal ions in biological systems' published in 1953 in *Biological Reviews*. The following year, Bob was elected to a permanent Lectureship in Chemistry at Oxford and a Fellowship at Wadham College. Together with the ebullient Warden Sir Maurice Bowra and young colleagues, he helped transform Wadham's academic standing.

Over the next decade understanding of the chemistry of the transition metals underwent a revolution, largely due to L.E. Orgel who was aware of crystal field theory formulated in the 1930s by a German physicist H. Bethe. Orgel showed how crystal field theory gave an understanding of the roles that partially filled shells of d-orbitals of metal ions play in governing electron spin states, optical and magnetic properties, thermodynamic stabilities and the kinetics of ligand exchange. Williams made important contributions to this development, choosing topics to enable him to understand the properties that he considered would underlie the selection and function of these ions in biology. For example, using model complexes of iron he showed relationships between Fe(II) and Fe(III) spin states and redox potentials, which is key to understanding the function of cytochromes and chains of electron carriers. A definitive review in *Advances in Chemical Physics* in 1964 [volume 7, pages 359–407] demonstrated the relationship between the optical and magnetic characteristics of the haem group. He was the first to account for the intense blue colour of the copper proteins, cupredoxins, and he brought together EPR physicists from the Clarendon Laboratory, and the botanists who had purified deep brown ferredoxins to provide the first evidence of the sulphide bridged iron dimer, [Fe_2S_2].

Although not yet working on proteins in his own laboratory, he was in close touch with biochemists. When Max Perutz published the crystal structure of haemoglobin he discussed with Bob Williams the likely significance of the spin state change from high to low at the haem Fe(II) on oxygenation. Bob pointed out that this spin transition would decrease the ionic radius of Fe(II) causing it to drop into the haem ring in turn changing tension on the Fe-histidine bond, a trigger of haem–haem co-operativity. Bob Williams had an interest in the chemical processes of respiration and of the roles of chains of catalysts within mitochondrial membranes. Why does biology employ chains of catalysts with functional groups reducing oxygen at one end and, at the other, oxidizing hydrogen atoms? Within his own laboratory his students were investigating conductivity in organic materials and intensely coloured so-called, mixed valence compounds, in order to understand short- and long-range electron transfer. In 1960, he wrote an imaginative paper in the *Journal of Theoretical Biology* [volume 1, pages 1–13] setting out ways of converting the energy of reaction between oxygen and hydrogen at long range into localized proton gradients and connecting that to ATP production. These ideas contrasted sharply with those of biochemists then hunting for so-called high energy phosphorylated intermediates. A lengthy correspondence ensued between Peter Mitchell and Williams debating these ideas. Mitchell was subsequently awarded the Nobel Prize for Chemistry for the chemi-osmotic hypothesis of proton coupling.

A long and fruitful collaboration began in the mid-1950s with Bert Vallee, at Harvard Medical School, who had analysed zinc in red and white blood cells. After the isolation of the zinc containing enzyme, carboxypeptidase, the replacement of Zn(II) with the spectroscopic probe Co(II) ion, the first example of isomorphous replacement in proteins, enabled the chemistry of the metal site to be explored. In Oxford, Williams and his group investigated the chemistry of vitamin B_{12} whose structure had been determined by his colleague Dorothy Hodgkin. He explored the chemistry at the cobalt ion within the cobalamin ring particularly the formation and stability of the then unique cobalt–carbon bond present in the co-enzyme.

He now turned his research to the structures of metalloproteins themselves with the establishment in 1970 of the Oxford Enzyme Group. This brought together David Phillips from protein crystallography and Rex Richards in the development of high field NMR spectroscopy of proteins. It had become apparent to Bob that NMR offered the possibility of studying the structures of proteins in the solution phase hence giving access to the dynamics of proteins critical to function, but not available from protein crystallography. He used novel NMR methods to study electron transfer proteins, kinases, cytochromes, iron and calcium proteins seeking connections between mechanical movement and biological function. For example, he showed that certain proteins underwent major shape changes on binding calcium that triggered a cascade of chemical events within a biological cell. He went on to propose for several metal proteins a more general connection between their mechanical movement and biological function. Aware that metal ions of rare earth elements behave as powerful magnets Williams and his Portuguese student, Antonio Xavier, devised ways to bind these ions to proteins, the strong local magnetic fields spreading the magnetic resonances giving much finer detail. This work now finds application in the use of contrast agents for whole body NMR imaging in medicine. The Oxford Enzyme Group, together with the local company Oxford Instruments developing high field magnets, became a world leading centre for NMR of proteins.

In the latter part of his career, Bob turned to study mechanisms of biomineralization. Crystallites of minerals embedded in an organic polymeric matrix, provide materials of high mechanical strength or great hardness invaluable for biological scaffolding, grazing and cutting. With Steve Mann and Carole Perry, Williams elucidated ways in which these complex materials can be assembled in biological organisms.

A gifted man and true polymath, Bob ranged across many fields always inspired by the chemistry of life and the roles of metals. He readily admitted that he was not a gifted experimentalist himself, indeed was frustrated by the slowness of experimental proof. He was generous in sharing his insights and in allowing his students to go on to take these ideas forward into their own careers. With his quick mind and fertile imagination he always sought to connect facts to discover the larger picture and underlying principles. This made him an inspirational teacher. His knowledge of chemistry, biochemistry and geochemistry was encyclopaedic and always evident in his tutorials and lectures. The lectures he gave together with his friend and colleague from Merton College, Courtney Phillips, were remarkably popular, full attendance being maintained until the end, an unusual occurrence in those days, and received enthusiastic applause. These lectures provided the foundation of an original and influential textbook, *Inorganic Chemistry*.

Throughout his career, Bob wrote over 800 papers and reviews. He also published a number of original books setting out his insights into inorganic chemistry, and the inorganic chemistry of life, with his former student Frausto da Silva, setting out the factors underlying the selection of elements by biology. His last book *Evolution's Destiny* written with geochemist R.E.M. Rickaby, explores the geological and environmental chemical changes of the Earth over millennia describing the involvement of the elements as well as selection in the evolution of organisms.

His success led to the award of many honours. Elected a Fellow of the Royal Society at the age of 46, he was awarded their Hughes Medal (1979), the Bakerian Lecture (1981), and the Royal Medal (1995) and in 1972 was awarded the Naperian Royal Society Research Fellowship. He also won medals and awards from the Royal Society of Chemistry, the Biochemical Society (The Sir Frederick Gowland Hopkins Memorial Lecture and The Keilin Memorial Lecture), and the International Biochemical Society. He served as President of the Dalton Division of the Royal Society of Chemistry. He held honorary degrees from five universities and was elected a Foreign Member of the Swedish, Portuguese, Czechoslovakian and Belgian Science Academies.

During his year in Sweden, Bob met Jelly Büchli, who was born in The Netherlands; they married in 1953. He was devoted to Jelly, his two sons, Timothy and John, and their three grandchildren. Bob was awarded the MBE for leading the development of public parkland alongside the River Cherwell, Oxford.

Failing health had recently led Jelly and Bob to move from their family house in North Oxford to a nearby apartment where in his favourite chair with piles of papers on one side and a pile of reference chemistry books on the other he continued to write. Bob Williams died in the John Radcliffe Hospital after a short illness on 21 March 2015. We shall cherish the memory of a remarkable scientist and inspirational teacher. ■

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This article draws on an interview by H.A.O. Hill with Robert J.P. Williams published in *Coordination Chemistry Reviews* (1993) **122**, 1–39

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