J Biol Inorg Chem (2016) 21:1–3
DOI 10.1007/s00775-015-1328-5

INTRODUCTION

The science of RJP Williams

Andrew J. Thomson[1]

Received: 22 December 2015 / Accepted: 23 December 2015 / Published online: 13 January 2016

Professor Robert Joseph Paton Williams, known to all as Bob, was a pioneer in advancing our understanding of the roles of the chemical elements, particularly metals, in life and evolution (Fig. 1). When he began his research career in the late 1940s it was widely thought that only six or seven of the 90 or so chemical elements were of importance in biology. Over some 65 years at Oxford University, Bob, with his research teams, explored the biological roles from a chemist's perspective of many other elements, especially metals such as calcium, molybdenum, iron, cobalt, copper, and zinc. His research led to the emergence of a new discipline, called, somewhat paradoxically, Biological Inorganic Chemistry.

It was my great good fortune, in 1958, at the age of 18 years, to be interviewed at Wadham College, Oxford, by Dr RJP Williams for a place to read chemistry. Subsequently he taught me both as an undergraduate and then as his DPhil student in the Inorganic Chemistry Laboratory, Oxford University. Bob was an inspirational teacher. His knowledge of chemistry was encyclopaedic. He always sought to connect facts to uncover underlying principles. He had a quick mind and fertile imagination. After my doctoral studies he suggested that I might go to the USA to work with a biophysicist, Barnett Rosenberg at Michigan State University, who had discovered that platinum salts could cause inhibition of cell division in certain bacteria. The outcome was the identification of an active species, now known as cis-Platin, a very effective anti-tumour drug. Happily my scientific interactions with Bob continued throughout the rest of my career at the University of East Anglia, Norwich. I owe him a huge debt.

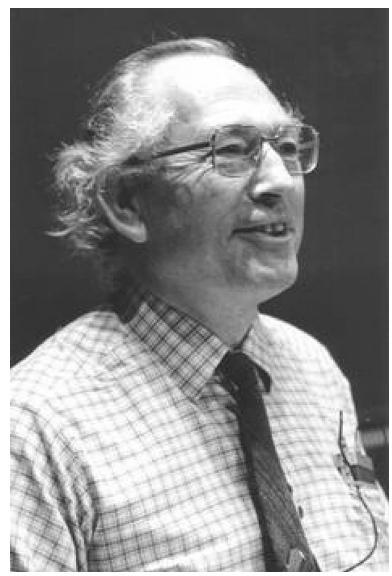

Fig. 1 Bob Williams

Bob's inspiration in science came in his teenage years from reading Darwin's "Voyage of the Beagle". This kindled a deep interest in biology. He also noticed, when at summer camps during the Second World War, the practice in agriculture of adding certain inorganic mineral chemicals to improve crop yields. Thus, rather precociously perhaps for a teenager, he formed the following view. Alongside Darwin's proposal of the evolution of the fittest he suggested that the course of evolution must depend on a

This article is based on a talk given by AJ Thomson at a Memorial Service for Professor RJP Williams on Saturday 24th October, 2015, in Wadham College Chapel, Oxford.

✉ Andrew J. Thomson
a.thomson@uea.ac.uk

[1] School of Chemistry, University of East Anglia, Norwich Research Park, Norwich NR6 7TJ, UK

chemistry of organisms that concerned mineral elements, as well as organic chemicals, a chemical fitness. This idea was to provide a leitmotif for his research throughout his entire career.

Bob won a scholarship to read chemistry at Merton College, Oxford, in 1944. For his undergraduate research year he chose to work with an analytical chemist, Dr Harry MN Irving. Irving was interested in the organic reagent dithizone that extracts metal ion complexes into organic solvents. Bob used this method to establish an order of the relative stabilities of metal–organic complexes along the latter half of the transition series manganese, iron, cobalt, nickel, copper and zinc. His first paper was published in Nature in 1948 describing the Irving–Williams series, as it became widely known [1]. Bob concluded that the same stability order had to apply in biology if it was general. Thus, he saw a parallel with the selective uptake of metal ions by organisms living under the pressure of the environment.

Bob has recounted an amusing anecdote from that year. He was giving his first research seminar and in the front row sat Dr Linus Pauling, a hero of Bob's who happened to be visiting Oxford. Throughout his talk Bob was frequently interrupted by Pauling until eventually Bob told Dr Pauling that if he persisted in interrupting his talk he would not be able to continue. Pauling listened while Bob explained that Pauling's view of complex ion stability did not fit his 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 apologised to him. This story reveals a young man of remarkable self-assurance and determination.

After a period as a Research Fellow in Uppsala, Sweden, with the Nobel Laureate Professor Tiselius developing a form of protein chromatography he returned to Oxford to a research fellowship at Merton College. He won a permanent post as a teaching Fellow at Wadham College, and a lecturer in the Inorganic Chemistry Laboratory. Over the next 15 years with his research group of undergraduate and doctoral students plus research fellows he investigated the chemical, catalytic and electronic properties of many metal ion complexes. He chose to study those with properties that might underlie a possible biological role. This was a period when the ideas of crystal field theory were first being introduced by L.E. Orgel, J.S. Griffith and others to rationalise the optical and magnetic properties of transition metal ions as well as their thermodynamic and kinetic stabilities. Bob contributed papers on the redox potentials of iron and copper, on optical and magnetic properties of iron, molybdenum and copper complexes, on electron transfer reactions, on the chemistry and physics of mixed valence compounds and on small molecule binding to various iron complexes and vitamin B12 (cobalt) complexes. From his laboratory during this period emerged students who were to become well known scientists including P. Braterman, P. Day, H.A.O. Hill, B.R. James, and J.M. Pratt.

Throughout this time, and often unknown to his own chemistry research students, Bob was developing contacts and holding discussions with many biochemists and biologists. In 1953 after reading his seminal review on "Metal ions in biological systems" [2] Bert Vallee, a medical biologist at Harvard Medical School, contacted Bob. A long collaboration, and friendship, followed including the first studies of the chemistry of zinc proteins such as carboxypeptidase and alcohol dehydrogenase. In 1961 a lengthy correspondence initiated by Peter Mitchell took place following Bob's publication of a general solution for the nature of the energised intermediate in oxidative and photophosphorylation. Bob had suggested the highly original idea of a proton gradient instead of an isolable phosphorylated organic compound. This led to the emergence of the chemi-osmotic theory. After Max Perutz had solved the X-ray structure of haemoglobin, the oxygen carrying pigment of blood, Bob gave him tutorials on the spin states of haem iron. He suggested a mechanism of communication between the haems underlying the highly cooperative haem-oxygen binding. This entailed, on oxygenation, a switch in haem iron spin state causing iron-histidine bond length changes. Perutz was subsequently able to demonstrate this mechanism of cooperativity and acknowledged Bob's contribution. Bob was early in providing an explanation for the intense blue colour of copper electron transfer proteins now known as cupredoxins. Thus, he made many highly original contributions to the emerging field of bioinorganic chemistry providing an imaginative and very broad chemical insight into the very particular properties of metalloproteins.

These discussions with biologists convinced Bob that the structures of many proteins could not be static but must have regions of mobility, or flexibility, underlying their operation some even being like miniature machines. X-ray crystallography could not then easily reveal motion. He therefore began to study proteins themselves turning to the development of the spectroscopic technique, nuclear magnetic resonance NMR, which could allow the observation of protein motions. Early development work in this area involved H.A.O. Hill, P.J. Sadler, and J. Wright. This gave rise in 1970 to the establishment of the Oxford Enzyme Group bringing together Oxford scientists including Rex Richards a world leader in NMR, and David Phillips who had determined the first X-ray structure of an enzyme. Together with other Oxford scientists, including J.R. Knowles, G. Radda, and K. McLauchlan, a large rolling grant was won from the UK Science Research Council. The following years were to be perhaps the most productive and scientifically rewarding of Bob's career. He was able to demonstrate structural changes and mobility in

Fig. 2 Bob Williams lecturing on protein NMR

proteins, for example, in those that are triggered by addition of calcium ions, and in haem-containing proteins that transmit electrons. Working with I. Campbell, C.M. Dobson, R. Dwek, B.A. Levine, R.E. Klevit, G.R. Moore, G Williams and many others the Oxford Enzyme Group became a formidable unit for the study of protein NMR. The Group also developed the technology of NMR with the help of companies especially the Oxford Instrument Company who eventually became world leaders in building high field magnets, now widely used in NMR, EPR and clinics for MRI (Fig. 2).

One final topic in bioinorganic chemistry was to capture Bob's imagination, the field of biomineralization. Together with his students S. Perry and S. Mann, Bob sought to discover how biological cells make crystals of inorganic minerals such as calcium carbonate and the iron oxide, magnetite, and together, with connective tissue, fashion them into the remarkable shapes of skeletons, shells even abrasive teeth. Using yet another form of instrumentation, electron microscopy, he was able, together with an expert technician, J. Skarnulis, to detect the elements and follow changes in structure with growth.

Bob also had a strong commitment to undergraduate teaching that resulted in the two-volume text "Inorganic Chemistry" (OUP) written with Courtney S.G. Phillips, his friend and colleague from Merton, who initiated the project [3]. It was a unique treatment that systematised the chemistry of elements across the periodic table. It was written after their experience of giving a year long course of lectures to Oxford undergraduates that apparently received spontaneous applause at the end of the final lecture.

By 1990 Bob had ceased experimental work and begun to reflect on his early hypothesis of the fitness of the elements for biology and their significance for the direction of evolution. Together with his friend J.R.R. Frausto da Silva, Professor of Chemistry at Lisbon University, he wrote three research books exploring the nature of life as chemical systems, a very different approach from that of genetics and proteomics. Fittingly his final book, written with R.E.M. Rickaby, was entitled "Evolution's Destiny: co-evolving the chemistry of the environment and life" [4].

Bob's influence was far reaching. He was instrumental in the development of Bioinorganic Chemistry in Portugal. Frausto da Silva sent his student, A.V. Xavier, to Oxford for doctoral study with Bob on protein NMR. On his return to the University of Lisbon Xavier built a research team of international renown isolating metalloproteins from sulphate reducing bacteria, in collaboration with J. LeGall, a microbiologist from Marseille.

Honoured across the world Bob was elected a Fellow of the Royal Society and became the Napier Royal Society Research Professor in 1974. He retired in 1995 to an Emeritus Fellowship at Wadham and Emeritus Professorship at the University of Oxford. His attractive personality and imaginative enterprise brought the brightest of students and research fellows to his door. He was in turn generous in encouraging their independence. Many went on to build distinguished careers often based upon ideas and inspiration from him. At least six have been elected Fellows of the Royal Society.

Bob was a determined and combative fighter for his views. However, he found great delight in his family, his two sons, Tim and John, and his three grandchildren. But most of all he relied on his wise mentor, his beloved wife, Jelly.

This volume of JBIC contains original papers, reviews and anecdotes contributed by Bob's former colleagues, associates, admirers and friends. It is a fitting celebration of Bob Williams the man and of his extraordinary and imaginative contributions to science.

References

1. Irving HMN, Williams RJP (1948) Nature 162:746–747
2. Williams RJP (1953) Biol Rev 28:381–412
3. Phillips CSG, Williams RJP (1965) Inorganic chemistry parts I and II. Clarendon press, Oxford
4. Williams RJP, Rickaby REM (2012) Evolution's Destiny: Co-evolving Chemistry of the Environment and Life. The Royal Society of Chemistry