A CELEBRATION OF INORGANIC LIVES

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H.A.O. HILL

H.A.O.H. Can you recall what stimulated your initial interest in science?

I think I know what attracted me into science and that really was that at my school, Wallasey Grammar School, I had two very good teachers from the age of 15 onwards. One of them, Mr. Livesey, was a chemistry teacher and he was an extremely intellectual and interesting teacher who really was quite hard on us and made us learn the subject in depth and in detail. He himself had a very good degree from Cambridge University and became a schoolmaster only because he had lost his position in a metallurgical company in the 1930s. The other master, Mr. Eggleshaw, was a completely different kind. He was a sportsman, had been in the cross-country running team at Cambridge, and he taught mathematics. He intrigued us because of his very great general interest in science, music, poetry, anything he came across, and because he used to supply us with books to read. Some of those books I don't think he understood. At various times he gave me books on things like the universe, say a book by James Jeans, books on the nature of science by various authors, even on such things as quantum theory. So I came across all these things before I was 18 and that was long before I thought of going to university at all. Of course we were taught in a rather peculiar way because our school education was during the war. Some of this teaching, especially from Mr. Eggleshaw, occurred in school at night time, some time between 8 o'clock and 12 o'clock in the evening, since we had to "fire-watch", which was the name for staying in school all night, helping to protect the school from incendiary bombs.

H.A.O.H. Was it your idea to apply to Oxford?

The answer is no. We were told at certain times in our development, say round about 17, that the school thought we, or in my case I, might be of such a standard that I could get into either Cambridge or Oxford. They were, and are, the top universities in Britain, and you got in, in those days and if you had not much money in the family, by earning or being awarded a scholarship on an examination set by Oxford or Cambridge. Those examinations were quite separate from the national examinations. I tried to get into Cambridge but I was told that I wasn't good enough and then I applied to Oxford and was awarded a scholarship. I think I got in more on my knowledge of physics than on my knowledge of chemistry because at the age of 18 (this may sound rather peculiar, and it was because of the teaching I had) I could reel off the quantum theory of the specific heats of gases and a part of the Einstein theory of the quantum theory of solids. I can't help feeling that that would have impressed any examiner. But this quirky knowledge all came about through that midnight teaching during fire-watching and the intriguing way in which the man Eggleshaw taught and interested me in problems, whether I understood them or he understood them or not. So, no, I did not choose Oxford, I was sent there.

H.A.O.H. You came up to Merton College: did you benefit from the Oxford system of education?

I take it you mean the tutorial system and the close way in which one teacher stays with one pupil for much of the time he is at Oxford, that is in my undergraduate period from 1944 to 1948. The answer really is quite difficult. At first I was really very frightened by the system and I found it hard to know exactly what was required. I would be set an essay on a subject but I was not given very much guidance as to how I was supposed to tackle it, though I was given certain references. Moreover, I was taught by somebody who really had stopped having an interest in chemistry in the period round about, say, 1920 to 1930. Although he went on teaching it, he did not actually keep up with the developments which were crucial to an understanding of modern chemistry. So I had rather a difficult time at first knowing quite where I was in relation to up-to-date knowledge or up-to-date ideas in chemistry. The result was that I spent a great deal of time just reading in the library and finding out whatever I could on whatever subject was given to me, and some others which I found interesting. I am quite sure that some of the accounts that I then made up would have been pretty garbled. It was only really during perhaps the last year of this education that I began to understand something of the fundamentals of the subject. But I don't think I could ever say that I was properly taught anything about such subjects as the value of thermodynamics or valence theory in chemistry through the tutorial system. I think I picked it up through lectures as many another person would have done in any university. The great advantage of the tutorial system is that, in fact, you are to some degree informed as to how you are doing all the time. Although that isn't an assessment which goes on your record, you are constantly being watched. So, yes, I think I benefited considerably from the Oxford system, being in a College close to people, undergraduates and tutors as well as lecturers, all of very considerable ability and knowledge but some of whom were really father-figures, like my first tutor.

H.A.O.H. Would you like to hazard a guess as to the opinions of your tutors on your ultimate success?

I think they could not have suspected success. I think they could have only seen that I was a reasonably good undergraduate. I finished, say, well certainly in the top quarter. I don't think I showed any promise of being of any real ability until — I hope I add modestly — I started to do research with Harry Irving in the fourth year as an undergraduate.

H.A.O.H. You then did research which led to the Irving–Williams rule. Now it is taken for granted, but was it in any way controversial when it was first published?

I chose to go to work with Harry Irving because Harry was interested in organic reagents for metal ions in solution and he had started to work with a reagent called dithizone. This reagent was specially suitable for the quantitative analysis of very small amounts of zinc and I was intrigued already by trace metals in biology. So I immediately started my research on that subject. The method that was then used was really rather crude. What it amounted to was that you extracted zinc from aqueous solution with the green organic reagent dithizone into an organic layer. But you did this following a sort of recipe. So you chose a pH of, say, around 5, you took the solvent, say carbon tetrachloride or chloroform with green dithizone in it, and added to it zinc in an aqueous solution. You shook the solutions together by hand in a separating funnel for three minutes and then you measured the colour developed in the organic layer which had extracted zinc as a red zinc dithizonate. Now the problem with this is that the system didn't come to equilibrium in that time so it irritated me right from the very beginning that in fact this method was not based on any firm principle, it was just a sort of cookery-book recipe. I decided to build a shaking machine (which irritated everybody in the place) and I would leave the aqueous solutions of zinc and the organic solutions of dithizone together in separation funnels on the shaker for various periods of time and see when they came to equilibrium. (I actually did six at a time and went out to play hockey. It was very noisy.) In that way I learnt the principles of complex ion formation in the aqueous phase and extraction of complexes into the organic phase. Now within a period of, say, a month, I could see that the standard procedure ran very far from equilibrium and so in fact you could extract zinc with dithizone at a much lower pH. I then decided I would do the reaction in the reverse direction. I made zinc dithizonate in an organic phase and back-extracted to equilibrium the zinc into a more acid aqueous phase. By following the two, the forward reaction of extraction into the organic phase and the back-extraction from the zinc dithizonate into the aqueous phase, I could obtain the equilibrium position for the zinc dithizone extraction system. Harry Irving and I could then work out algebraic equations which showed that the extraction depended on the stability constants of the zinc dithizonate in the aqueous phase

[1]. Now, knowing that, the question was: why was it specific, or said to be specific, for zinc? The answer was that it wasn't specific for zinc at all, it was only highly selective. What happened was that, if I did the extraction reaction with copper or nickel or in fact any of the metals from the first transition series or even cadmium, mercury, or bismuth, they were all extracted. I could get an equilibrium binding constant in water for the dithizonates of them all, assuming now that the extraction constant was the same for every one. Looking at these, I thought that this was very peculiar, because it turned out that copper was more easily extracted than zinc and nickel, and they were more easily extracted than cobalt, which was more easily extracted than manganese, while magnesium and calcium were not extracted at all. You see that this is close to the first transition metal series in the Periodic Table. We then asked ourselves, what does this series mean? And I think before Christmas, that is in about three or four months' research as an undergraduate, we had found in tables, standard compilations, that the only thing that fitted the extraction or stability series was the sum of the first two ionisation potentials of the cations in the series. So the stability constant I measured was directly related to the electron affinity of the ion; if you like, the metal ion was acting as an ordinary standard Lewis acid. This gave us what was, in fact, the Irving–Williams series. We did not include other elements such as cadmium; that is, we separated the elements of the first transition series from such elements on the basis that, when you are examining a long series, say from manganese to zinc, the size of the ions is decreasing at the same time as the ionisation potentials are increasing. Cadmium does not fit. So you have a regular series in the effect of the Lewis acid property of the central ion only along the Irving–Williams series. Then I happened to find in *Chemical Abstracts* an account of the work that Jannick Bjerrum had published in his thesis in Copenhagen during the war and we wrote for a copy of this thesis. Bjerrum had measured stability constants of reagents such as ethylenediamine and ammonia directly in water and he had observed the same stability series but made no comments. We looked up extraction series using reagents like 8-hydroxyquinoline and found that the order of extraction of 8-hydroxyquinolinates for the elements from manganese to zinc was exactly the same as for dithizonates and exactly the same as Bjerrum's order. This order was also true for binding by many other reagents, e.g. oxalates. So we, Irving guiding the work all the time, had a fixed order and I tried to persuade Harry Irving to publish that as quickly as possible. What really stimulated him to publish it was that, during my Easter holiday, it must have been in 1948, I went across to Liverpool University library and there saw in *Nature* an article by Mellor and Maley from Australia where they had put down another stability constant series but it was rather a jumbled series with all sorts of metals and from all over the Periodic Table. It had no systematic feature and was not one which could be general for different reagents. That prompted Harry and myself to write the work up as quickly as we could and publish in *Nature* [2]. I know now, that, at the same time, Melvin Calvin was working roughly along the same lines. Funnily enough, he published at a very similar

time to us but only a part of the Irving–Williams series, three metal ions, showing the relationships of stability constants to ionisation potentials. We had a much more extensive view of the problem than either Mellor and Maley or Calvin and his collaborators at that time. And so in a sense we had come out in front. For me this was a most wonderful moment and gave me confidence that I could do research and generate useful ideas. It all happened while I was an undergraduate!

Now this series didn't give rise to any sort of controversial points of view in 1948. The only controversy that occurred about the series was later, from 1953 on, when people started to think in terms of crystal field theory and the contributions of angular polarisation of cations to stability and binding along the transition metal series. What I think has happened from that time onwards is that chemists have concentrated far too much upon symmetry-dependent factors, such as are given by crystal field theory, as a way of trying to explain the Irving–Williams order when, in fact, experimentally the stability constant series is largely independent of the symmetry of the binding groups which are held by the metal ion. It is the Lewis acid acidity in the sense of the decrease in radius and the increase in ionisation potentials that is the major contribution to this series. The crystal field term, the symmetry-dependent term, is something on the top of that. That was controversial by 1955 and remains, to some degree, controversial because many textbooks today explain the Irving–Williams series as if it comes out from a crystal field theory, which it does not.

There is another set of inorganic chemistry ideas which was debated in the period from 1950 to 1970 and in which I was involved [3]. I refer to the "a"/"b" (Chatt, see Fig. 1) or hard/soft (Pearson) descriptions of acids and bases. Chatt made no attempt to relate "a"/"b" to fundamental properties, but both by use of the language, "soft" and "hard", and in later discussion, Pearson related his classification to ionisation potentials and electron affinities, which is close to an electronegativity approach. This is the approach of Pauling and Mulliken to element/element affinities in solids. I had done something not very different in 1954 [3] and subsequently [4]. The reaction is simple enough if you consider a reaction in solution, especially water. The acid/base reaction is

$$M(H_2O)_n + X(H_2O)_m \rightleftharpoons MX(H_2O)_o + (m+n-o)H_2O$$

The problem is the effect of water on altering the affinity of M for X from that in the gas phase. The effect is that large acids, M, prefer large bases, X, more than would be expected. Size as well as electronegativity is important. For cations, I classified by the ratio of ionisation potentials to radius. There is a very good book on the subject [5]. I believe the "hard/soft" classification is misleading when applied to classifications of reactions in solvents, especially water. But I do not deny the value of electronegativity scales, and soft and hard, for gas-phase reactions.

H.A.O.H. I understand that you had an "encounter" with Linus Pauling when he was Eastman Professor in Oxford. How did that occur?

Fig. 1. Bob Williams and Joseph Chatt in conversation.

The very first lecture I ever gave was when I was still a fourth-year undergraduate and I gave the lecture on the Irving Williams series or stability of complex ions in the summer of 1948. It so happened that Linus Pauling sat in the front row of the audience and almost immediately after I started the lecture he began to ask questions. I was unused to even seeing that being done, never mind facing it, so after about the third or fourth question I had to say to Professor Pauling that if he continued to ask questions I couldn't go on with the lecture. He then looked a little bit put out but he stopped asking questions. After the lecture he went to Harry Irving and said to Harry, "You know, that post-doc of yours should be used to having questions asked and shouldn't be, in effect, rude to the people who are asking the questions." Harry only said to him, "Oh no, no, no, he isn't a post-doc at all." So Linus said, "Well, anyway, that chap who is studying for his doctor's degree with you." "No", said Irving, "Williams hasn't got a degree at all yet. He is a fourth-year undergraduate." On learning that, Linus Pauling actually came to me and said that he was sorry that he had interrupted me in such a way and he didn't realise that I had no experience in lecturing at all. I had only small exchanges with Linus Pauling after that in Oxford but, of course, during the lecture I had surprised him with plots of stability constants against ionisation potentials. He had had a different idea about the stability of complex ions and the oxidation state stabilities as well, which he had already published and which did not really fit the data that I provided. I also had another exchange with Linus Pauling when I worked on the empirical theory of the stability of metals and alloys (I suppose you could call it), i.e. their latent heats [6].

Pauling had a way of treating such a problem based on counting electrons in order to explain the stability of metals and this didn't take too much account of the actual intrinsic energies, ionisation potentials, of the electrons in the atomic shells. So Harry Irving, myself and Professor Hume-Rothery, who was a metallurgist, wrote a paper on the stabilities of metals, that is their melting points and boiling points pointing to atomic energy levels. Of course Hume-Rothery went on developing this and other ideas about the stabilities of alloy phases and some of these were based on electron counting, similar to the ideas of Pauling but much of it was dependent on electronic energies. This led to a rather rough exchange between Pauling and Hume-Rothery but didn't really involve me very much. Curiously this same exchange came up again after I had written a review of Pauling's biography, only a couple of years ago, when Pauling wrote complaining that really other people's views on stabilities of metals and alloys did not fit some data as well as his own. I replied that I still did not believe that. But that is only a by-the-by. So I really didn't have all that much to do with Linus Pauling, although I met him a few times at various conferences over the years, and admired him greatly. I still do.

H.A.O.H. You spent some time in Sweden as a post-doc in 1950 and 1951: why Sweden, why not the USA?

I think the answer is very simple indeed. Towards the end of my fifth year (summer 1949 that would be), when I had done about two years' research, Harry Irving and I went to Copenhagen to see Jannick Bjerrum and talk about complex ions and complex ion stabilities. I then went on to visit Professor Claessen in Uppsala to discuss gas chromatographic techniques, which were becoming of great interest to a friend of mine in Oxford, Courtenay Phillips, with whom I later wrote the book on inorganic chemistry. I had an interest in chromatography myself, but only really through talking to people and reading the literature on separation methods. When I went to Uppsala I also learned about Tiselius' work on protein separation. My visit was a very pleasant one. I learned a lot and also knew I had a lot of things to read. One of the reasons for deciding to go back there to do a post-doc, which was at the back of my mind, was that if I was to understand metals in biology then I needed to understand metal binding to proteins. Tiselius was, of course, the man who had shown how to separate proteins by electrophoresis and he received the Nobel Prize for that. When it came to doing my post-doc (1950–1951) I applied for American money and was awarded a Rotary International Fellowship, but that Rotary International Fellowship was an international fellowship. I could choose to go to whatever country I liked, so I chose to go back to Sweden really in order to learn the use of chromatography and electrophoresis, and how metal ions would bind to molecules and proteins. Perhaps I ought to clarify a little.

I think you have to understand that the idea of studying metal ions and their interaction with biological elements, materials, proteins, substrates and so on, had come to me very much earlier, even when I was at school, and that was really due to a set of accidents. I had learned a lot of chemistry in school but during the holidays say in 1942–1944, schoolboys were virtually forced to work in agricultural and forestry camps in order to aid the war effort. During that time I met up with older people who actually worked for their living, either in fruit farms or forestry camps or in other sorts of agricultural camps, and they, either by accident or through questioning of one kind or another, told me that they had to supply certain chemicals to growing crops. Some of the things they supplied, such as lime, were obvious and people thought that that was to do with the control of pH but clearly there were also elements involved, i.e. calcium salts. They also supplied potassium phosphates and so forth. And, in fact, agriculturists already knew, when you read around a little bit, that various trace elements were required for healthy plants and animals. So it occurred to me when in school, before I went to Oxford, that these elements could be some essential part of biological systems. Scientists generally believed in the Darwinian hypothesis that the shapes and sizes of plants and animals as they evolved adapted to circumstances (through successive mutation) and therefore that they improved their physical and mechanical functioning through evolution. (I had read Darwin because my father had one of his books.) If that was the case and since there had always been various elements in the soil and environment, and these elements have different chemistries, it stood to reason that the plants and animals as they evolved would have learnt to use and optimise chemical elements, i.e. actually optimise the function of the different metals of the periodic table as far as they were available to living systems. This gave me a general hypothesis — and it was the sort of hypothesis I have always liked (that life is based on inorganic catalysis and control of organic chemicals) — on which to work for the rest of my life and actually that is what I have been doing ever since. Both my undergraduate thesis (1948) and my D.Phil. thesis (1950) refer to the problem. All my research has been directed at this problem.

So going away to Uppsala rather than to the United States was based on two things. I already had an interest in chromatography, which was a method to separate out the things that bound to metal ions, and at the same time I wanted to study metal ion interactions with proteins, and that you could study by electrophoresis. So I thought I could learn two things in the laboratories at Uppsala. It was a natural choice really since there was no USA laboratory with such skills in analytical separation methods as those that existed in Uppsala. Of course you must remember that Svedberg, who had just about finished his career then, was also in Uppsala. He had the Nobel Prize for the development of another analytical method, the ultracentrifuge, so I think the choice of Uppsala was really based on the fact that this was a very fine laboratory to learn about separation methods of organic molecules both small and large, bound or free from metal ions, and so greatly enhance the potential to do work on metal binding to organic molecules, which was essential within biology.

At that time, of course, by working on chromatography in the laboratory one naturally uncovered things about chromatography, although that wasn't the initial intention. So while I was in Uppsala in 1950–1951 we developed the method of gradient elution analysis [7]. Gradient elution analysis is now the preferred way of running most chromatographic systems and it is very interesting to see how your education helps you when you go away from your own immediate discipline. The method that Tiselius had been using before I arrived was called displacement analysis where he changed the nature of the eluant solvent in steps. Now if you use his procedure to separate molecules on a column there is a hidden assumption that the different components of the mixture have a single affinity constant for the material in the column. In other words they obey what is called the Langmuir absorption isotherm. If they don't have such a single affinity but there are a multitude of sites where they can be absorbed, then they will obey a different absorption isotherm, the Freundlich absorption isotherm. If you run a substance which obeys the Freundlich isotherm on a column while employing steps in solvent composition for elution what you find is that, for every eluted fraction and especially at the steps in solvent composition, there are some amounts of every component in the mixture. You don't, in fact, fractionate to a high degree of purity although you do fractionate. When you use a solvent gradient for elution, the gradient in fact keeps chasing the more strongly absorbed part of a given substance forward towards the solvent front. The tail of a component catches up to the peak so that the peaks appear as symmetrical peaks and give close to 100% purification of the material. These gradient methods, and we did generalise them not just to solvent mixtures but to pH and salt gradients and so on, are now probably the major method in liquid chromatography.

The other method which I devised there was in fact continuous fractional crystallisation on a column which later became known as the Baker–Williams column [8]. Once again, this was an attempt to fractionate proteins on columns but it failed. However, it worked as a method of fractionating high polymers and though it was never very successful, it was employed by various industries for a while. It was displaced later by Sephadex methods, that is by separation in a column on the basis of size and not on the basis of absorption. In the fractional crystallisation method, you imposed not only a solvent gradient down the column as it was running but a temperature gradient was also imposed from the outside. This is indeed very, very like a volcano, which is the sort of system I describe later in the description of those things I might like to have studied in geochemistry. One can think of making a sort of miniature volcano in the laboratory and watching the inorganic elements being fractionated as the melt is pushed up (or down) the funnel of the rock. Anyway, that is in large part an aside but it did bring me in contact with a completely different group of people, which provided a very fine education. I met, for example, A.J.P. Martin, who had a Nobel Prize for chromatography and he visited me in Oxford and dined with me in Merton College soon after I came back from Sweden. This was a great feather in my cap, at age 26. We discussed then the basis of chromatographic fractionations using gradients. All this chromatographic work was of very great value later because it showed how flow systems work and how you have to look out for all sorts of problems other than those that you associate with equilibrium. This knowledge has become, in relatively recent times, extremely useful to me in discussing the problem of flow of ions in a biological system as opposed to their equilibration at sites.

H.A.O.H. What caused you to first put forward the idea of the importance of metal ions in biological systems: was it due to some article in the literature, to the reading of biological textbooks or did it come out of the blue?

Where did the idea come from to study metal ions in biological systems? I think I have given an answer to that. It was not due to anything in the literature, although I immediately read the literature once I got started. I read some of the literature on trace metals and trace elements before I came to Oxford. I bought a little book myself with some prize money I got at school. I forget what it was called now. It was really about agriculture and trace elements in agriculture. It was related to my holiday work in agricultural camps. I didn't read biological textbooks at all at that stage, except the Darwin book I mentioned. The only other book I know I read a little later is that by Baldwin [9]. That's about all the biochemistry I started to read for some years. You must remember that the Oxford chemistry course is in a sense restricted even to this day and was then very restricted indeed. You were not taught anything about biological systems whatsoever. The chemistry of biology was left to the biochemists, physiologists, and so on. We were taught with a great stress on physical thinking and method and how you used method to uncover facts about chemicals. We were not really taught to think in a very systematic way either in inorganic or organic chemistry or, to a certain extent, even in physical chemistry. I believe that my book with Courtenay Phillips was, in its time, the first book to try to give inorganic chemistry systematic themes.

My first paper on metal ions in biological systems was actually written in 1950–1951; I had finished writing it when I was in Sweden. It was published in 1953 in *Biological Reviews* [10] after it had been refused by *Chemical Society Reviews*. This first paper, which was actually called "Metal ions in biological systems", brought me into contact with quite a few biochemists. Most of them at that time, I say this rather guardedly, were opposed to the idea that these metal ions had any significance. Even some time later, when I talked to Sir Hans Krebs, he said to me, in no uncertain terms, that it was a great mistake to set out on one's career to study metal ions in biological systems as these metal ions were largely impurities. He explained that, at the stage in the development of biochemistry, say around 1955–1960, biochemists were unable to purify their proteins and get them free from contaminating metal ions at the trace level. Now a quite opposite approach was held, actually in University College, London, by a man who later became a professor, Dr. Crooke, and he encouraged me to give a series of lectures in University College, London, in 1954–1955 where I outlined some of my ideas. These lectures were actually published as a softback publication [11]. I don't suppose more than a hundred copies were printed. I have still got one of them. I find it most interesting! Now another thing that encouraged me was that, as a result of the review in *Biological Reviews*, I got in touch with Bert Vallee or rather he got in touch with me. Bert at first (when he had just seen my paper) was, I think, a bit put out that I had hit upon some ideas which he in part had also hit upon. He had obviously the same interests as myself because he had worked on zinc, the analysis of traces of metals by spectrographic analysis, and he had made a very interesting observation. There was a very clear-cut feature of blood cells. The red blood cell had a totally different metal ion content from the white blood cell. The white blood cell has a lot of zinc in it whereas the red blood cell has very little. He immediately started to pursue that by analytical methods and actually that is what he has done for much of the rest of his life in a very successful manner. So it was the publication of the *Biological Reviews* article that brought me into contact with Bert. It was only about two or three years later that we met in, I think, 1955 when we discussed and published together thoughts concerning his finding that there was zinc in carboxypeptidase and why it should be zinc and not another metal in such an enzyme system. The report is in *Faraday Society Discussions* [12] and the meeting was in Oxford.

In answer to your question then, my first interest was very early but I do not think I would have got anywhere but for the interest of a few biochemists; inorganic chemists began to wake up about ten years later.

H.A.O.H. You are now best known for your many contributions to the study of metal ions in biology but you have worked on a wide range of topics, many of which have been taken up by those who were your pupils. Is there any subject amongst these that you regret not being able to continue or which have been left fallow?

Yes, I have always loved to wander and I would have liked to wander further. You ask whether there are areas where I would have liked to have gone. I think the answer will be "Yes" in just a minute. But let me remind you of the sorts of areas that I have tried to look at. At first it was just the stability of complex ions, looking at the relevance of donor/acceptor properties and size selectivity, even ring ligands, and their extractability and both these things are extremely important in biology. The ability to move molecules through non-aqueous phases is obviously extremely important in the uptake of elements, and the binding is as important in the cell. Now there are features here which I did not touch myself, or hardly at all, and which are of great importance but they have been developed by others. One is the kinetics of these uptake reactions. At first I didn't think that these kinetics were important in the biological system but I now think the kinetics of the reactions are of extreme importance. I myself didn't touch on that area and I still think that we have poor knowledge of the kinetics of exchange of metal ions from proteins and that this knowledge will be fundamentally important in homeostasis.

Secondly I have described chromatographic methods. This leads to thinking about phases and phase transfer [13]. I believe this to be a very difficult area in biology but of extreme importance.

There are various areas in spectroscopy where we developed the first ideas of charge transfer spectra as far as metal organic molecules were concerned [14]. That was done with Leslie Orgel's help. At the same time, I was obviously interested in magnetic properties of complexes and what they can tell you and we wrote papers on magnetic properties, especially spin states of iron. Another side of complex ions is their redox potentials, which of course are just the ratios of stability constants for different oxidation states. We developed in the 1950s and 1960s a whole set of papers on trying to understand redox potentials in model systems in order to appreciate the variety of redox potentials which you see within a series of biological molecules, say the haem-proteins [15]. That was very well developed with pupils, some of whom, such as Brian James, are now professors. Turning back to spectroscopy, there was a clear relationship in my mind between the colours of various minerals and their electronic conductivity. It was fairly obvious that those things that absorbed pretty well across the physical region, black substances as I called them, were likely to be conductors of electrical current. With Paul Brateman and Peter Day I started to examine those lattices which had mixed valences [16], lattices which had metals in two oxidations states. In fact, we kept a small "black book" in which we wrote notes on black inorganic solids. That could have gone, and has gone, a long way further, though certainly not in my hands. Peter Day is a world leader in this field. I always used the data to analyse what went on in biology and in fact that was the reason for studying all these systems.

I think an area which becomes more and more interesting is one I started less than perhaps ten years ago, which is the way in which biology handles minerals and develops minerals for their various purposes. Here, the intriguing thing today, and it is for others to develop the subject independently from biology, is to see how you can put minerals, either in the amorphous or crystalline states, together with organic molecules in order to make substances with interesting physical properties. Here, chemists are rather badly trained because, although they are trained in electricity and magnetism, and therefore delve into the properties of compounds and lattices where electronics or magnetic properties are of interest, they do not have any training in mechanical properties or today even in the Phase Rule. They don't know, for example, what a sheer modulus is or perhaps even a Young's modulus. They have never done any mechanics at school or university. There is a whole area of chemistry where you have to knit together the mechanical properties of matter with chemical knowledge. This is usually just dealt with by industry and there are very few academic chemists, certainly in Britain, who bother to know anything about mechanical properties. That's an area which I would certainly like to see developed.

To give you another area where I think chemists have played an insignificant role, that is people who are just trained directly in chemistry, and where I started and stopped almost immediately, is within geochemistry. Geochemistry is of interest to me as far as metal ions in biology are concerned because, of course, plants and animals have to get the metals out of the soil. I did publish one geological paper on the uptake of trace elements in the Skaergaard intrusion of Greenland [17]. That paper was to show why metal ions fractionate into rocks from melts. It gave a theory of trace element separation based on crystal field theory, which actually replaces some of the work that was done by Goldschmitt and others much earlier in the century. The work led to a bit of a clash with the local, i.e. the Oxford, geochemists who just didn't believe in the use of crystal field theory at all at the time. Although originally I tried to publish these ideas in a long paper with them, they would have none of it and it finished as a note in *Nature*. In fact, the paper had a surprisingly light impact at first even amongst geochemists. This is surprising in view of the fact that the fractionation of elements is extremely exciting in quite a lot of other ways in geochemistry. One of the ways of studying the rocks at the edges of the tectonic plates and of studying volcanoes is to analyse the way in which elements fractionate between melts and solid phases. You can, for example, look and see the way in which the rare earths are fractionated in these zones. A volcano is effectively the remnants of a chromatographic column. A volcano, at least the melt–solidus equilibration, is like a column flow and its formation is linked historically with the trace element composition of today's rocks. There is a whole world in geochemistry, soil chemistry, and so on which the inorganic chemists have stayed away from, perhaps because of complexity, but again it is of great, great interest to industry and, of course, to geochemists.

As a footnote, I add that my views on ion selectivity, in rocks, trace element uptake, suddenly took on importance in 1970 (11 years after the original paper) when a New Zealand geochemist wrote a book on the problem, much of which was based on my views as you can see from his introduction [18].

A final area which I might have developed but did not was my view of how to design cyclic chelates for metal ion selection. This was put forward in a paper in 1953 [19]. I am a poor organic chemist and I made no attempt to follow up the idea which was later developed very extensively and deservedly won the Nobel Prize for three organic chemists. I had noticed the value of porphyrin and chlorophyll in biology and this indicated to me a way of using such chelates in analysis. I even suggested a compound!!

So those are areas where I might have gone and I think some are still left fallow.

H.A.O.H. Professor Bert Vallee and you have had, how should one say, a very eventful relationship. How did that begin and do you ever regret that a closer relationship between you, and your two research groups, has not occurred?

My connections with Bert Vallee started by exchanging letters back in 1953 or 1954. I don't keep letters so I don't know the exact date. We became good friends and he was extremely supportive as far as I was concerned for many years from 1954 to 1970. We worked pretty closely together. We were constantly exchanging ideas. It was zinc and a general interest in metals in biology that brought us together. We both worked on the zinc dithizone method and it was an interest in zinc biochemistry which caused me to agree to go and work in his laboratory for a summer, I think, 1956. While we were working together, we developed ways of looking at metalloenzymes in much more detail than had been possible before. We used spectroscopy to follow the binding of reagents such as *o*-phenanthroline to zinc in alcohol dehydrogenase and carboxypeptidase etc. [20]. You see, if you could use these inorganic reagent procedures, you would have been able to find metal ions without spectrographic analysis which was terribly difficult in those days although Bert, of course, had made an art of it and had been and is still extremely successful. So that was one thing. The other reason for going was that, naturally enough, from the Irving–Williams series, I was greatly intrigued by the fact that you might be able to substitute any metal ion with any other metal ion in the coordination spheres which proteins provided and then to look at reactivity. We had already found from the literature and published that the Irving–Williams series is not just a series of stability constants but is actually, because it is a Lewis acid sequence (again nothing to do with the crystal field), the sequence of Lewis acid *catalytic* ability. The cupric ion stands well clear of anything else in its ability, say, to hydrolyse organic esters and amides and so on. It is much better than zinc. The curiosity was then that zinc was actually used in the first true hydrolytic enzyme that had been found (i.e. by Bert); that was carboxypeptidase. The curiosity was why zinc? The argument went that, if we switched metal ions, perhaps we would be able to find out why zinc was used [21]. The second advantage of switching the metal ion, of course, was that you could switch to a metal ion which had the potential to give you a great deal of spectroscopic and magnetic information about the reaction site. (N.B. I was responsible for a mistake here which cost Bert dearly [22].) We wrote an article later in *Chemistry in Britain* [23] about metal ion substitutions to find out about metal ion sites in enzymes. This led me to much wider thinking and to the idea that you should try to substitute calcium by lanthanides or you should try to substitute potassium by thallium and so on. Later, we showed how to use these isomorphous replacements. Work with Bert after 1956 developed partly at long distance, although we were meeting at conferences and so on. I was visiting his laboratory for a day or two when I was in the States over the years, until 1965 when I went over to Bert in the United States for a whole year.

I sat in Bert's lab in 1965–1966, although I was working with Gene Kennedy experimentally using Bert's equipment on the uptake of magnesium into *E. coli*. I wanted to find out if magnesium uptake was under genetic control, that's to say whether there were pumps for magnesium or not. And in fact we discovered that there were pumps for magnesium. (It was shown by others at about the same time that such pumps existed.) I think we did one of the more careful pieces of work to demonstrate this and later on Gene Kennedy and a graduate student, Joan Lusk, with whom I worked, went on to find the gene which was responsible for this uptake pathway for magnesium.

I talked a lot with Bert during 1965–1966, gave seminars to his group, even gave a Grand Rounds talk in the hospital and of course we worked on the general idea of the entatic state [24], which was resisted by many inorganic chemists but is now accepted. I also worked with another man for whom I have the greatest regard, Warren Wacker. We published on magnesium and calcium [25] long before these elements became popular in biochemistry journals. I thoroughly enjoyed my work with Bert.

At the time I was working with him for this longer period, Bert had become a much more powerful figure. At first (1955), we were just two young people working at a fairly low level of recognition in two different countries. We could help one another. But both of us in 1965–1970 were becoming quite well known in the field and I think really the development of our different styles was a bit of a problem for our ability to work together. You see, I think, just as is the case with children, that as you grow up you often grow away from one another. In our cases we both had to establish ourselves in our geographical worlds. Especially, I feel that the American world is extremely competitive and there you really do not want to risk falling under the shadow of somebody else or risk too much in public. (The imagination is second to the experiment by a long distance in USA.) Even if there was no real danger, you may perceive that risk and so I think looking at the set-up in Bert's world, (USA) he could have viewed me in part as friend and in part as rival. Now for myself I like working very much on my own and not as if I am a part of some larger team or larger group so I think in some sense our drifting apart was natural. I like risking ideas publicly but American science is not like that. Our styles, especially as we became — what shall I call it — heavyweights, were very different and probably we couldn't have worked together comfortably for much longer. It was much better that people like you, Allen, and later others, went from my laboratory to learn from him. I do not ever underrate Bert's work, which many in the USA have done and still do.

To finish the talk about Bert Vallee and myself, I want to stress that I have always had a great admiration for the way he tackles problems and for the fact that he is dedicated to get a result with which you cannot quarrel. He does not want to speculate if he can avoid it; he wants the scientific method to work just by continued testing and testing of what you think you know. You never publish things without a multitude of checks. I am afraid I am not very like that. I tend to rush into things and, well, maybe get my fingers burnt or maybe I am proved right but soon I tend to move off to something different. There again you see our styles were quite different and I think, given the different ways in which we pursued the subject of elements in biology, it was probably best for us both that we didn't work closely together after

1970. Perhaps now today we could sit down and work together again in a different and more relaxed atmosphere.

H.A.O.H. The relationship between electron transfer and the generation of proton gradients, the field of chemiosmosis, still attracts much interest. How did your contribution to that topic come about and, the 64 dollar question, why did you not do any experimental work to test your ideas, which, at the time, were quite new?

Before I turn to the events in the development of chemiosmosis and theories of chemiosmosis, I think I ought to try to summarise where I had reached in the period towards the end of 1965 in my work on metal ions in biological systems. We had published some 70 papers directed at the problems by then. I think if you look at the work that had been done (in my group) you will see that it had largely been on model compounds. All the time I kept my eyes on the biological systems as best I could, and I wrote about them, but I was not really ready to enter into any direct work on biological compounds of any size, although there was a long study with you and John Pratt of vitamin B_{12}, which is a bit big, but it was like studying a small molecule [26]. There were no real problems that were different from, say, studying cobalt dimethylglyoxime or some such similar complex. Of course the B_{12} work was extremely revealing and it showed how, in a biggish molecule and with specific groups attached to the metal, you can in fact get very different properties of a metal centre from those you expect in small molecules such as cobalt hexamine. So we learned a great deal from models. We also learned to look at biochemical systems and then search for parallels with models in order to understand biochemical

Fig. 2. Allen Hill and Bob Williams enjoying a joke.

systems. But I don't think we came very near to learning some of the most important and intrinsic features of the inorganic chemistry of biology from those early models. I sometimes think that what people do even today with models doesn't actually give you a feel for the biological significance of some of the observations others have made on biological systems.

During the course of the work on these models, I picked up a good deal of information about the cytochrome chain, that is the electron transport chain in mitochrondria. And what was surprising was that there seemed to be a series of metal ions, mostly iron ions, in isolated protein complexes but strung together. And the question was: why should you have a series of catalysts with only one functional group at one end say for doing a reaction with oxygen and a functional group at the other end of the chain for doing a reaction say of hydrogen? What was the middle electron transport for? We were already deeply intrigued by electron transfer in biology and we still are to this day. The immediate parallel is, of course, some sort of electrochemical fuel cell. So I thought about this during the period 1958 1960 and then wrote a paper in the *Journal of Theoretical Biology* describing a way of converting the energy of the reaction between hydrogen and oxygen at long range, or of converting photochemical energy, into a series of localised proton gradients and, as described in the paper, connecting that further to the formation of ATP, which I knew to be the overall fundamental step in biological energy conversion [27]. When I wrote that paper I also included references to electrochemical cells and the fact that we had to have the two reaction centres separated so that the products could not diffuse to one another, the products in this case being hydrogen ions and hydroxyl ions, before the energy was stripped from this gradient of hydrogen ions between the two centres to make ATP. In other words, diffusion controls are the essential feature of energy capture together with the proper location of catalysts in space.

You ask why I did not do any experiments. The problem was that working in an inorganic chemistry laboratory I had never handled mitochondria, I had never handled chloroplasts, I had never even handled any biological organism at all and I really didn't consider that worthwhile trying with so little experience. You have to remember too that at that time I had also set about writing, with Courtenay Phillips, the two-volume book on inorganic chemistry which took us six years [28]. I was a tutor at the time and I had a set of experiments ongoing on model complexes and they continued actually until 1965 or 1966. So really I had enough on my plate. I couldn't have done the experiments myself at all. What did annoy me strongly and still irritates me is that, at the beginning of 1961 when my paper on the coupling between hydrogen and oxygen reactions or photoreactions in biology and proton gradients and then on to ATP formation had been published, the coupling scheme was the subject of a discussion and frankly an unpleasant sequence of exchanges with Peter Mitchell.

The correspondence started when Peter wrote to me asking me to explain my paper to him. And I did that in February 1961. He wrote in reply to my explanation saying that he thought he understood what I wanted to say but did, in fact, describe something which I did not wish to say. He then, I think, was rather surprised because the next thing I wrote back to him included — and it definitely did include — a description of chemiosmosis as well as local proton theory but I definitely preferred the latter. We had a further exchange of letters (which are now all in the Royal Society archives) until some time towards the end of March 1961. What was to my mind a great shock was that he should then consider it within his rights to publish the chemiosmotic theory in *Nature* in June 1961 without any reference either to our correspondence or to my paper or in fact to an earlier paper which I had written in *The Enzymes*, which he stated clearly that he had read. I objected to him again when he wrote his little book without references. Now there come moments when you are uncertain yourself of where the balance of justice should lie in such an exchange and argument between two people who are not directly in contact but are writing by letter. It is, however, very, very hard for me to see that I could have behaved towards him in the way he behaved towards me. That still rankles to this day. I would add, however, that he went on to do experiments and stayed fighting with the subject from 1961 onwards much more closely than I did. He deserved much credit, but certainly not all of it. I still believe that the way in which I formulated the theory of energy capture is better than a chemiosmotic formulation, especially as it was done initially, in the sense that chemiosmotic theory did not contain any circuitry or flow of protons through the ATP-ase or diffusion control of reactions which, I believe, are all part of the energy conservation mechanism. I proposed the protons returned via the ATP-ase, he did not. (I hope you see, however, that my views were partly based on the inorganic chemistry of electron transfer as studied in mixed-valent solids.)

I have gone on to try to prove my hypothesis by looking at molecular systems, particularly at proteins, over the last 30 years. The two proteins I have chosen since 1970 as "models" for bits of the energy capture system are in one part cytochrome *c* and in the other part phosphoglycerate kinase. The phosphoglycerate kinase study, which has been going on now for the last 15 years or so [29] is an attempt to show how the ATP formation could occur by conformation changes. The work on cytochrome *c* from 1971 has turned out to lead to a way of discussing proton movements, gated diffusion, within a hydrogen bond network formed by a protein, those proton movements being stimulated by redox reactions. The coupling is then mechanical between conformation changes of helices in all the proteins, i.e. a series of movements connects electron-driven conformation changes and ATP formation [30]. Now, once again, this is only a hypothesis based on related knowledge but I think it does show how, in fact, you could put the pieces together very much in the way I thought of in the 1961 beginnings. You would have a local diffusion of protons through a circuit which would drive the formation of ATP.

I do think that the problem between myself and Mitchell was really one of those episodes in the history of science (maybe on a small scale) where personalities clash and where people think of how they ought to go about an exchange of views differently. It shows how secretive natures actually can cause a great deal of difficulty. I don't think that I want to talk too much more on this topic because I do know that the history will be published after both myself and Peter Mitchell are dead. Those who live then can look on the episode and decide for themselves who said what first and whether the history of the discovery is correctly described in textbooks of biochemistry today. History depends on careful enquiry, though it is usually obscured by propaganda, especially in today's science.

H.A.O.H. You were one of the key figures in the formation of the interdisciplinary venture, the Oxford Enzyme Group. How did that occur?

My involvement with the Oxford Enzyme Group, formed in about 1970, came about as follows. I was approached by Jeremy Knowles, who is now the Dean at Harvard, and who was, and is, a very valued friend. He in turn had been approached by the professor of the Organic Chemistry Department, Professor E.R.H. Jones. From on high, that is from the Research Councils, had come the message that it would be interesting to know if there were any expensive pieces of equipment which chemists in Britain should have but had not got. It was said that if they could think of expensive pieces of equipment which they desperately needed then the way in which they might be able to get them would be to apply in a group. Now I know now that Prof. David Phillips was also involved in the initial negotiation of this but as far as I knew then about it, it really came indirectly through Prof. E.R.H. Jones and directly to me through Jeremy Knowles. I had already started, when I returned from Harvard in 1967, to change the direction of my research. I started to look at the NMR of proteins because I knew by that time that I had to change the direction of my research away from models. I had also become a biochemistry teacher as opposed to a chemistry teacher. I realised, and I still firmly believe this, that you can only understand the function of metal ions in biology through the study of proteins. The two go together, metal ions and proteins, and it is the two together that really make a biological system. You must understand proteins but it is not just proteins, it is proteins plus the metal ions, i.e. the inorganic environment which was there before life, that makes life. Now having got that into my head, I had to find a method for the study of proteins. The method that I chose was NMR from reading a great deal while in Harvard and, in fact, discussing with you in Oxford. You will probably remember your earlier trip to Tokyo to buy JEOL equipment [31]. We set out at first to use the best NMR machines that were available in 1967, which were in Harwell and in I.C.I. (Runcorn). With Jeremy Knowles' approach, and the notion that we could get expensive equipment for ourselves, I was immediately filled with the possibility of buying a very large NMR machine for Oxford and I have no doubt that I would have bought the wrong NMR spectrometer or spectrometers but for advice. But I definitely think that I was one of the main people, if not the major person, who forced the idea of doing the NMR spectroscopy of proteins onto a group of people in Oxford and this formed the corner stone of the Oxford Enzyme Group. Quite a different approach was being followed by George Radda who wanted to do the NMR of enzyme reactions and substrates bound to proteins. That was a route I didn't wish to follow because of course that would tell me nothing about metal ion sites. As I said, we had actually started looking at proteins such as myoglobin using instruments which were stationed in Harwell or in I.C.I. but that was a most inconvenient procedure and anyway the proteins were not very amenable to study by the 220 MHz Varian instrument which was a carrier wave instrument in 1968. The introduction of a really satisfactory NMR spectrometer for measuring proteins was, I think, in large part due to the fact that we elected (Sir) Rex Richards to help us as chairman of the Oxford Enzyme Group on the advice of Prof. (Sir) E.R.H. Jones. Rex brought together Keith McLauchlan and Iain Campbell and they searched the highways and byways in the manufacturing world to find out how we could, in fact, get a high-resolution spectrometer which was based on the Fourier transform and not on the carrier wave procedure. In the end, we chose to work with Bruker and Oxford Instruments. I think that decision actually transformed the scene as far as the study of protein NMR (and chemistry NMR was concerned worldwide). Some of us, of course, knew that Ernst, who won the Nobel Prize in 1991, had developed a theory of this procedure and how to use it. So my group, including

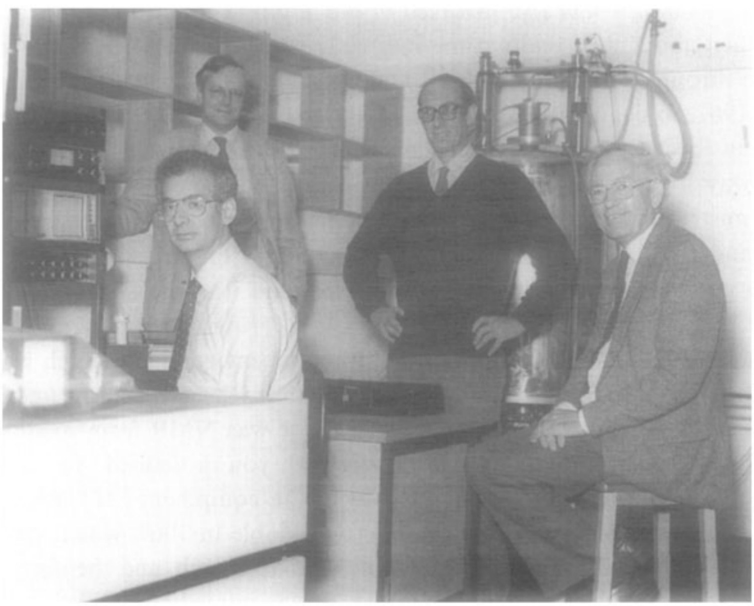

Fig. 3. Today's leading Oxford figures in the study of large biological molecules; Raymond Dwek (seated), Chris Dobson (behind) and Iain Campbell with Bob Williams.

Campbell, just set about from the very beginning to try to analyse protein structure by FT NMR and in fact we were very successful. Everyone does it now. I never doubted that protein structures could be done by NMR after our initial success [32]. It was a matter of perseverance. There were all sorts of reasons why I think we were not as successful in the end in reaching the objectives as quickly as the group that Wüthrich led in Switzerland but I won't go into this at this time although I can elaborate on it if you wish. It has a lot to do with prototype instruments and instrument development. We had, however, a very great deal of success in our studies and we certainly learnt a lot about the nature of proteins. We, especially Campbell and Dobson who started with me, are still at the forefront.

The idea that I wished to concentrate on more than anything else at that time — and I want to stress this very, very strongly — was that I wanted to learn about the dynamics of the proteins more than the structures because I could not believe the static representations given by crystallographic studies, though the outline static structures provided by crystallography were and are correct. I cannot believe that these representations really are at the heart of the nature of proteins. In my view, a protein has evolved as a dynamic structure and the evolution of the dynamics is every bit as important as the evolution of the so-called static structure which people often struggle to preserve in their minds. In fact, the object that they are looking at, the protein, is a part of a machine and a constantly working machine. In such a case, a snap image of an apparently rigid structure is not really what you want. You need an image of machinery working. For me, the machinery of interest is metals plus proteins in dynamic action. The Enzyme Group was a unit within which I could work to this end. In fact, I believe the dynamics are being more and more recognised. I have written a review on this topic [33]. Let me finish by saying that the Oxford Enzyme Group was a remarkable success. There was the general success of the group, of course, but here I am talking about my own work. It allowed me to turn away from models to study metals in proteins. I should say that, in 1967, I had stopped teaching chemistry and took a cut in salary in order to teach biochemistry (1967–1974). I hardly published again in inorganic or chemical journals. All our papers, there must be over 200, on electron transfer proteins, on kinases, on iron proteins, on calcium proteins, and so on have a simple objective, to use NMR to demonstrate connection between mechanical movements and biological action. I do not think that the significance of these findings is yet recognised since, to this day, there is too much emphasis on structure in biology. We have to uncover the dynamics of metal ion/protein interactions.

H.A.O.H. You were appointed the Royal Society Napier Research Professorship in 1974. Obviously, that allowed you freedom to continue actively your work on nuclear magnetic resonance spectroscopy but was your later work on what we might call bioinorganic solid state chemistry stimulated by what I believe is one of the aims of the Napier Professorship, an interest in cancer?

When I was appointed the Royal Society Napier Research Professor in 1974 that did allow me a very great deal of freedom to work within the area of NMR on proteins and with a group of very, very able people. Undoubtedly I didn't know so much NMR but they taught me NMR as we went along. The question you ask there, however, is about the relationship of the study of bioinorganic chemistry in the solid state, the biominerals, and did it originate from thinking about cancer. The answer to this is no; I did not even take the point that the Napier Professorship was, in fact, related to cancer as a very strong lead. I spoke with Professor Rodney Porter about it — he was on the appointing committee and he told me that if I got somewhere near cancer that would be fine but that if I didn't nobody would be too surprised. What I took the task to be, was a wider view. As a matter of fact, if you read the description of the Napier Professorship it states something along the lines that the professor should investigate potential causes of any disease, where the disease is not understood. Now in this general area I think the study of metal ions is vitally important. For one of the things I believe, and I have believed it for some time, is that actually cancer is a loss of homeostatic balance in a cell, which comes about in many ways at the DNA level, i.e. it is not a particular disease with a simple cause. The loss of homeostatic balance would then be relayed through a large number of different features of a cell and one of these I believe will be the calcium levels. The calcium levels then feed back and cause more changes. I think, as you can read in my most recent papers or my book with Frausto da Silva [34], that elements such as calcium are in homeostatic balance not only with themselves but with the whole phosphorylation control system. This means that the calcium/phosphorylation balance is a statement of the nature of a cell. You could, therefore, equally well say that a cancer cell arises because of a loss of phosphate homeostasis. But, you see, these two in an integrated organism are completely knitted together. You can even extend that and find that these two elements are knitted together with the homeostasis of other elements. So you may say that the homeostasis of zinc and iron are wrong in a cancer cell. If this is the case, then what we will find is that there are feedback circuits between such ions as calcium levels in cells, phosphate and other ions in cells and the proteins which interact with them, which means, of course, that the feedback has to be all the way to the DNA. If you get even small damage of a certain kind in the DNA, e.g. loss of regulation of a kinase or a calcium balance, it could, in fact, cause a damaging effect through a huge amplifying interaction via the multiplicity of controls where calcium–phosphate and other ion systems interact. This could be cancer since the cell loses its homeostatic identity. So I say no, I didn't really bother too much and I am still not bothered too much about the direct study of cancer although I have lectured on cancer, even in the Cancer Research Institute in London, along these lines and I have published my views [35].

Just as a side remark, however, you might notice that the platinum drug $Pt(NH_3)_2Cl_2$, which was developed by Barney Rosenberg, was a research topic with which I was involved but not too directly. Barney asked me many years ago, before

1975, to be his consultant on the platinum programme. I refused to do that but I did send my pupil Andy Thomson to work with Barney and in part it was Andy in Barney Rosenberg's laboratory who discovered the precise nature of the platinum drug. Andy's only experience with me was really in the spectroscopy of square planar platinum complexes. But at least he had an insight into platinum chemistry from Oxford which proved useful in an attack on a cancer drug. In fact, the first meeting on platinum drugs in cancer research was run by me in the Inorganic Chemistry Laboratory, Oxford. Barney is another man with whom I have lost contact. He is remarkable in his imaginative approach, which does not fit well in the USA scene.

The start of the study of bio-minerals had nothing to do with cancer, though there is a connection via asbestosis, but to do with the fact that NMR studies were getting to be too difficult for some new students. I then thought of something different for them to work on. The work has been wonderfully well continued by my two early pupils Stephen Mann and Carole Perry [36].

H.A.O.H. Both nuclear magnetic resonance spectroscopy and inorganic biochemistry are now successful fields of research and still growing rapidly. Are there any other subjects that demand much greater interest from inorganic chemists?

That's an almost impossible question but I think I would stress again that I believe that the inorganic chemist is not looking at material science with the fullness of that subject in view; he is missing out on all the mechanical properties of matter for the sake of the electrical and magnetic properties. And I think that will change fairly rapidly. Fairly soon now some bright young men and women will get hold of the mechanical properties of materials and relate them to the chemical composition, just as we do with electrical and magnetic properties. But I haven't seen that happening yet in inorganic chemistry laboratories though protein chemists are aware. That is one of the things I could well have taken up. The other area I would certainly take up would be self-assembly, the way in which crystals assemble, and then the way in which non-homogeneous systems can assemble through recognition of surfaces. I think inorganic chemists could play a very big part here simply because they can see their atoms so easily. The major study would use the electron microscope, a tool not employed thoroughly in bio-inorganic chemistry yet by inorganic chemists.

H.A.O.H. One used to hear that chemists or biochemists were somewhat apprehensive about giving seminars in Oxford because you would be in the audience. Did you realise that you had this reputation for asking what were taken as challenging questions?

I did not realise I had the reputation for asking what were taken as challenging or even aggressive questions. I have never thought of that. I genuinely think that I have asked questions only in the sense that I have not understood what the man (or woman) said in the lecture. Being naturally inquisitive and somewhat excitable I tend to jump into something rather quickly and say basically, "I don't understand what you (the lecturer) said there". That is not intended to say that what you (the lecturer) said is wrong. It is intended to say that I (Williams) don't understand what you said but I would like to know what it is that you have said so that it's clear in my head. I realise that if that's said in a wrong tone it would sound fairly aggressive. But as people get to know me, I don't think they think I have any damaging intent. I hope not. I think my intent was fairly much to try to put my own point of view and at the same time to try to understand somebody else's. In today's science, you cannot hide your light under a bushel. We are competitors for money and fame as well as enquiring scientists and sometimes the going is rough.

H.A.O.H. How would you summarise your contributions since you left this "model" work, i.e. the work on small metal complexes?

My contributions since I left model work have been on different levels. The first level really was to investigate through spectroscopy the nature of metal centres in such proteins as zinc and copper proteins, haemproteins and in the iron oxo-bridged system. We also worked together, you will remember, on the vitamin B_{12} enzymes. There were several fairly orthodox examinations of metal centres within proteins. Some parts of it, which I didn't actually do but I managed to stimulate other people to do, were extremely interesting. For example, I brought together Whatley, Thornley, Hall and Gibson in a team to look at the nature of the iron-sulphur centres and they actually solved the Fe_2S_2 centre [37]. It was necessary to get a top class physicist, Thornley, on the problem. Another parallel type of work, which was done experimentally by others, not by me, but I had long discussions with them on the interpretation, was the ligand field spectrum of carbonic anhydrase. This work was with Lindskog, a pupil of Malmstrom, when he came and visited me and stayed in Oxford for a day or two [38]. The work has been up-dated by Bertini's Group in Florence. We also interpreted the spectrum of ribonucleotide reductase for Reichard though later on, of course, it was more beautifully examined by Ehrenberg in Sweden. In fact, quite often people came and still come to me to discuss various aspects of the spectra or the nature of the compounds they had seen in biology or in compounds, proteins, they had separated. I had an exchange with Klug some time back where Klug thought that his collaborators had found a copper protein in the nucleus of cells. I stressed that I didn't believe that the copper proteins would be found there (though one or two have been now) and that they would be zinc proteins. I believed that he was finding copper through using EPR spectroscopy since of course you find copper everywhere if you use EPR: it is sensitive to very small traces of copper. Later, and by hard work, Klug and his collaborators found zinc fingers. This was a part of my work after the model period finished. Another part of my work really was just arguing about the nature of protons and the way protons drove ATP formation and I've continued with that debate really on what I suppose you could call a semi-theoretical basis. I am just looking at the systems and saying how I think they work. My stress here is on flux or flow in a system rather on static steady states. Again, in a direct sense, this work has been greatly advanced experimentally by others and not really by myself, but I have maintained sufficient interest in it to read and to write about it. At the same time, we have provided in-depth knowledge of how the component proteins work in electron transfer and phosphorylation. This has involved us in very detailed NMR work as mentioned before. Here I must mention yourself, G.R. Moore, A.V. Xavier, and P.E. Wright. Then, of course, there is the NMR work on the other proteins, especially calcium proteins, which really was based on my intention to find out about the mobility of especially metalloproteins. If you put together that work with the work on flow of ions, then you begin to get a more general conceptual idea of how an intact biological system will work or could work. (An example is given by the work with B.A. Levine and later R.E. Klevit [39] on calcium proteins in messenger systems.) Biology works, I believe, like some giant machinery with intensive feedback. The feedback depends upon a flow of metal ions of different kinds with very different rate constants, including, of course, sodium and potassium, magnesium and calcium but also zinc and iron, which are a part of the homeostasis of the system. Of course, homeostasis depends on feedback. That's one side of the feedback, the ion flow; the other side of the feedback system is the interaction of those metal ions with proteins and through the proteins to DNA and then back again to synthesis or destruction of proteins. So I have to try to describe a huge organised system in terms of the single proteins I investigated, which is very hard to do. It is like trying to imagine a bicycle or think about how a bicycle works when you are just looking at the bits lying on the floor — the saddle, the chain, the wheels, and odd pieces. It needs a great act of imagination to be able to get through to the whole system from the pieces. But I have tried all the time to keep in my mind this central issue. After I left models and while investigating bits, I have always tried to draw diagrams of how the bits, that's the proteins that I study, fit into a cellular or even a multi-cellular system. So I would say that my contribution has been to attempt to drive people back to looking at whole systems, to go away from the models and broken-down pieces which we normally examine, and to put inorganic chemistry into the context of real biological systems. Of course this has involved exchanges on electron transfer, proton tunnelling, enzyme action and so on but they are not the centre of the attack.

H.A.O.H. You said previously that you left "model" work to others. Do you not agree that the study of, for example, metalloproteins or metalloenzymes only provides information which "models" how they appear in vivo?

I don't agree that studying extracted enzymes and proteins is similar to modelling. I think you are working on bits of real systems but you do have to use your imagination to see how they fit into the whole body of the cell.

H.A.O.H. You have been active in commenting on, and criticising, some aspects of the development of scientific policy in the United Kingdom. Did that have, could it have had, any effect?

Now we have a very big jump to the development of policy. I have criticised scientific policy in the United Kingdom a great deal. I believe that it is led incorrectly. I think the first point of a scientific policy must be to make sure you have a reserve of trained people for your needs. A great lack in Britain or the United States is trained people. It is not just money for research, it is not necessarily good research ideas that hinders us, it is that the right number of people are not being produced in the education system. And this, I believe, stems especially from the class society in Britain, that is, from the nature of public school education, the way that's affected the university attitude to technology and so on, and the way it has led to a downgraded state education. It's left Britain stranded with a very fine intellectual level at the top but no high technical skills in those people who have this intellectual capacity. These are the relatively rich. Those who have not got money, perhaps 80% of British people, are not trained to be able to do very much (especially to govern!). If you are missing all those people, then I think you cannot expect to produce a very fine society. This affects science to the greatest degree. At a lower level, good equipment in large enough quantities will not be produced and looked after without large numbers of trained people. It is that fine equipment together with the intellectual and technical approach that you need in order to achieve anything in science, whether it is in an academic science or in an industrial science. It is also necessary to train a large body of such people to produce wealth. I do not forget that you need a great deal of money today to achieve your ends as a scientist but the money for research comes second to trained people. So I think a lot of agencies and groups of people who keep shouting about putting more money into British research now (lots of scientists seem to do that) are misguided. What the scientists should do, and I would name all the societies, the Royal Society, the Royal Society of Chemistry, and so on, all of them should be screaming at the government to put more money into school education first. If you had an educated population in Britain and USA then you'd get a great deal of pressure from that population, who would understand what you were about, to do more research and to do more thinking in science. They would be willing to pay because they would see the benefit. Science could be treated even as a general cultural activity in society, much as music or poetry or any form of art is. I believe that is science's proper place in the end. Its proper place is not just to create material goods and comfort, this can be seen to be achievable, but to create a full life with human satisfaction. If you wish to create human satisfaction in a complex, civilised society you can only do it if you have trained people. It's no good suddenly offering complex music, even music like that of Beethoven and Bach, to somebody who has had no chance of hearing and learning about the music of great composers before. He has to hear it and learn to listen when he is young to really get into it in the right way. That goes for chemistry too but we don't treat it like that. We in Britain treat it in some rather offhand way culturally as if it's something which really we don't want to do but have to do in order to make money and to be comfortable. That is a thundering mistake. The other thing I think is incorrect is this incessant drive to do research faster and faster with no thinking about purpose and consequence. Here, many scientists are at fault. It is now the case that universities are being pushed around. They are being forced into research with objectives (often in large groups) when they don't necessarily wish to do that and maybe research should be of second-level priority for many scientists. Scientists might want to teach at an intellectual level in science without much of a research aim or a material outcome. They are being pushed in the wrong direction from the Science Research Councils in Britain who in turn are pushed by government caught in their own propaganda trap of material wealth. I think all that is a mistake. It will drive intellectual people away from science and more into borderline subjects or art subjects where they can develop themselves, have time to read and think, and are not forced into directed teams. The people in the research councils who see research in terms of big groups and teams are themselves already old men and out of the top of the system. So they look at research and think "Yes, I could organise a big team to do this or that". They don't seem to see the position of a young person who is just joining this team. He will, in fact, be lucky if he gets anything better than a hand on some machinery under the direction of some other person. I don't believe that's an imposition a society should put on science enquiry in a university. Industry is quite different; it has different objectives.

Have my talks and writings had any effect? I don't know. Time will tell. I notice that there are more people who say these things now and maybe, if I keep on, something will come of it. You know it's like water dropping on a stone: it takes a long time to change ideas and you may not live to see results. I think I shall just keep on saying what I think, in the same way I have said it in the past.

H.A.O.H. I have always got the impression that you certainly don't seek committee work yet presumably there have been instances where you considered it important to engage in the organisation of various bodies.

Allen, to explain my attitude to committees I have to first say something about myself. I know that I am excitable and I also know that I easily become frustrated when nothing seems to be happening in the way I want it to happen. So the first problem with sitting in a committee for me is that I find myself getting, in a way, just generally agitated. Some people don't suffer in that way and can use a committee to develop things in the way they want them to go. I do believe that committees are essential because we live in a democracy and must listen to all types of opinion on almost everything we do. I also know they slow up action by individuals, often for good reason, but I am not a suitable person for them. There is a second thing. I have a great love for the work I do, which comes from myself not committees, and I think that I can do it in a way which is interesting. I can also enthuse the young and I have managed to teach a lot of very, very good people how to do chemistry and how to approach it in an imaginative way. If you give your time to committees of all kinds you find that really you have no time to look after young people. Again, you have no time to read. Most chemists today hardly read anything. They write papers, but they don't read papers, never mind literature. They just don't have time because they are sitting on committees, organising lots of different things, and, if I may say so, in universities they are too much in laboratories. Perhaps they are even doing too much experimental and organisational work without thinking about the subject enough. So I have kept away from committees. In college in Oxford you are supposed to do your share of the general work of the college. I have never done that so perhaps it could be said that I am at fault. In the laboratory I have had to do very little committee work and again you could say that is not what you should do. But here I have a defence in the sense that I was elected to a Royal Society Research Professorship and in that position one doesn't expect to do much committee or organisation work. I would never have accepted a chair with headship of a department, I would be no good. I have not worked in committees in the University either, not on Faculty Board committees or General Board committees at all. On national committees I have also refused to serve on occasions. I have on one occasion been on an international committee. I found that, at my very first meeting, there were at least 20 distinguished people sitting round a table. All of these people seemed to me to be spending their time working on very small problems, and very small details within those problems. I just couldn't stand that. I walked out and I resigned immediately. I have not worked for societies like the Chemical Society either, or even for research councils in large measure. I have tried my best, in fact, to avoid all those jobs. I think one reason is my intrinsic unsuitability from my nature and the second is that I really thought that I could do a job in chemistry for young people in a way which others perhaps could not. This may be a conceit, but it made me decline all opportunities of preferment through committee work either locally, nationally or internationally. I do not and did not wish to climb a political ladder. I am very glad to see that there are those who love to so climb. They do an excellent job and deserve the rewards of that kind of life; it is not for me.

Just recently, since I have retired, I have of course changed and now I am in charge of various things within my college, that is, Wadham College, Oxford, of which I am proud to be a member. I am, as you know, the President of the Dalton (Inorganic) Division of the Royal Society of Chemistry in Britain. But I still do not wish to sit on committees generally since I now want to give my time to writing books which will explain my work and also my attitudes to society. As we stated earlier, I have often quarrelled with the way in which science is run and I would like to put my quarrel down in writing. Do we as scientists really believe that we can continue with a materialist approach for another 200 years when we look back at the last 200 years? Where should we go?

H.A.O.H. You have always worked at the University of Oxford. Presumably there have been advantages and disadvantages in doing so?

Again, I think the answer to this question lies in my nature. I like to have a base from which I can work and the base has to be some place in which I feel secure and where I know my way around so that I do not have to be fighting my way through a new system in order to get it in order for myself. In Oxford, I have a close family life. I know, too, the people with whom I have to work, experts in different laboratories, and the libraries, where they are and what they contain, so that I can get the information I require or the contact I need as quickly as possible in an atmosphere which has been extremely friendly to me all the time. Therefore I did not take sabbatical leave in the way I could have done. I did not travel to foreign laboratories or other laboratories in the way I might have done. I preferred to stay and work locally with the people I know. I do not think I lost and I avoided a lot of scrambling about and re-establishing of my base.

I even do this within the neighbourhood in which I live. I find that now I know the neighbourhood I can actually work with the people to try to improve it. So I do work with neighbours trying to make sure that the area round us, which has some fields as well as some houses, is made better for the people, some rather rich, some rather poor, who live in it. That takes a little time but it is certainly not committee work; it often involves my using a shovel and a spade to clear up a ditch for example. And it is this local activity which I like. I want to build myself into things and systems rather than be engaged in ones about which I know little and for which I have very little feeling. If I went into politics I would stay in local affairs. National affairs are for others. So Oxford University and Oxford itself is effectively my place for living a full life.

I suppose I should add that I have little need for things around me in my private life. I am very content to live in a very modest way really. I don't have great ambitions in the way I live. I don't care for machinery from typewriters up; I prefer a pen. It goes without saying that we are a close family on which I depend to a degree which could not be elaborated upon here.

H.A.O.H. You have had many students, post-docs and collaborators. I seem to recall that one of the pleasures of working with you was that you don't run what is known as a "tight ship", seeming to prefer a more "relaxed" form of supervision or collaboration. Is that correct?

No, I do not run a tight ship. I never have done. I believe that after the initial period of fairly tight supervision and watching a person you must choose to let him or her go. You can guide all the time but if you try to dominate or organise too tightly then I don't think you give young people the chance to explore on their own. The thrill for a young person is to come to an older one and to say to him I have found out something that you don't know and I'll show it to you. They love to do that. So if a student does an experiment and can explain it to you – what they have observed and the explanation – and especially if it is not what you expected, then there is a moment for the student which nobody can give them; students must get it for themselves. The Irving–Williams series gave me that joy. So I again think that, in an experimental science, you must try your best to give as much freedom of action as possible to those who work with you. I have found that this procedure works. Very occasionally there are young (and old) people who try to take advantage and are just plainly sloppy or disorganised (or selfish) and you just have to put up with them and manage them as best you can. But for the most part, and I am now looking over a period of more than 40 years, I have had the good fortune of having very distinguished and able young people working with me and they have gone away from me and proved themselves as independent thinkers. That is my boast.

H.A.O.H. Of your research students and collaborators, some 50 people now hold academic positions. Can you trace their careers back to the time they spent with you?

The answer for many of them is obviously yes. Consider someone such as say Andy Thomson who has developed a technique which was not running at Oxford at any time, magnetic circular dichroism. Now he developed this type of protein study so as to engage in an examination of haemproteins or iron–sulphur proteins. They are the types of protein with which we worked in Oxford, although Thompson himself actually did not work on anything of that kind. He worked with me on platinum compounds and really just worked on the ligand field spectroscopy of these compounds. So he learnt some lessons from me but then went his own way to develop a related field. Some other students have gone much further away from the subjects that I am interested in. Take, for example Michael Pope, who worked with me very early in the 1950s on polymers and especially condensation polymers, that is on the chromatography of organic polymers. After he left me, he worked in the United States and turned his attention, and has continued to turn his attention, to polymerised inorganic compounds, especially polymolybdates and polytungstates. Now there is a connection which is through a friend of mine in the United States called Lou Baker who was working on the condensation reactions of molybdate and tungstate. I arranged for Michael to work with him. It was with Lou Baker that Michael Pope started his career research work. So in one sense he is now a student of Lou Baker and not a student of mine. In another sense he researches on condensation reactions. So far this supposes you look at development of people from a pure research topic point of view. There are some others who have gone further away. Professor Littler, who works in the University of London, is concerned with the way in which houses should be constructed in order to make them efficient in every possible way, including energy losses and so on. I don't think you could say that that connects with my work at all but he studied with me about materials. So there is a great diversity really from the people who are more straightforwardly working on lines which I think I might say I initiated and people who went a long way away from the things that I did. Occasionally I said to people when they left me: "All right, I will stop working on this subject if you continue it when you take up your new position." That happened, for example, with Philip Mitchell who works at Reading University on molybdenum in general and I just said to him after he had finished his D.Phil. on molybdenum compounds: "Okay, you take over molybdenum."

H.A.O.H. Who, in turn, were the older men or women from whom you received advice, ideas, stimulation or criticism?

Obviously I must first mention Harry Irving with whom I did my D.Phil. and Tiselius with whom I did my post-doc. I was also greatly helped by Dr. C.S.G. Phillips when we worked together. Then in a curious way, I think Hinshelwood helped me because at least he gave me a job and at times he set me challenges in conversation. One of them was to look at the catalysis of the reaction of CO_2 and water and I did that with a student, Dennard [40]. I think we actually solved the problem of the catalytic reactions of CO_2 and water, describing a cyclic intermediate. That cyclic intermediate is not far from the intermediate that is now accepted as the one through which carbonic anhydrase catalyses the reaction in biology. Subsequent to that, of course, I was greatly helped by Bert Vallee but he is really just about of my own age. There were senior people who helped us in the States, especially Prof. Eric Ball in Harvard. He told Bert and me to stick together. We did for a long time. (There were many in Harvard who I think hindered Bert Vallee a great deal and caused him to rather despise the Harvard system.) At home I was not greatly helped later by senior people. I think that most of the biochemists thought that the work we did on metals was not going to lead anywhere. The inorganic chemists just showed no interest for more than 20 years and many of the professors of inorganic chemistry in Britain are only waking up now. Views are changing very quickly, of course, with the knowledge of all the different iron proteins, all the different zinc proteins, enzymes and fingers, the calcium chemistry, the knowledge that metals are interacting with the genes and so on. I think that I was not greatly helped over my career, but neither was I hindered. I was more or less left to get on in my own way, which was a blessing as it turned out. I feel sorry for the driven nature of much of chemistry today, there is no time for thought.

H.A.O.H. What do you think are the most promising new aspects of inorganic biochemistry?

I think that the inorganic chemist has a very big role to play in biochemistry and in the study of integrated biological systems in the future. In the first place, he can develop ways of examining the biological materials. For example, through electron microscopy he can help with the designing of stains. He can help by making contrast agents for whole-body scanning by NMR. In fact, I put forward the idea of using gadolinium in a paper given at the Royal Society some time ago [41]. There are many potential applications of probes. He can study, as you do so successfully, sensors for biological systems of various kinds and the theory of sensors. He can then move away from the probing of biological systems, or the tools for probing biological systems, and go directly to the study of drugs. A whole range of new inorganic drugs are bound to be developed in the next 10 or 20 years. It takes a long time to bring them to fruition but all the same I think it is a very interesting way to tackle the problems of viral infections rather than the problems of, say, antibacterial agents. I think the antiviral agents will often be inorganic compounds. The platinum anti-cancer compound is working in that direction in the sense that it attacks the DNA. Because a virus is often hidden as a provirus, you must force it into the open by attacking DNA before the immune system can tackle it. As far as cancer is concerned, there will be many attempts to cure cancer but I think that's a matter of killing cells and it is an extremely hazardous attack. There I think we just have to be lucky if we are going to get inorganic drugs as successful as the platinum series of drugs. Another great interest is to develop understanding of biomaterials and not just as replacements for bones or teeth or damaged tissues of various kinds but actually to develop them so that we have a better understanding of the mechanical properties of matter. I think here we are very feeble in our knowledge and we have been very slow to develop. It is a matter of putting large organic polymers together with microcrystallised or micro-bits of amorphous matter, just to see what you can get in comparison with, say, bone and sea shells. I think this will involve a long, long study of varieties of polymers and varieties of crystallised materials. Then, of course, inorganic chemists can try another role, which is to look back at the origin-of-life story and here I don't think you can look at it very directly. What you should do is to say to yourself what could be a possible way of starting synthetic chemistry on earth? I have in mind the use of surfaces of sulphides. I think the reactions on the surfaces of iron sulphides will be extremely interesting as put forward in part by Wachterhauser. This field could develop very strongly in the future. It really might replace the sort of phosphine chemistry that organometallic people do so much today: that is using sulphides in their place.

I think another interesting area of bioinorganic chemistry will be in considerations of evolution. That is the way in which, during the course of time, the element availability has changed due to the changing atmosphere partly due to the influence of life itself. In particular, I draw attention to the fact that, when oxygen became available on the surface of the earth, it completely altered the levels of various elements such as copper and zinc which increased, selenium which changed to selenate, molybdenum which changed to molybdate from thiomolybdate and there was also the loss of iron. These changes also made possible changes in the chemistry and biochemistry in the sea of elements such as the halogens, which could be oxidised when oxygen appeared, and therefore combined with organic matter. These developments, I believe, are crucial to an understanding of the whole of the nature of living systems today. In particular, I think the coming of oxygen was coincidental with the development of multicellular life. Multicellular life depends on the ability to utilise both zinc and copper, which were previously locked into sulphides and therefore were much less use to life. I believe this will be a very interesting area for inorganic chemists to study in the future in some depth. It will mean, of course, understanding a great deal about different forms of life. Some of the forms of life may be those taken from the deep ocean vents and there I think nickel will be more important than it is today in multicellular organisms. It's clear that nickel had a role in the hydrogen world but whether it has an important role today or not is a moot point for it seems to be only involved in one or two rather obscure enzymes. Anyway, I think we will have to turn to the way in which these elements are distributed in the cell now and why it is they are distributed in this particular pattern compared with the pattern of distribution a long, long time ago. Here I return to the integrated activity. I think this is a very, very intriguing area for inorganic chemists. We have tried in our book [34] to push these ideas to the limit of today's knowledge but there is an enormous volume of work to be done.

Finally, I think I myself would be most interested in trying to study circuitry and flow systems, mimicking them and finding out exactly how to study them. I believe these exchanges of metal ions from one place to another and their flow and an understanding of that flow is absolutely critical to the way in which a biological system works. We know, of course, about nerve communication with sodium and potassium currents. We know quite a lot about calcium communication through mechanical devices and so forth. What we don't know about is the way the cytoplasm behaves as a chemostat. We know more, in fact, about the way iron behaves in bacteria than the way zinc behaves in higher cells. Although there are a lot of indications of how zinc might behave, at the present time there is very little firmed-up knowledge of its activities. So there are a whole host of different areas into which inorganic biochemistry can go apart from the orthodox ways of studying the variety of enzymes and the variety of structural proteins which contain metal ions.

Somehow the bio-inorganic chemist has not yet woken up to the majesty of his task. We have to say that we know that life is not organic chemistry. Life is the catalysis and control of energised organic reactions in water by inorganic elements.

H.A.O.H. You once said that you like nothing better than writing poetry and climbing Welsh mountains. Is that really true?

Let me take the second point first.

Going away to the mountains is something that a lot of scientists do and I often ask myself why because I am one of those who do. I think actually it is to get away into a different realm where you put yourself in contact with a different level of significance. If you are in a place where it is obvious that you are a rather small object, a human being seeing the huge expanse of the sky and the great distances of the mountains going away and away from you, and when you are far from other people then there's a slight element of perhaps fear, mystery, an element of the unknown entering your mind. This is absent in science study. I think that you quickly become conscious of the fact that studying, especially analytical studying as in science (which is empirical studying, breaking down things) can't really give you the satisfaction which you need of being part of a synthetic whole. You can't get to a whole feeling. I can't see myself or feel myself as a scientist in the context of universal images which are the common language of art and religion. I go to the mountains or even the local countryside to recover certain feelings which you can only really describe in religious words. Science study gives me a different feeling. It is often to do with positive personal assertion, egoism. I think that the mood of tranquil integration into a larger experience is given perhaps to everybody if they allow the mood to come upon them. (I am not a believer in God.) The way I get that and this is true for many a scientist, is to escape into the mountains.

Another way you can get to this state of mind is certainly to listen to music, to read poetry, or to study another person's perception through visual art. You need tranquil contemplation as well as activity, which is most of science. Here I should add that I often go into the mountains with three close friends not chemists, a

Fig. 4. Bob Williams in his favourite land: the hills of North Wales.

historian/industrial manager (Mr. Clive Fell), a vicar in the English Church and interested in literature (Rev. James Fraser) and a musician (Mr. Tom Wess). There is a communion in our times together which I would not live without and it is enhanced by being in the mountains. They and my wife, especially, have given me greater insight into the Arts than I would otherwise have and I would not do without this. It has nothing to do with science.

Now as far as writing poetry is concerned, I think that has to be a joke because I can't write poetry but I have always loved poetry and so, yes, I get a great deal even from the memory of lines of poetry (or prose) which I was *forced* to learn at school, not so much from reading it now. I do very little reading of literature or poetry, and as for writing poetry I never try to write poetry anymore. But I always wish that I could have done that. I love literature; I don't have anything like the time I would like to read. I thoroughly enjoy, say, the classical Russian novels and writings of that sort. For once again when you are reading that literature you get this sense of a larger world outside yourself. After all, what we do as scientists is very much a private work for a short time which is then made public and we argue about it. We go into a chemical laboratory and there couldn't be a drearier physical place to work in. If you look around you there is nothing that is beautiful or touching in that environment. You work with equipment and you produce data and you examine the data. You then expose yourself to criticism. It's all an egocentric activity, driven in the first instance by a need to be identified, though it is often smothered by expressions about human progress. The syntheses that science makes are always empirical and ephemeral or else science must have an end. These science syntheses never have a true global content which fulfils some need, some demand, inside people. It takes but a minute to transcend this world by picking up a book, for example a Russian novel. So, yes, there is a side of me which is looking for a bigger content, which might have been expressed in poetry I could not write, than I believe science can ever give to me and that is in part through the natural world and partly through culture. Going back to my schooldays, it was my teacher, Eggleshaw, who was a great help in introducing me to general concepts through music and particular books and many were not science books. I think that's probably the best place to stop because I would not want to say that I like nothing better than writing poetry or rather than being in the Welsh mountains. I have thoroughly enjoyed the whole of my life working in chemistry and allied subjects but chemistry is not the whole of me. If I started again I would like to do something totally different but only given that I had had the experience of working as a chemist. I frequently think "What a marvellous opportunity I've had since not only have I tripped over some ideas but I have worked with remarkable people trying to demonstrate them." I really believe that we have started a subject of great impact in inorganic biochemistry. I finish by saying, "Thank you to all with whom I have worked and talked. Inorganic chemistry is alive in you".

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