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VIDEO INTERVIEW TRANSCRIPT

Flower, Roderick: transcript of a video interview (14-Apr-2016)

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Flower, Roderick: transcript of a video interview (14-Apr-2016)*

Biography: Professor Roderick Flower PhD DSc FMedSci FRS FRSB HonFBPhS HonLLD HonDSc (b. 1945) trained as a physiologist at Sheffield University, subsequently receiving a PhD in Experimental Pharmacology from the University of London and a DSc in 1985. After 12 years working in industry at the Wellcome Foundation, he left to take the Chair of Pharmacology at the University of Bath in 1985. In 1990 he returned to London to establish a new Unit at the William Harvey Research Institute, Barts and The London School of Medicine and Dentistry. During this time he was Head, on a part-time basis, of the Clinical Pharmacology Department, and was President of the British Pharmacological Society (2000-2003).

[1]. STARTING IN JOHN VANE'S PHARMACOLOGY LAB

Because my father was in the Royal Air Force, I spent a lot of my young career in boarding schools and I have to say I was not a very good student. My favourite subjects were physics, maths and chemistry, but interestingly enough throughout my entire career as a schoolboy I was never taught any biology, which was pretty extraordinary really because the 1950s was the time when Watson and Crick were elucidating the famous structure of DNA [deoxyribonucleic acid], and huge changes were taking place in other sciences as well. Linus Pauling's book was having a deep influence on chemistry, for example, and physicists were preparing to get ready for the launch of the standard model a few years later. So it was a very exciting time in science, but somehow that excitement didn't filter through to the schoolboy lessons, I have to say.

I got into pharmacology and science, I suppose, almost by accident. Although I was always interested in science subjects at school, I never really excelled academically at these schools, and so I left with rather, I wasn't quite sure where to go when I left school. I saw an advert for a laboratory technician to operate a computer, which was posted in *The Daily Telegraph*, this is about 1965. And in those days of course a computer was not simply a desktop machine, it was a device that filled one or two rooms, and required constant supervision. And I thought the job might entail doing that, which was something which quite interested me. So I was invited for an interview and, but when I got there I found out that the job had already gone. But John Vane, who had posted the advert in *The Daily Telegraph* said, 'Well, maybe you'd like to apply instead for a technician job in my pharmacology laboratory?' I'd never heard of pharmacology, I had no idea what it was, and I had to go back that evening and look it up. But I said 'Yes,' I'm not quite sure why but I said 'Yes.' And as soon as I joined the laboratory, I realised this was something which fascinated me deeply, and that I really wanted to work with for the rest of my life. So in a way it was a big chance, but I'm glad it turned out that way.

[2]. THE DISCOVERY OF ANNEXIN, AND STEROID ACTION IN INFLAMMATION

I suppose the single discovery I'm most pleased with really, is the discovery of the protein, which is now called 'annexin A1', as a mediator of steroid action. And this was the result of quite a lot of work on steroid action in the '80s, which culminated in a single experiment which demonstrated unequivocally that steroids caused the release of a soluble protein which had steroid-like effects on other cells. This, when it was finally sequenced and cloned, turned out to be a very important property of the protein, which is now well-

* Interview conducted by Professor Tilli Tansey, for the History of Modern Biomedicine Research Group, 14 April 2016, in the School of History, Queen Mary University of London. Transcribed by Mrs Debra Gee, and edited by Professor Tilli Tansey and Dr Apostolos Zarros.

recognised, and this protein has become firmly established, and is a member of a panel of substances which controls and hastens the healing response in, following injury or inflammation or infection.

Whilst I was working on steroid action, and in particular on the problem of how glucocorticoids could block eicosanoid or prostaglandin synthesis, I hit upon the idea that they probably did this by controlling in some way the release of arachidonic acid from somewhere in the cell, because the release of arachidonic acid is the great limiting step in prostaglandin synthesis. I had the idea perhaps that steroids were interacting with receptors in the cell to cause changes in the transcription of key proteins, and that one of these proteins was released outside the cell and was having these effects in suppressing prostaglandin generation. The problem was how to test it, and this is at a time when the main tools we had were bioassay. And here history came to my rescue in a way, because I remember Otto Loewi's famous experiment, in which he demonstrated that vagal stimulation of one isolated heart released a substance, he called it 'vagusstoff', into the perfusate, which when bathed over a second heart, caused the second heart to slow down, thereby showing the chemical transmission of the nervous impulse in the heart.

And I remembered that and I thought of a way of adapting that to my particular problem. I had two lungs, two perfused guinea pig lungs, or guinea pig perfused lungs, I should say, perfused in series so that the effluent of one went into the second lung. I found that by infusing steroids into the first lung they would eventually release a protein which had an effect in the second lung. I knew it couldn't be the steroids that were having the effect in the second lung, because I was able to block their effect by adding inhibitors of protein or RNA [ribonucleic acid] synthesis. So we had a very neat experiment, pretty much based on Otto Loewi's famous experiment which quite clearly demonstrated a transferable factor generated in one piece of tissue and transferred in the perfusate, pumped through the second tissue to produce a biological effect. And that's in fact the effect we also saw when the protein had been cloned and sequenced, and we were able to prepare it in a highly purified form.

[3]. JOHN VANE'S RESEARCH LAB, THE ROYAL COLLEGE OF SURGEONS

Vane's laboratory at the Royal College of Surgeons was a very interesting place to work in the mid-60s. Actually, he shared the laboratory with Gustav Born. They were both, both of these distinguished people had their own groups, but managed to live alongside perfectly peacefully and without any major problems. One of the nice things about this Department was that three times a day everybody would meet in the middle by a coffee machine and we'd have coffee in the morning, coffee after lunch, and tea in the afternoon. And the great thing about this meeting point was everybody came, including the cleaners, everybody was there, anyone could speak to anyone else, everyone could suggest ideas, and it was often over a cup of coffee in the morning that the best ideas were batted backwards and forwards, or criticised, or demolished.

These were discussed in a completely free and open fashion between the two Departments and between personnel, and it was a wonderful mechanism for catching up-to-date with what people were thinking and for generating new ideas. It's a great shame that you can't do that sort of thing today because of health and safety prevents you from having coffee machines in the laboratory, but I can testify to the enormous power of having, of meeting your colleagues on regular occasions throughout the day to exchange ideas.

[4]. JOHN VANE

Throughout my career I've been really lucky with the people that I've worked with, and I suppose top of the list has got to come John Vane. I first met John when I was being interviewed for this post, which I mentioned, as the laboratory technician, and I became eventually his technician and I worked with him for two to three years before I went to Sheffield to read physiology as a degree course. But John was an extraordinary person. He was an amazing lateral thinker and intuitive scientist. He was very impatient, he loved his bioassay techniques because he got results in real time. He hated waiting around for them but I learnt an awful lot from him and, really, John made a series of extraordinary discoveries. The one which everyone knows him for, of course, is the discovery of the mechanism of action of aspirin at the molecular level. But also he made immense contributions to the development of angiotensin converting enzyme

inhibitors. It was his original idea to use agents which blocked bradykinin breakdown as inhibitors of angiotensin converting enzyme, and it was his input into E. R. Squibb & Sons, which resulted eventually in the development of captopril, a drug which revolutionised cardiovascular medicine.

So John was an extraordinary person. I came back later to the Department as his PhD-student, and I then was invited by him to join him at the Wellcome Foundation as a member of his new Prostaglandin Research Group. And I remained there with him for 12½ years before leaving and going to the University of Bath. But then five years later almost, or just over five years later, we were back together again because John had rung me up from London to say he was thinking of starting off a new Institute in London. I went to the University of Bath, but then some five or so years later we were back together because John had telephoned me to say he was thinking of starting a new Institute in London and would I like to be part of it? John Vane had moved from the Wellcome Foundation himself, a year after I left, so that would be about 1986, and he had been given some space, just a couple of rooms, an office and a lab or something, at what used to be Bart's Hospital Medical College campus on Charterhouse Square. And he had the idea of maybe gathering around him some former colleagues to try and start another independent Group, and he rang me up and said, 'Would I like to join him?' And after thinking about it for a while, I said 'Yes,' but I had no idea about the way this venture would eventually turn out.

[5]. PROFESSOR OF PHARMACOLOGY, UNIVERSITY OF BATH

I think one of the most challenging parts of my career was when I moved from industry, that's to say the Wellcome Foundation, to my first major academic appointment, which was the University of Bath. I moved in 1985 and I was, I held the position of Professor of Pharmacology. I found the, I was used to a sort of scientific ethos where everyone exchanged ideas and exchanged and talked about science all the time really, not only during work hours but out of work hours, and we often socialised a lot. For example, in those days we knew each other very well, our families and so on. And this was in my opinion very, very important for the sort of creative process. When I moved to Bath I was sort of looking forward to having something like this except on a much grander scale, being able to interact with people from different disciplines, because Bath of course was a multidisciplinary University. But, in fact, I found the reverse actually. Hardly anyone in the senior common room wanted to talk about their work, their science, their students. Mostly the talk was about disputes over space and disputes over promotions. So I found this a bit uncongenial, and actually a bit disappointing, and actually it was a major challenge to find other outlets for my desire to discuss science in depth with people.

One of the good things about Bath was the opportunity to interact directly with some really excellent physicians. You see Bath has been a centre for the treatment of rheumatic diseases for centuries, and the Royal Mineral Water Hospital, which is where this, a lot of these physicians worked, was home to a number of really excellent physicians. And because I had an interest in inflammation and its control, we naturally worked together and published lots of papers where we worked on patients or samples from patients, and were able to try and translate some of our ideas into clinical observations. And I think this is very, very important if you can do it. Another thing which sprang almost directly out of this interaction with the clinicians was that I managed to start off a Faculty of Postgraduate Medicine while I was at Bath, specifically to cater for the interactions between clinicians and scientists at the University and between the scientists at the University and the clinicians in town. So these were very, very productive years for a variety of reasons; very, very synergistic interactions there.

When I went to Bath I was frankly a bit shocked that no one in the University hierarchy really asked me about how my research was going. I mean obviously my close colleagues did. But what they did ask me was how much money I'd managed to bring into the University. And I found this really to me, for somebody who has always regarded science as a vocation, extremely distressing, and it reminded me of Thomas Beecham once said, 'The British public don't like music, but they like the noise it makes.' And I felt almost the same about the University's attitude to science: they didn't like the science but they liked the money it brought in. And I found this extraordinary. And in fact it was one of the reasons, in a way, why I was very

happy to accept an invitation to go back to London in the end, to a community of people I knew were very interested in science, and very interested in talking about it and discussing it.

[6]. THE WILLIAM HARVEY RESEARCH INSTITUTE

So 1989 saw me leaving Bath and heading towards London. I'd given up my full-time academic career at Bath in the expectation that I would be able to make my own way again in London, even though I had no particular promise of any money at that time. I was very lucky that I was able to get through the generosity of Eli Lilly, a five-year stipend to set up a Chair of Biochemical Pharmacology, and after that I managed to obtain a Wellcome Trust Programme Grant, and subsequently Wellcome Trust Senior Fellowship awards, which kept me going for most of my career there. But to begin with, the Harvey was just an informal collection of Departments on the Charterhouse Square site, but we took a big step forward in formalising this in 1990 and 1991 when we created a completely free-standing, self-supporting Institute within the Medical School grounds, but not dependent upon them, and we called this of course 'The William Harvey Research Institute', and we set it up as a medical charity registered with the AMRC [Association of Medical Research Charities]. And the following year we also set up William Harvey Research Ltd, which was a commercial spin-off company which enabled us to trade our ideas and dispose of intellectual property that we may have in exchange for research funding.

We were very lucky, largely again through John's influence, to receive major funding from Ono Pharmaceutical, and they kept us supplied with a good supply of grant money for about five years, and even a bit more, a bit longer than that. And this enabled the Institute to expand from about 30 people up to about 100. And we had very, very good times, very, very productive and 'The Harvey', as we called it, quickly established itself as one of the premier sites for training postgraduate pharmacologists in the country, if not the world. However, there was a downturn in the global financial markets in the late 1990s, and this eventually found its way through to funding sources for the pharmaceutical industry and, eventually, Ono had to stop the funding stream, and we were suddenly a bit cut-off without our major benefactor. Although we had other grants coming in from a variety of sources, we realised that we'd have to take some action in order to preserve the structure of The Harvey, and in particular protect the careers of the young people who had really grown up by now and matured in many cases into very, very fine scientists indeed.

So one of the options that we considered was actually merging with the Medical College, and we'd had discussions with them over the last, say between 1995 onwards, but when I was Director of the Institute, from 1998-2002, it fell to me to put the final pieces in place in the negotiation, and also to sign off the merger deal. And in exchange for our assets, both material and intellectual, the Medical College agreed to stabilise the careers of certain key individuals within the Institute, such that they could be taken onto the payroll, the staff College payroll, thereby protecting the structure of the Institute for the next, well, until now really. And it's worked out really well thanks largely to the inspired leadership of subsequent Directors, but the Institute now has over 350 people and runs its own degree courses, postgraduate courses, and is probably the largest Institute in the world that deals primarily with pharmacological matters and pharmacological affairs.

[7]. BIOASSAY

Virtually all the work in John Vane's laboratory utilised bioassay as a method of investigating problems, and this was a tradition which John had inherited. The British pharmacological tradition had its roots really in the physiological tradition, and so bioassay was its key technique. In fact, I think it was Gaddum who said, 'Pharmacologists are jacks of all trades, but they have one technique which is their own, and that's the technique of bioassay.' I think, paraphrasing, that's roughly what he said. But all, we all became very skilled at doing bioassay in his lab, and these were not simple bioassays to do. Not only did you have one piece of smooth muscle in organ bath or in a cascade, you often had five or six, sometimes more all being perfused, maybe in sequence or in parallel, with either perfusate from perfused organs, or blood from animals, or even human volunteers. And it's extraordinary the sensitivity of these assays, and how quickly they responded. And the really good thing about them is their speed really, and it was this which enabled John

to make two big discoveries, or John and his colleagues. One was the discovery of something which he called 'RCS', 'rabbit aorta contracting substance'. Nobody knew what that was at the time. It had a half-life of 30 seconds, so you can only detect it immediately after its generation, using pieces of isolated smooth muscle. And this subsequently turned out to be thromboxane A2, but the significance of this was [that] John had observed, together with Priscilla Piper and others including me actually, that aspirin blocked the production of this substance. And it was John's realisation that this actually was a substance which came from the cyclooxygenase enzyme, which actually enabled him to crack the whole aspirin enigma.

Another good example was the discovery of prostacyclin. This was discovered at the Wellcome Foundation by the Prostaglandin Research Group, which at that time was headed up by Salvador Moncada. And in this instance, it was the disappearance of the biological activity of prostaglandin endoperoxides which raised everyone's eyebrows and caused them to find out what was happening to the biological activity, only to find it was being transformed to a completely different substance, which itself had a very, very short half-life. Prostacyclin doesn't last more than a few minutes, about five to eight minutes in normal physiological solutions. And so without bioassay, really, you'd never have detected it. So it's an extremely powerful technique, and I know it's largely been supplanted by other techniques these days, but in my opinion it still has a lot of power. And the good thing about it is, once you know that the compound you're dealing with has a particular set of biological actions in a bioassay, then you are very, very confident that that's what it really does *in vivo*. And this knowledge has helped me on many occasions, because when I first discovered the activity of lipocortin or annexin A1, I knew it had very, very potent biological actions. And the fact that it didn't work in this assay or didn't work in that one *in vitro*, didn't bother me at all, because I knew it had those effects and the only question was: how did you explain them?

[8]. LEARNED SOCIETIES; THE BRITISH PHARMACOLOGICAL SOCIETY

I think the role of the learned society in science education and development is one which everyone should appreciate. I explained earlier really that when I went to the University of Bath, not many people were interested in discussing research, and it was really during this time that I became seriously interested in learned societies, because they always seemed to me to be the last place you could go where you could actually talk about science with other practitioners in an open and constructive way. I'd always been, I'd always been an attendee at meetings of the Phys Soc [The Physiological Society] and also the Pharm Soc [British Pharmacological Society; BPS], but during my time at Bath I began to take a very serious interest in the [British] Pharmacological Society. In those days this was a much smaller society than it is today but we used to have four meetings a year. And, in those days, pharmacologists used to go to all four during the year. One was encouraged to do that as part of one's training. So the result was you knew most of the people who went to the meetings on regular occasions. You may not remember their names, but you could certainly recognise their faces. You knew where they worked, you knew roughly what they worked on, and the other thing was you always tried to put in an abstract at each meeting. And this was another very important aspect of your training, as was, of course, presenting an oral communication in exactly 10 minutes and fielding questions from some of the top brains in the field. But it was more than that, because these societies provided a sort of a cradle for the development of younger Members, and more senior Members of the Society often acted as mentors for younger Members and would often for example telephone them and say, 'Have you seen there's a good job going that would just suit you?' or 'Would you like to come to my lab, I've got a demonstration of a bit of equipment?' It was very, very friendly and open, and there was a lot of interaction between those two halves of the membership.

I'm afraid a lot of that seems to have disappeared now, and there are various reasons for this. Many learned societies have reduced the number of annual meetings, so that's one reason, so you don't get to see people so frequently. A second reason I think is there are so many more meetings to go to these days. For example, when I started out as a young pharmacologists, you went to four meetings of the BPS per year, and IUPHAR [International Union of Pharmacology] once every three or four years, and that was your quota of meetings. But now there are so many no one can afford to go to all of them, so you have to be very selective. And I think the important thing about learned society meetings, and probably about all meetings actually, these days anyway, you don't go there necessarily to learn things because if that's the case you might as well stay

at home in your office and read papers on your PC [personal computer], or download something off PubMed, or something, and read it. The reason you go is this exchange of information, ideas, students, techniques, transgenic strains of animals, and it's the human contact. Science, at the end of the day, is a human activity, especially these days. I think the days of a lone scientist have probably gone. Maybe not completely true, but certainly largely true, and most science is done in groups these days, and actually often in worldwide consortia. Just look at some of the genetics papers that have come out recently with 100 authors or something.

So, I think, the nature of science has changed. I think the function of meetings has probably changed and I'm just sad in a way that perhaps so much of the original culture has disappeared, or is disappearing.

[9]. THE BRITISH PHARMACOLOGICAL SOCIETY, AND VARIOUS ROLES WITHIN IT

When I became more involved with the BPS, I agreed to take over the role of an Officer position. So, in those days, the Society was organised in a completely different way to the way it is today. It didn't have a permanent headquarters. The Officers were distributed around the country. There were no permanent staff, so everything had to be done using the help of your students, your postgrads, postdocs or postgrads, or else your PA [Personal Assistant], if you had one. So the first job I took over, the first major job I took over was Meetings Secretary, and this was a three-year appointment which involved organising four meetings a year for three years. And I had to travel around the country seeing people, checking up on their arrangements for their meeting. I saw all the abstracts that were produced, I helped sort them into piles. I helped construct the programme and I helped, I vetted the entertainment suggestions, and so on. It was quite a demanding job and in those days if you were, once you were Meetings Secretary, you automatically went on to serve a further three years as General Secretary, which was the old name for 'President' as it's called now. So this was a further job with different responsibilities, including the general strategic direction of the Society, and often chairing many meetings, and most crucially of all, reading the social minutes after dinner of every meeting of the Society, which again I'm afraid is a nice tradition which has unfortunately gone by the wayside. But these years were, although they were very, very demanding, but in those days it was considered part of your overall obligations as an academic to help run the scientific infrastructure.

In fact everyone was expected to play a role in running the national science infrastructure, and so it was not exceptional to do these jobs. Nowadays it seems to have changed, and everybody seems to be so much more accountable for their time that any outside commitment doesn't immediately result in grant money flowing in. It's rather frowned upon in some circles, but it never used to be and, I think, it was, the Society was all run by volunteers in those days, and it functioned perfectly well.

[10]. REFLECTIONS ON PHARMACOLOGY

Well, I think pharmacology is as a subject, is, it's an enormously important subject, and I think once again it was Gaddum who said, 'Pharmacology is not merely the handmaiden of medicine.' I mean pharmacology started out really as a sort of sub-branch of medicine trying to understand how medicines work and so on. But, in my opinion, it's grown out of that role a long, long time ago. Of course that's a very important part of its job, but looking to the future you can see a role for pharmacology in designing drugs which are not used to treat sick people, but used to treat perfectly well people. In other words, drugs that can be used for human enhancement. And I'm not talking about smoking cannabis or snorting cocaine or anything, I'm talking about drugs which are genuine cognitive enhancers. To ask a provocative question, 'Why should you need to be sick in order to benefit from some of these really powerful drugs?' I mean in some ways we already do this, for example, the contraceptive pill. This is a drug which, it does have a clinical use, but most of its use is sort of a lifestyle use really, it's a lifestyle choice. So why not other drugs? You can have cosmetic surgery, so why not 'cosmetic' pharmacology? Well, once again we do to some extent: we have Botox injections and so on, but I can see enormous scope for expanding the use of pharmacology to treat normal people to enable them to enhance their lives in ways that they want to do. I think it brings a number of interesting problems for drug regulators and a number of interesting ethical issues, and of course interesting

issues for drug designers as well. But, I think in the future we'll see a lot more of these agents coming onto the market.

[11]. FUNDING OF SCIENTIFIC RESEARCH

When I began in science, the scientific world was totally different from the way it is now. Of course Government funding for universities was arranged in a completely different way. In those days universities received their funding directly from the Government and this was distributed to different departments, and the different Department Heads distributed the money as they saw fit. The notion of writing a grant for something was almost unheard of. For example when I was an undergraduate at Sheffield, the Professor of Anatomy was rapped over the knuckles for writing a grant for an electron microscope. And this wasn't just Sheffield. A friend of mine at Oxford told the same story: he wanted to write a grant for a big piece of equipment and was taken quietly aside and told that this grant money was for people who didn't have any other money and that if, as he worked at the University of Oxford, he should have asked Oxford first. So a well-organised Head of Department always had a bit of cash to fund experiments and people and students during the interim of their scholarship funding or something like that.

And, in fact, the other thing is that most of the experiments in those days weren't expensive. You didn't need high tech apparatus in most cases. You didn't need to produce transgenic mice, no one knew about that, of course. So a lot of the experiments probably cost just a few pounds to run. So a little bit of money went an awful long way in those days. The other thing is that there was a much stronger interest, I think, in science for its own sake in those days than there is today. When I went to the University of Bath I was a bit shocked that no one within the University hierarchy, except - obviously - people in my own Department, actually asked me how my research was going.

[12]. THE SOCIAL OBLIGATIONS OF A SCIENTIST

I think every scientist has an obligation, really, to society as well as his or her colleagues at the bench, and in recent years I've done quite a lot towards the understanding of the impacts of modern day science on security, and also on the control of biological and chemical weapons. And this all stemmed from a book which I read when I was an undergraduate in the '60s by Steven Rose on chemical and biological warfare. And this stimulated my interest, and it only really took hold of me when I'd been elected to the Royal Society in 2004, and they appointed me Chair of a committee which looked at in depth on scientific aspects of international security. And from there I've gone on to look at, for example, the impact of neuroscience on conflicts and security. This is a panel I chaired, had many distinguished neuroscientists on the panel. And more recently I've been involved in discussing the way in which scientific advice should be offered to the Biological Weapons Convention, and the Chemical Weapons Convention in order to enable diplomats to rephrase, reframe the Convention, if necessary.

[END OF TRANSCRIPT]

Further related resources:

1. Overy C, Tansey E M (eds) (2013) *Drugs Affecting 5-HT Systems*. Wellcome Witnesses to Contemporary Medicine, vol. 47. London: Queen Mary, University of London.
2. Reynolds L A, Tansey E M (eds) (2003) *The Recent History of Platelets in Thrombosis and Other Disorders*. Wellcome Witnesses to Twentieth Century Medicine, vol. 23. London: Wellcome Trust Centre for the History of Medicine at UCL.
3. Reynolds L A, Tansey E M (eds) (2008) *Clinical Pharmacology in the UK c.1950-2000: Influences and Institutions*. Wellcome Witnesses to Twentieth Century Medicine, vol. 33. London: Wellcome Trust Centre for the History of Medicine at UCL.
4. Reynolds L A, Tansey E M (eds) (2008) *Clinical Pharmacology in the UK c.1950-2000: Industry and regulation*. Wellcome Witnesses to Twentieth Century Medicine, vol. 34. London: Wellcome Trust Centre for the History of Medicine at UCL.

5. Tansey E M (intvr); Tansey E M, Zarros A (eds) (2016) *Flower, Roderick: transcript of an audio interview (14-Apr-2016)*. History of Modern Biomedicine Interviews (Digital Collection), item e2016068. London: Queen Mary University of London.