

AUDIO INTERVIEW TRANSCRIPT

Flower, Roderick: transcript of an audio interview (14-Apr-2016)

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Date of publication: 30-Aug-2016

Date and place of interview: 14-Apr-2016; Queen Mary University of London

Publisher: Queen Mary University of London

Collection: History of Modern Biomedicine Interviews (Digital Collection)

Reference: e2016068

Number of pages: 27

DOI: 10.17636/01014890

Acknowledgments: The project management of Mr Adam Wilkinson and the technical support of Mr Alan Yabsley are gratefully acknowledged. The History of Modern Biomedicine Research Group is funded by the Wellcome Trust, which is a registered charity (no. 210183). The current interview has been funded by the Wellcome Trust Strategic Award entitled “Makers of modern biomedicine: testimonies and legacy” (2012-2017; awarded to Professor Tilli Tansey).

Citation: 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.

Note: Audio interviews are conducted following standard oral history methodology, and have received ethical approval (reference QMREC 0642). Related material has been deposited in the Wellcome Library.

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Flower, Roderick: transcript of an audio 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).

TT: Tilli Tansey

RF: Roderick Flower

TT: To begin with Rod, could you say something about where you come from, your family background and your early education?

RF: Yes, well my parents, my father was in the Royal Air Force and so he was absent for a lot of my childhood. And because he was still on active service and posted around the world, we sometimes used to go with him, sometimes not. So, for example, I spent some years in the Far East with him when I was about seven. We were three years in Ceylon as it was in those days, and after that Penang. Then we came home, father was posted off somewhere else, and it was thought appropriate that I should be put into a boarding school, as were lots of children from service families at that time. We're talking about the 1950s now, late 1940s and 1950s. So I spent most of my young years in boarding schools, one sort or another, or living away from home while my father was often elsewhere. We never really seemed to have a family home that was a central, unmoveable fixture. I think partly because of the time I spent abroad, when I got back to this country, I found I was years behind in educational standards - if you want to put it that way - which was always a bit of a handicap. I always loved science and mathematics. In fact one of the things that really did turn me onto science was living in Ceylon and looking up at the starry sky at night and seeing the Milky Way and all the fantastic constellations in a crystal clear firmament. And I became very interested in astronomy, and that interest has persisted throughout my life, although not in a very serious way.

So, I have to say, I was not a good student at these boarding schools. I found out, and I now recognise, that in order to perform well, I have to be interested in something. So if somebody bored me, I switched off straight away and just lost interest. And I think that's a very, very personal thing, some people aren't like that, but I think what it does highlight is that when I look back on my career, the people who were most important were not necessarily the cleverest teachers, but they were the most inspiring. Some people were really inspiring.

TT: Would you like to say something more about a particularly inspiring teacher?

* 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.

RF: Well, for example I spent a short time at an academy where I was between one school and another, and there was a mathematics teacher there whom I found very inspiring. So much so that I spent a lot of my free time doing recreational mathematics in those days. So I always remember him. At my junior school, there was a Russian teacher of maths who also was very inspiring. He had lots of interests, for example in earth sciences, and I used to go with him in the morning to take readings from the school weather station and log them onto charts, and that's another interest which has persisted throughout my life. I'm actually a Member of the Royal Meteorological Society because of a continuing slight interest in that sort of thing. But anyway, I didn't really emerge from my school career with a very creditable performance, to be honest. And although I was interested in science, I really had no clear vision of where to go. And, incidentally, it's a bit strange because at neither of my boarding schools was I ever taught any biology, which is extraordinary considering the fact, for example, that in the 1950s, Watson and Crick did all their fundamental work on the structure of DNA [deoxyribonucleic acid]! So I knew nothing about biology at all, which maybe in retrospect wasn't a bad thing, because when I did become interested in it, I was able to come at it with fresh eyes, as it were.

But my favourite subjects were mathematics, physics and chemistry, but I didn't do academically well at them. So when I left, after a few odd jobs - including working in a bank for a while, which my father thought would be a good career for me - I became interested in what in those days was a very novel field, and that was computing. And in those days computers weren't things you buy in the Apple shop and stick on your desk. They were machines which took up one or two rooms with special air conditioning arrangements and so on, and which used to operate using reel-to-reel tapes. And these required computer operators, people who knew how to handle them if they went wrong and repair faults, and that sort of thing. And a lot of my friends at that time had that job, it was very well paid, and it sounded very interesting. So I applied for a job, which was advertised in the *Daily Telegraph* in the Department of Pharmacology at the Royal College of Surgeons (RCS) in Lincoln's Inn Fields, under Gus Born and John Vane, to look after a rather basic computer, which they used for logging animal behaviour, because there was somebody there in the lab at that time who was interested in the effects of drugs on animal behaviour.

But I had no idea what pharmacology was, I had no interest in anything biological, but I had this idea I might be quite good as a computer operator. However, when I went for the interview the first thing that John Vane said was, 'I'm sorry, that post has gone. We've just given it to somebody else.' 'However,' he said, 'we're looking for a general technician to help around in the lab. Would you be interested in that?' And I suppose it's one of those things I look back on as a defining moment. And I said, 'Yes, sure, I'll do it' and Gus Born also interviewed me, and so they offered me the job. And I suppose within a month or two of working there, I suddenly realised this was what I really wanted to do. I studied in the evenings for an HNC (Higher National Certificate), which was in those days, a way of alternate entry into some universities including Sheffield, your own *alma mater*. And I then left the College, and my job as a technician, and went to Sheffield University to read physiology, and using my HNC as an entry qualification.

TT: Can we talk a little bit more about your work as a technician? What did you learn as a technician, what did you do? Studying for your HNC - this was not part of your technician's training? How did the HNC contribute to your work?

RF: No it was not, it was a sort of allowance that technicians had in those days, because the salary was pretty pitiful. But what they did encourage - and everyone was very encouraging - was that they would pay for you to go in the evenings or half a day a week to college so you could further your education, which I thought was a very, very enlightened attitude really. And yes, well that's a good point. I learnt a lot about the practical skills involved in animal work, in bioassay, which is one of the main things that John Vane used, and general lab skills, weighing, measuring, all those sorts of things, making up solutions, making up drugs. But I also picked up a lot of knowledge from the people in the lab who were all very, very kind. And they were always willing to share their insights with me, even though I was nothing in terms of the overall organisation of the laboratory. I was the most junior technician. But that Department was pretty interesting for a number of reasons, and first of all it was run jointly by John Vane and Gus Born. The Department was like a very long corridor and they had one end each. And I know this flouts all management theory and so on, but it worked

really, really well because John and Gus were old friends. Gus was more interested in platelets and thrombosis, and he had his own people working on that, and he made huge contributions to that area. And John's end was mainly concerned with disappearance of hormones in the circulation and using bioassay to measure their half-life, and so on.

I worked mainly with John although I did do a bit of work with Gus as well. I learnt a whole range of practical skills from taking blood from humans, to preparing tissues from rats and even doing some large mammal surgery. And I found that this was very helpful when I went to Sheffield as a physiologist because I was probably the only one in the class who could walk straight into a lab and knew roughly what they were doing.

TT: Who else was around in the lab then? Was it a very large Unit?

RF: No, it wasn't that large. I suppose there was about between, well let's say a maximum of 30 people together at one time, roughly split into two halves with 15 people working with Gus and the other 15 working with John. There were some absolute stars there. One of the ones who had a huge influence on me was Sérgio Ferreira, a Brazilian scientist who visited the lab on several occasions for extended periods of time. He had a long term relationship with John and became a friend and, of course, he was responsible for a lot of the early work showing that peptides from snake venom can potentiate the action of bradykinin. And it was this that led John to make that seminal suggestion that since the enzyme that destroys bradykinin is the same one that activates angiotensin I to angiotensin II, an inhibitor of that would be potentially good anti-hypertensive drug. And I remember one of my jobs as a technician in those days was being involved with that whole angiotensin project very, very much in a technical capacity. So it was very, very exciting to live through that and see it, eventually, become captopril some years down the line - all at John's suggestion really.

And I think that's something which, incidentally, he never gets that much credit for, but, between him and Sérgio Ferreira, they really created that whole area. Mick Bakhle was somebody else who was there and he did an awful lot of work on the inhibition of the angiotensin converting enzyme [ACE] by peptides from snake venom. There were a number of others, we also had a lot of academic visitors there, which I think is very, very good for research departments, and I met people from all over the world. It was a good introduction to science and its international flavour really.

TT: And what determined you, or what encouraged you, to move to Sheffield, to go back to academic study, not to continue as a technician?

RF: I decided I wanted to make a career in pharmacology, but obviously I needed a degree in those days, and so I thought I had to go back to university. So I was at that time studying for my HNC at, I've forgotten what it's called, 'Essex Technical College' in Chelmsford, I think it was called in those days. And the tutor there was very supportive and said, 'You ought to go to university and I'll help you with your application form.' It's another example of somebody just helping in a very disinterested way, but making a big difference. So I did that. I didn't actually tell John that I'd done it until I got the offer from Sheffield, partly because he was such a powerful man, even in those days. He said to me afterwards, 'Well, if you'd wanted to go to university, I would have rung up somebody,' but I didn't want that in a way, because I would have always felt I was a bit of a fraud. But, as it happened, I got a place to read physiology at Sheffield. I would have perhaps have chosen originally to read pharmacology, but they didn't offer it anyway, but actually I'm pleased I did read physiology because I really enjoyed that course; it was very, very well constructed and I learnt a huge amount, not only about physiology but also about biochemistry. And the first year, which you probably remember yourself, Tilli, was this integrated biology year and actually, although I hated a lot of it at the time, in succeeding years I really came to appreciate the breadth of knowledge that that gave me. So that was very good.

TT: You just mentioned there, Rod, that you were reading physiology, but you might have liked to have done pharmacology. Had you applied for a pharmacology degree?

RF: No, there weren't that many around really. I was a bit constrained, because not all universities accepted HNCs for mature students, as I was in those days. I was also three or four years older than most applicants, so I was a bit limited for that reason too. But I wasn't disappointed actually, I really enjoyed my time at Sheffield. I made some very good friends, several of whom are still good friends and professional associates. I'll just say one other thing about that Pharmacology Department at the RCS, which was very seminal in lots of people's career actually. Looking back on it, it was, I suppose - one always has this impression - a golden age of science. Money didn't seem to be a major problem in those days, everybody worked together. The conditions were incredibly cramped, but that didn't seem to make any difference to the productivity. One good thing about it, which you can't do these days, was that every day we all met up, including the person who cleaned the lab, for coffee. In the middle of the two Departments there was a coffee machine 'ends'; there was a huge coffee machine and a trolley with cups and saucers on. Every day we met there at half past ten for coffee, again at lunch time, and again for tea at about half past three to four o'clock. I know it sounds awfully trivial, but everybody clustered around, from the Professors right the way down to the cleaners. It had a very flat structure, that Department. It's surprising the number of ideas that were generated at that time just by bouncing things around in conversation with a cup of coffee in your hand and discussing somebody else's results. You can't do it these days, because you can't have coffee machines in labs!

TT: No, absolutely not.

RF: A great shame, in my opinion, but there you are.

TT: That's a very interesting point. It's come out in several interviews and Witness Seminars: the importance of a coffee room or tea trolley.

RF: Exactly.

TT: Was there anything in particular that you felt you took away from Sheffield? Because you then did a PhD, but not in Sheffield?

RF: That's right, yes.

TT: You went back to work with John Vane. Was he at the Wellcome Foundation by that time?

RF: No, no, no, we were still at the RCS.

TT: So it was quite deliberate? You really wanted to go back and work in those labs?

RF: I did. Well, I really wanted to get back to pharmacology. I felt that doing a degree in physiology gave me a fantastic basis for understanding drug action. And the practical skills I'd acquired there were very, very good. It was a very, very good course, in my opinion, and D. H. Smyth who you remember also, I found very inspiring in his own way. And one of the things that I really liked about him was he had a way of making complicated ideas simple by putting them in a cartoon version. And he called this 'functional topography', which actually was the first time I'd ever heard that term. So rather than trying to show that things were connected by putting them at the end of signalling pathways or something, he'd place them right next door to each other on the cartoon and he used to say, 'I have no idea how these are connected, but they look as though they are and they behave as though they are, so I'm putting them together.' And I found that to be a very powerful way of communicating ideas, and one which I copied in later life when I had similar ideas which I thought were difficult to communicate.

Interestingly enough, when I read David Smyth's obituary in the *Biographies of the Fellows of the Royal Society*, I found out that he'd actually been criticized by many people in the Phys Soc (The Physiological Society), because they thought he was oversimplifying. But I didn't think that at all. I thought he made his complex

ideas very accessible to other people regardless of whether they were students like me or colleagues who maybe didn't work in the area, so I had no problem with it.

TT: So you come back to London for your PhD. How was that funded?

RF: It was an MRC studentship, I think, which John had got. It had always been my intention to go back to John's lab, although I was offered a post at Sheffield when I graduated. They said, 'If you want to stay on and do a PhD...' The main thrust of that Department was intestinal transport of solutes and dietary substances and ions, which was very interesting, and in fact one of my first papers was on choline transport, which I worked on as an undergraduate and finished it off on weekends when I'd finished my degree.

TT: Who did you do that with?

RF: Paul Sanford. And I could have done a PhD with him. He was another inspiring person, completely different from me, and that's maybe why we made a good team. But a very nice man and very, very encouraging. He looked after me, I used to go and stay with him at his flat and we used to go into the lab at weekends and work, something else you can't do these days. Yes, so it had always been my intention to go back and work with John, and in fact I worked back in that Department in pretty much every vacation from University, except one or two, where I was doing other things. And John said, 'If you ever want to come back, work in the vacation, I'll find some money to pay your travelling expenses.' So we'd actually done quite a lot of work together.

TT: You go in as a PhD-student, you've already got all the lab experience from being a technician and an HNC, you've done an undergraduate degree, you've done a very stimulating project as an undergraduate, and you've been working in the lab in the vacations.

RF: Well, I was lucky in a way because everything seemed to come together. And I got back to the lab just as John's original paper on aspirin had been published in *Nature*, together with two others from John's colleagues, Sérgio Ferreira and Salvador Moncada, who was also a PhD-student who started about the same time as I did, or actually just before I did. And there's another interesting point about that Department actually, getting back to the RCS's Department. At the same time as John published his paper in *Nature*, two people working with Gus Born had a very similar idea, which John didn't know that this work was going on and they didn't know what John was doing. So much for the coffee machine discussions - they didn't work on that occasion!

TT: [Laughs].

RF: I think, to be fair, they kept that project a bit secret. In the end all the papers came out in the same edition of *Nature*, and what they showed was that aspirin blocks platelet aggregation if you give it to humans. But they reached the wrong conclusion about its mechanism of action. But John's went straight to the heart of the enzymology as it were, so that was very important. John's paper was significant, because it was a very simple paper. He only looked at three drugs: aspirin, indomethicin, and salicylate. But the important thing he did was, he used an homogenate of tissue, which could catalyse the conversion of arachidonic acid to prostaglandins directly, and showed that you could block that by adding the drugs directly to the solution, so there was no way the results could be equivocal. And, of course, everything was measured by bioassay in those days, no RIA (radioimmunoassay), no mass spectrometry.

TT: I think it was Heinz Schild who called bioassay 'the English disease'?

RF: Absolutely. Well, I think it's a fantastic technique actually. These two papers had just come out, just as I joined the lab. Actually, I knew they were coming out because, and in fact I think, as a slight aside, what made John a genius - in my opinion - there's a definition of a genius which you probably know, I'm probably misquoting it, but it's 'somebody who sees what everybody else sees, but thinks what nobody else thinks'. And the point was, we knew already that aspirin blocked the appearance of a biologically active substance

coming out of perfused tissues. John and I had done something on that the previous summer. I've still got the kymograph traces. Other groups, such as Richard Gryglewski's lab in Poland, who was another colleague of John's, had also noticed it, and Priscilla Piper and John Vane had also noticed it. But John's great 'eureka' moment was when he realised that this material actually was derived from the cyclooxygenase enzyme that makes prostaglandins, which nobody else had thought of. So immediately, because aspirin prevents it, he said, 'Well, the obvious thing is that aspirin is blocking at cyclooxygenase,' and that was the intuitive leap that he made, that nobody else did.

TT: And what was your PhD on?

RF: Well it was on that. When I got there John said, 'Look, all sorts of exciting things going on here, so why don't you pitch in?' And so the first paper we published was, we looked at all the non-steroidal anti-inflammatory drugs we could get, and I tested them all on the cyclooxygenase preparations that we made, and we found out that the order of potency, if you like, matched their therapeutic order of potency, and that the levels at concentrations you need to inhibit the enzyme, were the sorts of concentrations you could find in blood after taking an oral dose. And the other thing was: drugs like morphine, which is analgesic but not anti-inflammatory, and also drugs like gold and chloroquine, which were anti-inflammatory but not analgesic, had no effect on the cyclooxygenase at all. So it was very, very specific effect. So that was one of my first papers co-authored with Gryglewski and another Polish scientist called Krystyna Herbaczyńska-Cedro. And, also, we published something else that summer which was also very influential, and that was with Joe Collier who was in the lab at the time.

Well one of the pieces missing in this developing story was the following question: if you take aspirin, does your tissue prostaglandin level go down in response to a normal therapeutic regime? I'm not talking about one-off doses, but the sorts of doses you'd take therapeutically. So Joe had, before I got there, designed this small trial using medical students at St George's, and the problem was how to measure prostaglandins. Bioassay couldn't be used for prostaglandins in blood, because they were removed on a single passage through the lungs. But there was one tissue where prostaglandins are very abundant, and that's in seminal plasma. So Joe Collier arranged this rather tacky clinical trial with medical students from St George's, male medical students of course, and the net result was I had dozens of samples of human seminal plasma, which I kept in the fridge by the coffee machine, until I was able to extract them with ether and measure them by bioassay. But, anyway, the upshot was after about two or three doses, you could see the levels of prostaglandins diminishing. We published that in *The Lancet*, and I think that was the first time aspirin had even been shown to inhibit prostaglandins in human subjects after a therapeutic regime.

TT: And that was shortly after you arrived there?

RF: That's right, it was, because Joe had already enlisted the students and he knew I was coming back, so he said, 'I've got just the thing for you. We can do this together. I'll collect the samples, you do the assays.' So that's what we did.

TT: You said something about getting 'all the non-steroidal anti-inflammatory drugs we could get' - did you just go to ordinary pharmacists or using drug industry connections?

RF: Yes, well a mixture really. Some we could get from chemical suppliers but John was a consultant for E R Squibb & Sons who were based in New Jersey, because one of his friends from his Oxford days, when he was in Burns' lab, was Arnold Welch. And Arnold became R&D Director of Squibb, and he was a very good friend of John's, and asked John to be a Consultant. It never bothered him to ask favours of this sort so he simply wrote to Arnold and said, 'Look, we need some pure naproxen, we need some pure this, we need some pure that.' And so the drugs arrived in the post, which was very, very convenient; we had samples of all the major non-steroidal drugs, which we were able to use in these enzyme assays.

TT: And did you do your PhD completely at the RCS?

RF: I did, yes, but I finished writing it up at Beckenham (the Wellcome Foundation) because after a couple of years the Department began to change. Well, Gus Born was offered the Chair of Pharmacology at Cambridge and went in, I think, 1972. John had hoped, I think, to succeed Gus as the Vandervell Professor of Pharmacology. But something went wrong with the rather byzantine process of appointing Departmental Heads, and he wasn't offered the opportunity - I don't know exactly what happened. But, anyway, he was offered the job of R&D Director at the Wellcome Foundation. In those days this was a completely independent non-profit making pharmaceutical company based in Beckenham, with a very interesting history, as you well know, with Henry Dale having been perhaps the most influential scientific member of that early enterprise. And Henry Wellcome having arranged in his will: that all the profits should go to a Trust. So it had a very interesting ethos that place. People never felt that they were doing it to make money for shareholders. And that, in my opinion, had an influence on the way people behaved.

When John took up this post, I think he was inspired by Dale and some of Dale's thinking about what pharmacology should be. He said to a few of us, 'Well, I'd like to keep this Department going down there. Would you like to join me?' So there were about four of us, Sérgio Ferreira, Salvador Moncada, although he left shortly afterwards to go back to Honduras for a while, Gerry Higgs and Geoffrey Blackwell. So we recreated the laboratory down there with a similar ethos.

TT: How did you find moving into the Beckenham labs? As you say it wasn't 'industrial' industry, like moving into one of the other drug companies. In fact it always used to be called the 'University of Beckenham'.

RF: It did, that's right, and that was very much the atmosphere down there. Well, I was a bit apprehensive to begin with, but actually I found it incredibly pleasant and interesting to work down there. I learnt an awful lot, interacting particularly with the organic chemists.

TT: That would have been something you hadn't done before.

RF: That's right. So I was able to speak to people and say, 'Look, if you want to design a drug to do this, how would you do it?' And they had some very good natural products chemists there, and they turned out to be important later on for me, because I was quite interested in extracting natural products and naturally occurring substances from biological fluids. I have to say, one of the things that distinguished working at the RCS was this very free interchange of ideas, such that anyone can supply ideas and people would pay attention. They didn't shoot you down and say, 'That's a stupid thing to say.' So everything was considered carefully, even some ideas originating from the cleaners! I got very used to this idea of doing science. If you wanted to stop everybody in their tracks, you walked into the lab and said, 'I've got a wonderful idea.' Everybody would down tools and say, 'Okay, let's listen to it.' We managed to transplant this ethos to Beckenham. We didn't have the coffee machine in the middle of the Department, but we did have a coffee room upstairs. The coffee there was better, actually.

So we recreated this ethos in the Department. We had lots of visitors and I think that having that Department, the 'Department of Prostaglandin Research' it was called, actually changed the nature of science at Beckenham as well. Perhaps it had always been a little conservative. I mean there were some absolute stars there, but the general tenor was you didn't publish too many things, you kept things under your hat. So when we got there we were publishing left, right and centre.

TT: So who else was there when you moved to Beckenham? Was John Vane a breath of fresh air moving into Beckenham at that time?

RF: Yes, he was. Everything changed when he came. He was very keen to recruit top notch people, and he really gave us our head. He said, 'I'm not going to tell you what to do, I just want you to go and do science in the way that we always used to do it, and see what comes out of it.' Well, the first fruit of it, really, was the discovery of prostacyclin. And of course the marketing department said, 'Oh, that's not really a drug. You'll never make any money on that.' But, nevertheless, analogues of prostacyclin are used for the treatment of

several conditions now, including some life-threatening diseases such as pulmonary hypertension. So, actually, that did turn out to be a very, very useful discovery. And there were a number of other small things that we found out, which were very important. And in the area of prostaglandin research at that time, things were really very exciting. The endoperoxide intermediates, which exist between arachidonic acid and prostaglandins, had been isolated, and we were able to use these as experimental reagents. They were highly unstable and had to be kept in dry acetone at -20°C until they were diluted into aqueous solutions and applied to bioassay tissue, or else they just decomposed spontaneously.

So this is once again where bioassay came into its own, because it was the only technique that responded quickly enough to enable you to do any experiments; otherwise the compound would have just disappeared, would have decomposed. So using that type of technique, there were three people. There was Richard Gryglewski, who was a visiting scientist from Poland, Stuart Bunting who was a very talented pharmacology student from Chelsea College, as it was in those days, and Salvador Moncada. They noticed that if you applied these endoperoxides to vascular tissue, then somehow the biological activity disappeared. And this led them to consider that it may be transformed into something that they could not detect using those particular bioassay tissues. Then they found out it had profound effects on platelets. I'd got a sample of this material that had been added to arteries, and I did some very simple chromatographic analysis, and I noticed that what was appearing was a compound which had a very similar chromatographic mobility to another compound which had just been reported in the literature by a Canadian group, who had no idea what it was there for. And I realised that the breakdown product was probably a compound that we now call '6-k-PGF_{1 α} ' [6-keto-prostaglandin F1 alpha].

And so we had the idea, we knew what the precursor was, which was the endoperoxide intermediate, we knew what the end product was, and that was very important in moving forward with this idea. Three simultaneous papers came out describing these discoveries, and the one that I had worked on was published in *Prostaglandins*, which was a leading journal of the time for disseminating this type of work.

TT: But that journal itself was quite a new journal. The whole field was just starting.

RF: It was at the time, that's right, yes, it was. It was very exciting. Once the potency of prostacyclin was realised and its biological properties catalogued, it became even more interesting. I remember one of the organic chemists, who was making analogues of prostacyclin, said to me, 'When I started off as an organic chemist at Wellcome, in, whenever it was, we thought that if we found a compound which worked at 10^{-6} molar, we were doing pretty well. Now we have compounds that will work at 10^{-9} and 10^{-10} M.' Actually, he made a bit of a gaffe. Once he was synthesising an analogue of prostacyclin and some of the substance splashed onto his hand. Even though he wore protective gloves it was enough to cause him to pass out, and he collapsed on the floor. And that, for them, was a big shock, they couldn't understand how you could have such potent compounds.

TT: It's the ultimate bioassay, isn't it? [Laughs].

RF: Yes - the ultimate bioassay.

TT: Can I just ask you a little bit about the organisation when you went to Wellcome, because you are part of John Vane's own research team, the Department of Prostaglandin Research, and John was the Research Director of all the labs?

RF: That's right, worldwide. Obviously he didn't come into the lab and put his coat on, do experiments, as he did in the RCS, but he maintained a very strong interest. He used to look at manuscripts, edit them, he used to make suggestions which were always very valuable. As you say, he had lots of other responsibilities, so we didn't expect him to really be a lab participant.

TT: You mentioned the organic chemist and the chemists. Did you have any involvement with other scientists in the labs?

RF: Yes, we did, yes. We were embedded in what originally was the Department of Pharmacology at Wellcome and so we became good friends with the pharmacologists there, and once the, I wouldn't say 'hostility', but once the apprehension of the people who were there about what we were going to do had been allayed, then we became very, very good friends, and we did a lot of good work together over the years. Not just on prostacyclin, but we were also interested in looking at other types of anti-inflammatories, and at least a couple of them looked very promising at the time although they subsequently died for other reasons, as drug candidates often do. That's just the nature of the field. Yes, but it was an interesting place to work because there was, because of Wellcome's strong interest in tropical medicine as well, they were a lot of people there who specialised in malaria and HIV [human immunodeficiency virus]. Actually it was during this time that the very, very first antivirals were produced.

TT: That was more in the States, though, wasn't it?

RF: Well, some of the work was done in Beckenham.

TT: I hadn't realised that there was so much involvement like this.

RF: Well, there was. You put your finger on an interesting point. It always used to be said, 'What's the point in competing with the US labs?' Because once we had visited Research Triangle Park (Wellcome labs in North Carolina), we found out that a lot of the stuff that we were doing was being done also over there. And I think John went through various phases thinking, 'This is stupid, a waste of effort,' but in retrospect I think probably it wasn't, because often if you get two different groups coming up with the same ideas, it increases your confidence in them. So there was always, there were people interested in prostaglandin at Research Triangle Park, and some things for example like the things that Hitchings and Elion were doing, they were restricted really to Research Triangle Park.

TT: By this time you've got your PhD and research skills, you're a staff scientist building up your own team as part of the Prostaglandin Research?

RF: That's right, yes.

TT: And the mechanisms of doing that, applying for posts and going for it, all the paperwork and everything. How did you do that, Rod? How did you start?

RF: Well, because of my interest in aspirin and I'd published a lot of papers by then on non-steroidal anti-inflammatories and how they work on the cyclooxygenase system, and I'd actually published quite an influential review in *Pharmacological Reviews* on inhibitors of the cyclooxygenase. I began to think about other anti-inflammatories and how they worked. In those days, prostaglandins were considered to be the most important inflammatory mediators, because we hadn't yet discovered cytokines, chemokines and so on, not as such anyway. It seemed to us that even if drugs like the corticosteroids and gold and chloroquine, didn't affect the cyclooxygenase in order to bring about an anti-inflammatory effect, they must somehow be affecting the prostaglandin system. I wouldn't subscribe to that idea today, but that's the way things were in those days. That's what we thought.

So I began to look at other ways in which steroids could affect prostaglandin synthesis, and steroids were a very interesting group of drugs. It's funny how different disciplines have their own intellectual territories. So for example, neutrophils and macrophages had always been regarded as 'pharmacologists' cells', but no card-carrying pharmacologist would be seen dead near a lymphocyte! On the other hand, immunologists worked mainly with lymphocytes in those days. So the whole area was carved up into different zones. The steroids were a good example of this: because they were hormones, or hormone derivatives, it was never quite clear who 'owned' that patch – certainly not pharmacologists. Anyway, everybody knew they were the best anti-inflammatory drugs without question, and there were a number of key ideas out there about how

they worked. The most influential at that time was an idea that Gerry Weissmann had originated and that was that steroids could stabilise the membranes of lysosomes inside cells.

TT: Gerry Wiseman?

RF: Yes, Gerry Weissmann.

TT: From Sheffield?

RF: No, no, no, sorry. That's another Gerry Weissmann from New York. I'm sorry, I should clarify. It's Weissmann.

TT: That was quite a leap, yes. Sorry to interrupt [laughs].

RF: No, it's okay, you're right. I hadn't thought about that. Yes, he had this idea. I think it was based on work he did in Cambridge with Dame Honor Fell, that steroids could prevent the breakdown of lysosomes, lysosomal contents spilling out into joints, for example, could cause cartilage breakdown. And Weissmann was able to demonstrate that if you isolated lysosomes and if you added quite high concentrations of steroids, then you could 'stabilise' them; in other words they were less liable to rupture. On the other hand, there was a whole community of endocrinologists who were looking at sex hormone action, and they'd found some very interesting things. For example, they observed there were receptors for these sex hormones in the uterus and they'd found out using radioactive oestradiol, that it became transported into the nucleus. In some way, those two parts of the field never really met.

One of the first things we did is we found out that if you infuse steroids into a perfused organ, you could block the release of prostaglandins, but if added it to a homogenised preparation, you couldn't. So that meant to us that the steroid was somehow affecting the supply of arachidonic acid to the enzyme, because that's the rate-limiting step. So with that in mind we looked to see whether we could find a receptor for glucocorticoids in guinea pig lung tissue. We did indeed find one, and we showed that antagonists of that receptor could block the ability of steroids to inhibit prostaglandin synthesis. And this put the thing on a new footing really. It meant that there was a genomic mechanism going on, receptor-dependent, and so on.

TT: Slightly anachronistic language there [laughter].

RF: Yes, that's true. There were a couple of other groups around, there was one in the States in particular who came up with pretty similar findings in a different system at almost the same time, so we were quite confident. Then the question was how's it doing it, and we pondered a long time about this, but I'd always been interested in the history of physiology and I remembered the classic experiment of Otto Loewi in which he stimulated the vagus nerve, connected to an perfused isolated heart, and found that a second heart bathed in the perfusate also slowed down. He deduced there was some chemical mediator released by nerve stimulation. I had the idea that we would see if steroids were causing the synthesis or the release or something in these cells, which was actually blocking the production of prostaglandins. I set up a rather complicated experiment using two lungs perfused in series, and we found out that's exactly what was happening - much to our surprise - and it was very, very dramatic. So we went through a phase of collecting what we called 'steroid conditioned media', where you infuse steroids into a perfused organ and then collect the effluent. We used normal effluent as a control. This steroid-conditioned medium contained this factor, and we found that this had very powerful pharmacological properties.

TT: Such as?

RF: Well, for example, it could reproduce the actions of steroids on a naïve perfused organ preparation and we knew it was something other than steroids, because you could block their action by adding glucocorticoid receptor antagonists or inhibitors of RNA synthesis. We also found it possessed very powerful anti-inflammatory properties in rats. So we were convinced that we'd found something important. We called it

a 'second messenger' of steroid action, and I think originally we had several names for it. We called it 'macrocortin' in those days. We were delighted to find that a couple of other groups began to report similar things in different systems. There was a group in NIH [National Institutes of Health], Julie (Julius) Axelrod's group, who found something similar in neutrophils, and a group in Italy, who we subsequently collaborated with, found something similar being released from macrophages. So we then made several attempts to purify this material, which we'd identified as a protein by now, and this proved to be very difficult. Things weren't so easy as they are these days, and we got to the point where we identified two species, one had a molecular weight of 15,000 and the other one had a weight of 40,000 or near 40,000, and we realised quite quickly one was a breakdown product of the other one.

And so we published a paper showing that this had very prominent biological activity and by pointing out that, we explained why steroids do some of the things that they do. We never made the claim that it was explaining all steroid anti-inflammatory effects, because we'd already shown that by influencing the genome you could influence all sorts of genes. But, nevertheless, looking at this particular subset of effects, this acute anti-inflammatory action, this macrocortin turned out to be the effector, which was exciting. We published several papers on that, and then by this time - it was about 1984 - the things began to get a bit difficult at Beckenham.

TT: So this is still at Beckenham?

RF: Yes. Well, I'd hit a bit of a full stop, because there was no one on the Beckenham site who could purify and characterize this protein. I'm not a protein chemist so I could have been stuck to be honest. And then, things got a bit difficult on the Beckenham site. There were several reasons for this, but in the end I decided I'd leave and I looked round and I saw a job at the University of Bath, Professor of Pharmacology. So I applied for that job and I went down for an interview and got the job, which is very nice, and I said to John, 'Look, it's my big opportunity now,' and he said, 'Well, you're doing the right thing just at the moment.' And so I left in 1985 to go to Bath, and in 1986 I think it was, Wellcome was taken over by Glaxo and John himself left in either 1986 or 1987.

TT: You just referred in passing to 'difficulties'. Would you be able to elaborate on that?

RF: Yes, well, there was one. John was very, very keen to hire brilliant people, and one of the people he was very keen to hire was Jim Black. Jim was an old friend of John's. They'd known each other from way back and I used to work with Jim when he used to come to the RCS to look at histamine release in dogs. Of course Jim's record of drug discovery was absolutely stellar, so everybody wanted him. But John managed to persuade him to come to Beckenham, and at the beginning it seemed like a marriage made in heaven. But again, and this is a slightly awkward thing to discuss, but John's view of discovering a drug and Jim's were pretty much diametrically opposite. John's idea was you did very, very good basic science and out of that, if you had the right people, would come ideas for new drugs. Jim wouldn't have any of that. His idea was you took a hormone, you modified it slightly through successive changes, you did lots of very, very careful bioassays to measure the potency, the shift in the dose response curve, and so on. And that was reflected in the way that the different Departments were set up. For example in John's Department, there were virtually no technicians, but they were all scientists, PhD-students and visiting academics. Jim's Department contained one or two scientists; the rest were technicians carefully constructing dose-response curves all day.

And so there was a completely different ethos really and, eventually, these fundamental differences in philosophy about science, or drug discovery anyway, gradually worked their way through into a bit of a schism in the organisation, and this caused John and Jim a lot of heartache. Eventually, Jim left. It wasn't an easy parting, to be honest, but these sorts of things took it out of John in terms of his stamina and so on. And, I think, partly because of that, partly because some other changes he'd made, I think he was criticised by Members of the Board, and particularly by the Chairman, who was not a very nice man, Shepperd, his name was. I didn't find him impressive at all, but anyway, he was the Chairman and caused a lot of problems for John.

TT: So you'd seen the writing on the wall?

RF: I knew something was happening and, yes, very sad really, because they were both individual stars, but later they mended their fences because John was somebody who didn't like to think that there was somebody he'd fallen out with whom he'd been friends, and he went out of his way to patch things up. It was John who certainly proposed Jim for the Nobel Prize together with Gertrude Elion and George Hitchings, for work on drug mechanisms and how to explore them. So, afterwards, they mended their fences, but at the time it was very difficult, and this breakdown in relations worked its way down the organisation. Wellcome employed management consultants who came and interviewed everybody. I thought it was a complete waste of time, but there you are, 'What am I? I'm just a lab rat!'

TT: Just before we move onto Bath, you mentioned - and this goes back to prostacyclin - a key word which comes to mind with the drug industry: 'marketing'. What was your relationship with marketing? Did you feel under any pressure from marketing? You've already mentioned, because of Beckenham, Wellcome was very different.

RF: It was very different. I didn't have that much interaction with marketing, but every time I did, I was always a bit dismayed by their attitude. Incidentally that brings me to a related point, actually, and that was that I was a bit disappointed with the pharmaceutical industry in general, because I noticed that lots of companies would simply not take risks. If they saw somebody else develop an H₂ [histamine H₂ receptor] antagonist, then they'd immediately start an H₂ antagonist programme, but they wouldn't do it on their own. I noticed this at Wellcome a bit. Nobody wanted to go into a completely new area and this was very, very much reflected in the attitude of the marketing people. If there wasn't a drug out there already like it, they had no way of knowing how to place something like their drug. So in my opinion they totally lacked imagination. John had had the same thing with, or Arnold Welch had had the same thing at Squibb with captopril, the ACE inhibitor, 'Oh no, we don't want those, we can't possibly sell drugs like that.' It's something I've heard repeatedly from other people who work in the pharmaceutical industry. So the marketing side of things was a bit of a dismal experience really.

TT: You then moved to Bath and it was a fairly new University?

RF: Well, it was a 1960s' University, and so it was not that young, but not that old either. It had its own traditions. It had been formed by the amalgamation of the, I think it was called the 'Bath School of Pharmacy', and 'Bristol College of Science and Technology'; they came together to form a coherent university following the 'Robbins' report.

TT: Was pharmacy very important in the creation of the University?

RF: It was important, yes. And the 'School of Pharmacy and Pharmacology', as it was called, was very important. And for a while it was a very high earner, and because the demand for pharmacy undergraduate places was so high, they always got people with fantastic A level results. I'm not a pharmacist, but it was a very, very good course. Students loved it and they turned out some really, really good graduates, like they still do.

TT: And was the pharmacy course part of the remit of the Professor of Pharmacology?

RF: Well, it was in the sense that we had three Professors in the School when I went there. There was a Professor of Pharmacology, that was me, a Professor of Pharmacy, and a Professor of Pharmaceutical Chemistry. The three of us together ran the School of Pharmacy and Pharmacology, which was quite large. And the arrangement was that every three years, one of us would become Head of School in rotation, so to spread the pain a bit! One of the things that went wrong right from the start for me in Bath was that the Vice Chancellor said, 'Unfortunately, we've had a lot of cutbacks recently, so we won't be reappointing the Professor of Pharmaceutical Chemistry, so I'm afraid you two will have to do the job between you.' So immediately my workload went up, but anyway, it was a completely new challenge for me. I did a lot of

teaching. Actually I quite enjoyed teaching, but you know what it's like the first year, you have to spend quite a lot of time preparing lectures, preparing notes.

TT: And this was a new, completely new, experience?

RF: Well, yes, some of the stuff I'd taught before. But, for example, I used to teach all the molecular biology to the pharmacists, and I remember one putting their hand up and saying, 'Do we really need to know this?' If only they could have seen all those biologicals in the clinic now!

TT: A constant refrain from students [laughs].

RF: I know, it is, yes. I said, 'Look, in a few years' time you're going to be grateful you know all this.' So I used to do all that. I used to teach a lot of basic biochemistry, basic physiology, a bit of pharmacology, and then I had my own pharmacology group. They were much smaller, of course. There was about 12-14 students per year. Again it was a very highly-regarded course, because we had this sandwich arrangement by which students were found posts during the summer vacation in their third year, in friendly pharmaceutical companies. Of course all those are gone now [laughs]. But in those days it was comparatively easy to find slots for them. They turned out some very, very good graduates, so I was pleased to be part of that.

TT: And what about your own research? Did you take people from Wellcome?

RF: I didn't take anyone from Wellcome, but I recruited some people who I'd known in London, who had similar interests. One of them was Susan Peers who was somebody who worked at King's College [London] on a very similar type of topic to me, and several others, well I'll talk about the others in a second. But there was one big advantage to being in Bath: when I was at Wellcome I had been approached by Biogen who said, 'We're very interested in this protein of yours. Is there anything we can do together?' Well my hands were a bit tied, because I also worked for a commercial organisation at that time. But anyway I told them everything I could about it. As soon as I had left Wellcome they contacted me again saying, 'We notice that you're free of commercial ties now. Would you be interested?' So I said 'Yes.' And that was probably the best decision I ever made, because their people were right at the very cutting edge of molecular biology and protein chemistry, and it didn't take them very long to isolate and sequence my protein. And so very early on in our relationship and my time at Bath, they published a paper describing the cloning of a gene for what we then called 'lipocortin' and, subsequently, 'annexin A1', and they demonstrated it had pretty much the same properties as the biological material. And they sent samples of the pure recombinant protein to me, and I demonstrated that it had the same biology as well. So I was very, very happy about that.

And there were some issues at the time about how it worked and that was largely because, going back to the early prostaglandin days, our idea was that this protein somehow prevented the release of arachidonic acid. We established that that's what it was doing. So the question was, 'How does it do that?' Well, generally speaking, the release of arachidonic acid from lipid stores is governed by an enzyme, phospholipase A2, so the 'Occam's razor' hypothesis here is that this protein inhibits phospholipase. And in fact, using pancreatic phospholipase, which was the only phospholipase we really knew about apart from the snake venom enzymes, it seemed to do exactly that. But there was a lot of dispute about whether it actually inhibited the enzyme or had an effect on the substrate. And I think the whole area got bogged down for a while in what I always thought was a bit of an irrelevance in a way. I knew it blocked the release of prostaglandins, so the question of mechanism was secondary. So, anyway, this recombinant protein turned out to be a very, very potent anti-inflammatory compound in rats, and had lots of exciting properties. We found out that all the biological activity was contained in the first 27 amino acids, so we were able to just synthesize that bit and still retain all the biological action. And during this work I was very much aided by a young Italian student called Giuseppe Cirino, Pippo Cirino, who came to me as a PhD-student on the recommendation of a friend of mine who I'd worked with earlier on this project at Wellcome. And he stayed with me for a couple of years, and did a lot of this work together with me and Susan Peers. So that was a very, very productive time. So that was good.

There were other problems though, and what I found was my administrative workload was increasing so much that I woke up one morning and thought to myself, 'If I don't do something about it, I'm never going to ever get back in the lab again.' I'm going to spend all my time behind a desk. And when I looked at most of my senior academic colleagues, they were mostly trapped behind desks most of the time. In fact it was almost unknown for a Professor to walk into a lab, and I found that astonishing. And there was something else about university life I didn't like and, as I said, I'd been brought up in this atmosphere of exchange of ideas - you get a lot of your ideas from talking to other people. And I thought to myself, when I went to Bath, 'I'm really looking forward to discussing things with other people in a multi-faculty University, such as mathematicians, engineers and so on.' And when I went there, no one was interested in talking about research. The only thing they discussed was promotions and space issues, and I found that very, very disappointing actually. I mean, obviously, my close colleagues talked about work but all the others, seemed mainly interested in political manoeuvring. Well probably I was being naïve to think that it would be different from this, but anyway, that's the way it was.

TT: And how was your research funded at that time?

RF: Okay, well I had grants, actually John gave me a little bit of money when I left the Wellcome Foundation, which was very nice of him. I got grants from the ARC, the Arthritis Rheumatism Campaign, and Biogen gave me some money because they were very keen to explore the biological activity of this protein, which at one time they thought might be a useful therapeutic. So they were gung-ho about it, and I had a very good relationship with them. In fact, I still keep in touch with them. And so things developed very well there, but I got to this point where I began to feel a bit unsettled, because I've always been interested more or less in experimental science; I'm not a political animal really. I don't enjoy administration, although I acknowledge you have to do it. I enjoy teaching, but I could see my time doing that actually diminishing to the point of nothing as well. So I'd obviously kept in touch with John, who by this time had left with the Wellcome Foundation and he had, well didn't do anything for a while, and then he was offered some space, through the intercession of a man called Derek Willoughby, who was very active in the early days of inflammation research.

Derek was based at Barts, as it was in those days, and he was amongst other things, a very good 'fixer', and he said to John, 'Why don't you come to Barts? There's a huge amount of space going begging there, you could just move in. You could start a new Department or something.' So John moved there, I think he had one office, he took his PA [Personal Assistant] from Wellcome with him and he recruited a couple of PhD-students, and so on. But we kept in touch and on one occasion I visited him and he said, 'I think it will be a good idea if we try to expand this operation. I think we could really, gathering together old friends who know how to work with each other, I think we could make this into something really special. Would you be interested?' So I said, 'Well, we'll talk about it,' because by then I obviously had a full-time university job, a secure job, pension, and a house in the Wiltshire countryside. But he said, 'Well, let me know.' So, anyway, we agreed to speak on the phone and I knew in my heart of hearts I'd only ever say 'Yes,' because I wanted to get away from this atmosphere where administration was really the only thing that I could do. And also this, how do I put it? Lack of interest in science. Nobody in administration was interested in what you did, the only thing they asked you about was 'how much money have you got?'

And I found that very, very depressing. It's common these days, but to me it was a big shock. And I think, for example, during my entire time not even the Vice Chancellor, Rod Quayle - who was a very nice man, also ex-Sheffield, by the way - I don't think he, or anyone ever asked me, 'How's your research going?' But all they ever asked me, 'You need a bit more money, can you get more money, can you do this?' So a bit of a shock to me really. So, anyway, when John said, 'Would you like to join?' I thought about it and said, 'Yes, okay.' John had called his two rooms in Barts the 'William Harvey Research Institute' and, it was a bit of a joke really, since there were only about five people in it. But anyway, he said, 'Well, come and join me because there are some other people who are going to come and join in, and we'll see what we can do.' So I did that. And it was a difficult thing to do because I had to give up everything and I really had nothing: I had no research money, no apparent career prospects; everyone thought I was nuts. But once again, Derek Willoughby was helpful, because through his connection with Eli Lilly he'd found out that they wanted to

fund an academic Chair in inflammation research and so he introduced me to the people at Lilly, who actually I knew anyway. And I went down to see them and they said, 'Okay, we'll give you some money for five years,' which was great. So I had a bit of research money, but that basically paid my salary, and so I then went out on that basis and began to get some other money from the ARC and elsewhere. I then began to recruit people. I'd bought back a couple of people from Bath and things began to take off.

TT: So Eli Lilly created a five year Chair for you?

RF: That's right. It was called the 'Lilly Chair of Biochemical Pharmacology' to begin with, and I was therefore called the 'Lilly Professor of Biochemical Pharmacology'. When that ran out, I obtained a Wellcome Programme Grant, so I was okay then. And Barts Medical School, as it was then, were very supportive actually and they said, 'Well, okay, look, you're taking a risk, we'll support you for a few months until your money from Lilly comes through.' They kept me going for a few months in between difficult times, so they were very nice to me.

TT: Could you say a little bit more about Derek Willoughby? Clearly he was an incredibly powerful mover and fixer.

RF: He was. That's exactly what he did. Derek was another person who began life as a technician with a man called Spector, who was a very influential 'old school' pathologist, and he worked with Spector for years and gradually worked his way up through the system, and eventually got a PhD and became very influential in the early days of inflammation research when people viewed inflammation as the result of a successive release of mediators like histamine, 5-HT [5-hydroxytryptamine; serotonin], bradykinin, complement and so on. And he mapped out this sequence of mediators appearing at different times in acute inflammation in rats. And he acquired quite a reputation for that work.

TT: Was this at Barts?

RF: Yes, this was Barts. He spent all his career at Barts. And he had a number of prominent collaborators and managed to get a lot of support - mainly from industrial sources for recruiting staff - so somehow managed to get things going. So he was very, very powerful and he was supportive, certainly of me when I first went there. We had a bit of a parting of the ways subsequently, but he was certainly important at the beginning.

TT: When you went to Barts you go there with your own money as Professor within the Medical School, and there's John Vane in this new venture?

RF: Yes, John had some Glaxo money. David Jack gave him some money actually.

TT: You were a professor; were you just doing your research, did you have obligations to the Medical School?

RF: No, none at all.

TT: So really, this was, it's almost back to the old Wellcome days?

RF: It is, exactly so, absolutely. And so John said, 'Well, look, there's you, Rod. I've asked Gus Born to join me from King's. Derek Willoughby's going to join. We also have on site David Tomlinson, who was Professor of Pharmacology here before you came.' He was based on Charterhouse Square site, and so he joined. And then Iain MacIntyre, who came from the Hammersmith, also joined in. And we took a big step forward in 1990-1991 by creating this completely independent, free-standing, self-supporting institute and having it registered as a medical charity with the AMRC, the Association of Medical Research Charities. We kept the name the same, the 'William Harvey Research Institute'. We were the Directors and we also created a commercial spin-out company called 'William Harvey Research Ltd', which we could use to barter intellectual property with people and so on. This was all completely independent from the Medical College.

They were, I think, a little bit nervous of the fact that there was no one else to fill up that space on Charterhouse Square, because by then all the non-clinical Departments, such as David Tomlinson's Pharmacology Department and the Biochemistry Department, had all moved down here (to Mile End). So it was almost empty, there was acres of space!

TT: They moved to Whitechapel?

RF: Yes. And down to Mile End as well. There was acres of space at Charterhouse Square - it was amazing. So they were only too happy to have a dynamic group, and by this time the Institute had grown from about six people to about 50, it was getting big. And so it was very important that we had a self-funding, self-supporting Institute as well as a commercial company. And largely again through John's contacts, we negotiated an agreement with Ono Pharmaceutical in Japan. Ono Pharmaceutical was a company who had a big interest in prostaglandins as therapeutic agents so they said, 'Well, look, we'll give you some money for five years, we'll send some of our staff over to train with you, and you come over to Japan once a year or twice a year and tell us what you've been doing. And if we see anything that we really like, we'll pick it up and run with it. But otherwise you can do what you like with it,' which I thought was very generous in those days. They put a lot of money into the Institute, and this enabled us to grow up to over 100 people, and the money was divided up into the different Departments. I had some, Derek had some, Iain MacIntyre had some, Gus Born had some, John had some, and so on. We were able to hire lots of staff. We paid rent to the Medical College, but it was probably peppercorn rent, to be honest.

And things went along very well at this point until, I suppose, the mid-1990s really, when the world financial situation began to deteriorate, and this began to have a knock-on effect on pharmaceutical companies, and in particular funding from pharmaceutical companies. And although Ono extended their grant by a few years they said, 'We can't renew it any further', they didn't say it, but the implication was they were having financial difficulties. They hadn't got a new drug in prospect and so on. So that time came to an end, and we parted good friends. That left us without a major source of money. In the meantime I got a Wellcome Trust Programme Grant and after that, I went for a Principal Research Fellowship, which, luckily, I got and held onto for another 13 years. So I was very happy. I managed to apply to the MRC [Medical Research Council] and ARC for other monies to support people and it all worked pretty well. On the research side, Biogen had had a change of leadership. Dick Flavell was the original R&D Director, who was an ex-Brit, Fellow of the Royal Society [FRS], and very much a supporter of the annexin project. He left to go to Yale or Harvard. The woman who took over from him was more interested in immunology, and so they immediately axed our project. So they lost corporate interest in us, which was a great shame, but this happens in companies. But they still continued to send me samples and we still published papers together for a while.

TT: Was anybody else interested in funding it?

RF: We tried to get lots of companies interested, we tried to get the Wellcome Trust interested in developing a short peptide but for some reason we failed. I think it was partly a question of timing really. Because now, today, people are interested again, and in fact, even as I speak, there's a clinical trial starting with the full length protein as a potential therapeutic agent. So we keep our fingers crossed. We did a lot of the basic biology of the compound, published lots of papers, and we found out lots of things about it including identifying the receptor. We found out it was a member of the formyl peptide receptor family and this was an idea which actually first appeared in the literature from a German lab. But when my colleague, Mauro Perretti looked at it in detail, he realised that this type of GPCR (G-protein-coupled receptor) has three subtypes, and he realised that the actual sub-type should have been what's called 'FPR-2' [N-formyl peptide receptor 2]. It turned out that's a receptor which also transduces the effects of other anti-inflammatory substances, so it's interesting you've got this GPCR which picks up anti-inflammatory lipids, proteins like annexin and other modulators. It's a very sophisticated bit of molecular hardware, actually. And it translates them into signals that suppress cellular inflammation responses and promote inflammatory resolution. So it's all tied together really nicely now.

So, but anyway, to get back to the Harvey Institute for a moment, in the late 1990s things had got to the point where the Ono money had run out, a lot of our other industrial sponsorship was running out, and we had to make a decision about where to take the Institute. By this time John was partly retired and one of the things we considered was merging with the Medical College and becoming their 'Division of Pharmacology' in effect. We had a lot of preliminary discussions with them about this, because my concern was that we had a lot of people who had grown up in the Harvey, and they'd got to the point where had they been in academia, they would be Senior Lecturers or Readers, but we couldn't offer them that career structure going on into the future. And I thought, 'Well, unless we can do something to stabilise these people, they're going to be off. And once they go, the Institute is going to collapse.' We'd had these discussions internally for a while, and when I became Institute Director, I was the one in the hot seat who had to handle it.

TT: When was this?

RF: 1998-2002 I was Director of the Institute, and we decided that we would actually go down that route, so it was left to me to do the final negotiations and the final signing off. I was very apprehensive about it because the Harvey had a lot of assets by then: I mean millions of pounds worth of assets, not only intellectual assets, but had a lot of equipment, all from grants and so on. So the deal we did basically was that we would exchange our assets in exchange for certain key people in the organisation being taken onto the permanent staff list. That's what we did, and I think it was the right decision in retrospect, although at the time it was difficult. I signed on the dotted line and that's what happened, we became one of the Institutes within the Medical College, self-governing really. A lot of talented young people became Lecturers, Senior Lecturers, Readers and Professors, most of them are Professors now.

TT: So you didn't really become the Department of Pharmacology?

RF: Well, apart from the remainder of David Tomlinson's group who had moved to the Mile End campus, and he subsequently left anyway, most of the pharmacologists, there's over 350, are on the Charterhouse Square site. We also run an undergraduate degree in pharmacology now. So we're probably one of the biggest pharmacological organisations in the world actually.

TT: Really?

RF: Yes, as I say, not everyone's a 'pharmacologist', but we all think in pharmacological ways.

TT: During all of this time, Rod, all these other perturbations of the Institute and everything, what about your own research? How did you manage, were you getting back to the lab?

RF: I was getting back to the lab, yes, and as I said, it was going very well. We had plenty of pure, 'annexin-1' as we now called it. All our predictions about its biological activity were pretty much fulfilled; it was a very powerful anti-inflammatory: it stopped white cells from migrating. It became clear that what it was really doing - and it's a bit of a fine point, but it wasn't really having an anti-inflammatory effect - it was having a pro-resolving effect. And this reflects a fundamental change in the way that we think about inflammation these days. It used to be thought that inflammation healed when the pro-inflammatory mediators ceased. In other words when there was no more histamine, prostaglandins, cytokines etc.

TT: That is, in the absence of...

RF: Exactly, then it just healed and got better somehow. But it's become obvious over the last five years or so, that's not what happens. What actually happens is the body produces a panel of anti-inflammatory or pro-resolving substances, which are phased in exactly when the inflammation beings to wane. These substances appear to restructure the tissue, to enable the engulfment and removal of white cells, and so on. So it's a very, very important part of the healing process. In most cases, if you have an inflammatory lesion and it gets better, your tissue is restored to normal function. So this discovery has revolutionised really, the way

we think about inflammation. It turns out anyway that annexin is one of these compounds, so it has anti-inflammatory properties, but, actually, they really are pro-resolving. It sets the scene for the healing process, partly by dampening down the existing inflammation, but also priming the tissues for remodelling, and so on. So that makes it pretty important and there are several other compounds that have been identified, for example, lipoxin A₄, and resolvin D₂, which are other lipid compounds derived from arachidonic acid.

So it turns out there's a whole bunch of these compounds whose specific job in life is to bring about healing in an active way, not a passive way. Largely through Mauro's work we identified the receptor, we made an annexin knockout, all the things that you do these days when you've got the money, and we made an annexin receptor knockout too, and we showed that steroids don't work properly in either of those models. And that's been very, very powerful technology for us. We also got some peptide analogues of the protein. In the meantime I became interested in other anti-inflammatories, 'Cinderella' anti-inflammatories really, and one of those was ACTH [adrenocorticotrophic hormone]. ACTH was the hormone which releases cortisol from the adrenal glands, and is part of the system that regulates your blood cortisol level. ACTH had been used as an anti-inflammatory drug from a long time, it's very good for gout for example. And it was always thought, quite logically, that the way it worked was to release cortisol. Then it was cortisol that was producing the anti-inflammatory effect. But on one occasion when I was going to Mexico for a conference, I'd taken a big pile of journals to read, and I saw an article by Jim Ritter entitled, *'Why is ACTH so effective in gout?'* And it just set me thinking that maybe there was another mechanism of action.

And again, to cut a long story short, working with Mauro Perretti and others in my group, we found out that peptides derived from ACTH can have a direct effect on melanocortin receptors in macrophages, neutrophils and other cell types involved in inflammation. So even in the adrenalectomised animal you still get an anti-inflammatory effect of ACTH. And that started a whole new line of research, which is still going on today, so that's very interesting.

TT: If we get to the more recent past, you were Head of the William Harvey until 2002?

RF: That's right, and then I handed over to Ben Benjamin.

TT: It's now shared, isn't it?

RF: It's now, yes, then it was Mark Caulfield and now Mauro's taken over.

TT: Did you stay in the lab? Were you still running research?

RF: Yes, I did. I had lots of other things I was doing.

TT: And did you still have Wellcome Trust money for this?

RF: I did, yes, I had Wellcome money for that. The last 4 years, I think, the money ran out or I just hit the buffers on it, so the College very kindly stepped in. Well, I'd been there for 25 years and they hadn't really paid my salary except on odd occasions, so they were very generous, they said, 'Don't worry, we'll pay it.' Yes, that's right, I was doing a lot in the lab, but I also had lots of other things which I did born largely out of my dissatisfaction with the way that science, the culture of science, at universities was heading. I became very seriously interested in learned societies because they were a place where you could go and talk about work, I mean research, without bargaining about space and promotions and that sort of thing. So I became very committed to the British Pharmacological Society (BPS) and I was on their main Committee for a while, then I became Meetings Secretary.

TT: Could you say a little more about the BPS in particular, when did you become a Member?

RF: Yes, it was in 1975 or something I think. I was actually my earliest experiences were with the Phys Soc [The Physiological Society] because of my connection with Sheffield, which I enjoyed a lot actually.

TT: So you did your first communication?

RF: I did. And actually it was The Physiological Society where I got a couple of important lessons about science. One of them was, you can argue all day long about data in someone's poster, but still sit down together and have dinner in the evening in a civilized way, and it was perfect. The other thing, the other experience I had which left a deep impression on me was that I'd written this paper on choline transport in the intestine and I'd sent it off to *J Physiol* [*The Journal of Physiology*] and, this is very early on, the 1970s. The Departmental PA came in one day and said, 'Rod, there's a phone call from Professor Feldberg.' He was somebody I knew because he was also working on prostaglandins and fever. He said he wanted me to go and see him at Mill Hill [National Institute for Medical Research]. I thought, 'Oh God.' But I put my best suit on, took the train to London, got to Feldberg's lab. 'Come in,' he said, 'Sit down beside me.' And he said, 'Now then, I've got this paper of yours here. Now you start off saying this, I think what you really mean here is that.' And he corrected it. 'Is that right?' And he went through the paper line by line and he said, 'Is that, are you happy with those changes?' I said, 'Yes.' He said, 'Okay, I'm accepting it for *J Physiol*.' He was a real gentleman. Actually, I became friends with him after when I grew up a bit, and he sent me a signed copy of one of his books, I've still got it. I keep it as a memento of a very nice man.

But when I went back to work with John we - since we got to Wellcome Foundation - all joined the BPS and, actually, I was, I think, the first BPS visitor to Australia, which was a new scheme they had just started up. Bill Paton had started it up and the thing was that one year, British pharmacologists would go to Australia and tour around the different universities, and then next year an Australian would come to the UK. So I was very lucky to be chosen as the first BPS Australian visitor. I made lots of friends and contacts over there, some of whom I've stayed in contact with for years. So that was a very nice experience.

TT: And did you regularly go to BPS meetings?

RF: Yes, I used to go all the time. We used to go to pretty much every meeting there was. And again the ethos was different in those days; we were encouraged to do that. It was part of our training and it used to be a matter of pride to get an abstract in at every single meeting if we possibly could. And it's surprising how often we managed it. There were four meetings a year and in fact in those days of course, four meetings of the BPS, plus IUPHAR [International Union of Pharmacology] every three or four years or whatever it was, that was pretty much all the meetings you went to. You just can't do that these days. And even the Phys Soc's gone down from, you used to have six or seven meetings a year, didn't you?

TT: We used to have eight or nine.

RF: Really? As many as that?

TT: Yes, yes. You're describing my background as well. It's just a wonderful education, you went to so many things. Now you go to these huge meetings with so many parallel sessions.

RF: I hate them!

TT: Can we continue your account of the BPS, during your time at the Wellcome and in Bath? When did you get onto the Committee and start to...

RF: When I was at Wellcome I was a BPS visitor to Australia, as I said. Then I had some other interactions with the BPS. I can't remember when I first went on the Committee because I was on the Committee a few times actually. It might have been when I was at Wellcome. But when I got to Bath and, as I said, I got a bit dissatisfied with the way things were going from the point of scientific culture, I realised learned societies were the only places anyone could go really and get that support that you need. And the BPS was very different in those days. One difference was that older Members used to look out for younger Members' careers and, for example, I remember Alan Cuthbert ringing me up and saying, 'Rod, there's a good job

coming up in so and so. I think you ought to apply for it.' And my very close friend, Julia Buckingham, who was at Sheffield with me, helped me and collaborated a lot on the HPA axis [hypothalamic-pituitary-adrenal axis] work, had the same experience. People would ring her up and say, 'There's a good job going at...' It just doesn't happen these days, you've lost that relationship between the senior Members of the Society and the younger people coming up the system. It's partly because the number of meetings has been reduced. And in those days you could go to every meeting, and whilst I couldn't remember their names, I recognised most of them and I knew where they came from and I knew roughly what it was they worked on, because I'd been to all the other meetings. So it was more of a community, I think.

TT: When you were at Bath you decided to get more involved?

RF: Yes, that's right, I took a conscious decision and I went onto the main Committee certainly there, and then I was involved in organising a meeting there at Bath, which was very successful. When I got to the Harvey Institute, after a year or two of settling down, I said I'd be interested again, and I was eventually voted in as Chair of the main Committee, and subsequently as Meeting Secretary. In those days you became Meeting Secretary for three years and then, automatically, became what we used to call 'General Secretary', which we now call 'President'. So it was a big commitment. You had six years of work for the BPS, which I enjoyed. It was a lot of work but I really enjoyed it and I met a lot of great scientists and other people. I got to see almost everyone in the country who worked as a pharmacologist, got to see their labs, what they worked on, it was quite an eye opener actually. So when I retired from that, I still kept some low level interactions with them and I'm now Honorary Archivist, at least my period of duty ends this year I think. And I've also come in on an *ad hoc* basis on various Committees, partly because I've been around for a long time I think, well, like Richard Green and Tom Blackburn, who you mentioned the other day.

TT: Well, I've interviewed both of them and they both talked about BPS.

RF: Yes, it was a formative experience, going there, four times a year or so.

TT: Talking about learned societies, BPS is not the only one. I mean in particular, you have been rather heavily involved in some of the more unusual activities of the Royal Society, I think.

RF: That's right, yes I have.

TT: Would you like to say a little bit more about how those came about?

RF: Yes, sure. Well it actually dates back to my time as an undergraduate and I suppose like most undergraduates, I was a voracious reader and during my first year I was looking for books in the bookshop which might be helpful, and I came across a series of books by Steven Rose called *The Chemistry of Life*, which I thought was fantastic, just the right level for a first year undergraduate. And I remember going back to the bookshop looking for other books by him, and I found a book on chemical and biological warfare [laughs]. And because it was by him, or edited by him, I bought it. And it influenced me a lot, the way I thought about biological and chemical weapons. And it's a bit odd in a way because it's like saying, 'Would you prefer to be blown to pieces by high explosive or poisoned with sarin or something?' Well, for some reason people find the notion of being gassed more repugnant than being shot and they find the idea of biological weapons particularly repugnant in an odd way the use of bullets and explosive devices isn't. Ideally you wouldn't need any weapons at all, but as it happens there are Conventions in place to ban chemical and biological weapons, and they are ground-breaking Conventions in the sense that they ban entire classes of weapons. So I became interested in that, but I didn't do very much about it until I was elected to the Royal Society in 2004, and by that time I'd spent a lot of time with the BPS, and so when I got to the Royal Society, somebody must have told them I had an interest in this, they immediately made me Chair of what's called, or used to be called, the 'Scientific Aspects of International Security Committee'. This was a Committee that met about two or three times a year, which surveyed the international security scene, reviewed developments in, for example, nuclear physics that might impact the construction of new weapons, new advances which may facilitate biological weapons, and so on. It was very interesting actually.

TT: And it was purely the Royal Society?

RF: It was run by the Royal Society but had a number of illustrious non-RS [Royal Society] folk on it as well. I learnt a lot and I got also to go around and visit nuclear facilities, and learned how they detected nuclear tests using seismographs and many other interesting establishments. It was very interesting. I was Chair for three or four years, and then I handed it over to somebody else. But no sooner as I'd done that than I got a request from the Royal Society to chair one of their panels for their 'Brainwaves' project. This was a series of four projects designed to explore the impact of neuroscience on society generally, and various specific aspects. There were four panels, and there were four reports subsequently published. One was a collection of general essays, really, about the scope of modern neuroscience and its impact on things like free will, decision making, things like that. The second one concerned neuroscience and the law, how advances in neuroscience may impact on the way that we make laws and so on. The third one was neuroscience and education, which considered whether there was anything we can learn from contemporary neuroscience which will make us better educators or teachers. And then, the fourth one was mine, and was the use of neuroscience in warfare and conflict and security.

That was an interesting panel to be on and chair. For a start, I met Steven Rose for the first time and we became friends. I told him that it was his book in 1968 that really triggered my interest in this affair. And so this whole process of gathering evidence from various experts and welding them all into a report, actually took about six to nine months. It was eventually published by the Royal Society and it made a big impact at the time, had a big impact on me as well because there were lots of things in there that I didn't know, because I'm not a neuroscientist by training. The press were very interested in it because it raised many intriguing possibilities such as controlling drones using brainwaves, smart drugs to promote pilot performance, and things like that. So it was full of all the things that make good scientific headlines as well as being a very interesting study. And then after that I was invited to write a review for *Nature Reviews Neuroscience* on the same subject, which I did with Irene Tracey, who was one of my colleagues on the panel.

And then, from that, I became more involved with, first of all, the Chemical Weapons Convention (CWC), which is, because one of the problems at the moment is, it's difficult to say what a chemical, and what's a biological these days. And with the advances in biology it's easy to make, for example, complex toxins using, for example genes from different organisms in arrays arranged in sequence, one can make some extraordinarily complex molecules. Likewise, organic chemists are much more skilled than they were when the CWC was framed, and can tackle the synthesis of molecules that would, at one time, been considered 'biological'. So there's this whole problem, it's called the 'convergence problem'. It means there's sometimes a bit of a grey area between the Biological and Chemical Weapons Conventions on what's covered and what isn't. I was involved with providing advice to the CWC about how to manage this type of phenomenon, so that there were no loopholes that could be exploited. And then simultaneously, and I'm still doing it, I did quite a lot of work for the Biological Weapons Convention in the form of chairing meetings which discussed advances in technology which might have an impact on the production of biological weapons.

So for example, high speed and low cost genome sequencing and polynucleotide synthesis and that sort of thing. All these things make it easier for someone to identify and modify pathogens. You can order sections of genes online now, and get them the next day. I mean it's incredible. So all these things increase the risk that somebody who does not subscribe to the Biological Weapons Convention, most likely a terrorist group, could make a pathogen which is deliberately constructed in such a way to evade the human immune system. That's obviously a very scary prospect. I've done three conferences on that topic, usually in conjunction with the American National Academy of Sciences, and these have been very good. I mean again I've learnt a lot and I'm doing one in two weeks' time, in Geneva, because one of the problems with the Biological Weapons Convention is that it needs new ways of feeding scientific advice to the Convention. It has review conferences every three years or something, but three years in biology these days is a very long time.

TT: So that's when they pick something up?

RF: Yes. The CWC has different arrangements and the Biological Weapons Convention doesn't have anything comparable. So the purpose of this upcoming meeting really is to come up with recommendations for the best way of providing scientific advice. And in a form that the diplomats need in order to help them. What's the best format for this? What's the best frequency? We had a meeting in Warsaw last year which dealt with some of these issues. It's interesting, and you meet a lot of people who are not mainstream scientists but also social scientists and so on, people who are health economists and things, who have an interest for other reasons, but have been placed by their government into this frame so they can take back ideas. When I started doing it, I have to say, I was deeply sceptical about the whole process. You can talk forever about these things, does it actually have an effect on the people who frame the Convention? But I've come to the idea that it probably does.

But the most important thing about it is that you get together with people every few years or whenever, and you establish networks of people around the world so if there really was an emergency, we know who to ring up in, say, Malaysia or wherever, and say, 'Look, we're really worried about this. Can you give me any information? Or can we help in any way?' And so on. And I know who to speak to in, say, Ukraine, because I've met them at these meetings and I've got their e-mail address. So you build an international community, which is dedicated to these sorts of tasks and it's got its own momentum, in a way. It's interesting, it's a bit odd for a pharmacologist, let alone a physiologist, to be involved in [laughs], but it's very interesting work, actually.

TT: One of the other interests you've shown throughout your career, to some extent you've already referred to it, and that's history; talking about almost trying to replicate Otto Loewi's classic experiment. Could you say something about where that came from? Did it seem something natural when you were reading scientific papers or was it an older interest? Or did you suddenly realise, actually, I'm interested in history?

RF: I was interested in history of science, I have to say that, getting back to what I said at the beginning, when I was at school my history teachers were so awful, it put me off for life. My wife Lindsay, to the contrary, had really inspiring history teachers and she loves it, and she's a very good amateur historian and very keen on the subject. But I had the reverse experience, and they really put me off. But when I became interested in science, I became very interested in history of science and the history of ideas, and so I read a lot of books on the subject. Actually Wilhelm Feldberg wrote quite a lot about it as well. I read a lot of that stuff, especially when I was an undergraduate, and so I was primed really with these ideas by seeing what other people had done. And actually it's a big disappointment to me these days that you stand up in front of a class of 100 medical students, as I used to do regularly until now, to find that no one's heard of, for example, Alexander Fleming, let alone John Vane, or perish the thought, Watson and Crick. The best response is 'Oh, it rings a bell.' That's comparatively recent history as well. So, I think, it's a great shame because, actually, what they're missing out is the matrix which supports their entire discipline, really.

TT: It's very interesting the way you've been talking about relationships at the lab level, then there's the national level with the BPS, and just now international relationships and networks. One relationship that you've not mentioned is with clinicians.

RF: Yes.

TT: Practitioners taking your drugs into the clinics. Have you had much direct involvement with clinicians?

RF: Yes, quite a lot actually, and when I was at Wellcome for example, there were a lot of clinicians there of course. I got to chat to them a lot, and got to see what their points of view were regarding drugs.

TT: Were these clinicians mainly in marketing or surveillance?

RF: No, they had a good Department of Pharmacology there, and they would do the 'first-in-man' studies actually in-house. So they had, you know...

TT: A panel of volunteers?

RF: Yes, pretty much. People, often internal candidates, used to volunteer, and they had a few beds in the Unit on the Beckenham site. In fact, I volunteered for a trial myself. I had a bit of interest because they were collecting blood after giving me hydrocortisone, and so I could measure my own blood lipocortin levels. The whole setup was there and they were pretty effective. When I went to Bath I had even more to do with them, in a way, because Bath has been a centre for the treatment for rheumatological diseases for centuries, and they had the Royal Mineral Water Hospital there. They had a pretty stellar group of rheumatologists, so I interacted a lot with them and I had people on my staff who worked down in the Mineral Water Hospital and held positions at the University, and we published papers on auto-antibodies to lipocortin in patients who had rheumatic diseases, and a couple of human studies on ourselves showing that if you inject hydrocortisone, you can measure the rise in lipocortin, and so on.

And one of my achievements when I was at Bath was to actually incorporate the clinicians into the University structure by starting off the 'School of Postgraduate Medicine', as I called it, which I thought was a good initiative, because there were lots of very, very good clinicians in town who would dearly love to interact with academics, but didn't have a framework for doing it. And likewise the pharmacologists at Bath and other people who would dearly like to have a close link with clinicians, but they couldn't do it either. So by forming this group it, I think, had a positive effect, at least for a while. I'm not sure it's still running now, but certainly to begin with was very healthy, and actually, incidentally brought a lot of money to the University as well because clinicians tend to be very well-funded to do trials and so all this money could be routed through the University and in a giant 'book-keeping exercise', actually swell their coffers as well. And then, of course, when I went to the Harvey Institute, they had a Department of Clinical Pharmacology in Barts Hospital, which was run by Paul Turner, who I'd known because he was a Member of the clinical section of the BPS. Paul had a heart condition, and after a succession of heart attacks, he eventually retired on medical grounds. The Medical School wanted to close the Department down, and so I went to see the Dean and I said, 'Look, you shouldn't do this, these people are potentially a great resource.' Clinical Pharmacologists are the last real generalists in medicine, and much to my surprise they were very amenable to my intercession and the Dean, Lesley Rees said, 'Alright then, you head it up!'

TT: Good on her.

RF: So two or three days a week I used to tramp over to the old carpet factory behind Barts which was where the Department of Clinical Pharmacology was, and I took over this Department on a part-time basis. I did find a couple of people there who were absolute stars. Mark Caulfield was one of them, and I pushed his career as hard as I could. He eventually got a Chair. And then there was the BPS, the BPS originally didn't have any accommodation. They've got premises at Angel Gate now, but at one time if you became the Meetings Secretary BPS paid for part of your secretary, and the 'office' moved around between universities. Everyone thought it would be a good idea to have some fixed accommodation. Looking out of my office on Charterhouse Square there was a flat roof next door and I said to the estates manager, 'Could we put a Portakabin on the flat roof?' 'Oh, yes,' he said, 'no problem. Actually we had one there a few years ago but we took it down.' So I said to the BPS, 'Would you like to come and have a Portakabin on the roof?' So anyway, so that was the first BPS office. Later when they got Angel Gate, they took that Portakabin off and at that time I said to the college authorities, 'You ought to move the Clinical Pharmacologists over next to the William Harvey Institute. You could build a Department of Clinical Pharmacology on that flat roof.' So again I was amazed that they said, 'Alright, we'll do it,' which is astonishing.

So they built a Department of Clinical Pharmacology on the flat roof, we got all the Clinical Pharmacologists over on the site so the Clinical Pharmacologists and the Basic Pharmacologists could actually talk to one another. I think that's been pretty successful really.

TT: **Lovely accounts of interactions with clinicians. Were you ever formally involved with drug trials of some of these compounds you were working on?**

RF: Only as an advisor really. When prostacyclin was discovered and was infused into human subjects, we needed to know whether it was inhibiting platelet aggregation, and for how long. And the way of doing that was the Born aggregometer.

TT: **That was to be one of my final questions to you: the aggregometer.**

RF: Well, this is how it came about. The trouble with the Born aggregometer was that you had to take the sample, spin it down, make the 'platelet rich' plasma, by that time prostacyclin had decomposed, because it's only got a half-life of eight minutes or so. So as it happens I'd just been to a talk on ion fluxes in platelets or something, and I had the idea that maybe you could monitor platelet aggregation by measuring the electrical properties of a solution of platelets. I'd been tinkering around with this with a chap called David Cardinal, who was an electronics technician at the Wellcome Foundation. The original model was two paper clips and an Avometer, but David said one day, 'I've been tinkering around with it and I think I've got it to work.' So I went down and sure enough, when you added collagen to samples of platelet rich plasma we saw a big change in impedance. What was actually happening was, the platelets were sticking on the paper clip but this was causing a change in impedance, which you can record. So he built this machine, and we were able to take blood straight out of the patient, put it straight in the machine and get readings straight away, which was great. And you didn't have to spin it, you didn't have to do anything with it, as long as it was anticoagulated. I published several papers on that and its use and Wellcome subsequently sold the patent to a firm called 'Chronolog Corporation', which also marketed Gus Born's optical aggregometer, so it makes both of them now. And this aggregometer, our aggregometer, is still in use in hospitals and research labs, although it never completely supplanted the Born aggregometer.

TT: **And it was your aggregometer that was used in the MRC Epidemiology Unit in South Wales?**

RF: Yes, that's correct, yes. The situation there was they had enrolled many miners on their myocardial infarction trial, and to make the whole project possible, they had to take their laboratory around with them in a caravan. So they had to have something that was easy to use and portable, and I either gave them a machine, or loaned them a machine, or I've forgotten exactly how the interaction started, but there were a couple of odd results which I never got my head around; but yes, the results were published and I was one of the co-authors in the end.

TT: **Well, of course, there was some problem, wasn't there a problem with the Born aggregometer.**

RF: Ah, that was interesting, yes.

TT: **Were you involved in that?**

RF: I wasn't involved with it, but I knew all about it, because it was happening pretty much under my nose when I was at the RCS. Yes, Gus Born invented the aggregometer. Basically, he observed that when you added collagen, the solution became clear as the platelets clumped together leading to an increase in light transmission. We had a Polish electronics technician in the RCS called Ziggy Sabikowski, and Gus told Ziggy to make a machine that could measure light transmission through the solution basically, which he did. Gus being Gus, he demonstrated this at a Phys Soc [meeting], or maybe it was the International Society for Haemostasis and Thrombosis or something. This is all secondhand, but this is what Gus told me: 'John O'Brien came and looked at it, and then subsequently went away and produced his own version, and later claimed that his was first.' Now, this really wounded Gus actually, and I'm not saying who was right, who was wrong. I think I know, but this caused a lot of problems for Gus, and he spent quite a lot of effort to reclaim the credit that he felt was being unfairly taken by O'Brien. But, interestingly enough of course Gus Born worked with the people who discovered penicillin and developed that.

TT: Heatley and Florey?

RF: That's right, Heatley and co. And I said to Gus once about the aggregometer, 'Why on earth didn't you patent it? Because they're sold all over the world these machines, you'd be a millionaire!' He said, 'Yes, I should have done, but when I worked with Florey I said the same to Florey and I said, "Why didn't you patent penicillin?" and Florey said to me, "Should we patent sunlight? It's a gift for all mankind."' And Gus said, "That was the attitude in Oxford in those days, and that was my attitude, and that's why I didn't patent it.'

TT: You've talked quite a bit about animals or *in vitro* or *in vivo* experiments, but one thing we also talked about is the platelet. Of course there's this paper about platelets as an experimental animal. Were you one of the people who really pushed platelets in terms of teaching?

RF: Well, of course this is going back many years now, we certainly used to use it as a teaching aid, and my point was that it was an easily obtainable single cell preparation from humans, and that differentiated it from just about every other test system you could think of in those days. They are easy to assay, they responded to agonists, antagonists, you could study metabolic events, and so on. So you could learn a lot by studying platelet aggregation, and so I thought it was an ace teaching aid. In fact, at one time, I rather facetiously considered writing a book called '*A Thousand Experiments with Platelets*' for undergraduate students. Of course now it's a bit different, because you can use U937 cells or some other immortal cell line, and it's a single cell population from humans, but in those days platelets were pretty much the only one that was available.

TT: I am interested in the fact that you actually have quite a few single author papers, which is quite unusual. Is this something that you have particularly wanted to do at particular times, write review articles, editorials. Is that something you initiated? Do you still initiate it?

RF: Yes, there are quite a few. I don't know quite how it came about really, but I think the first one I wrote on my own was *Pharmacological Reviews* when I was a PhD-student, which I wrote on my own and I said to John, 'Would you like to read it?' And he made some comments and I said, 'I'll put your name on it.' And he said, 'No, don't. You did this, so you take the credit.' I have written reviews with other people, it's often a nice experience, but it can be frustrating. So if at all possible, it's easier to write on my own, although it's a lot more work.

TT: I just wonder whether you saw it as any kind of obligation or as something you're passing onto another generation, your views and experience?

RF: Yes, I suppose so, in a way, if I write it on my own I can be quite idiosyncratic about what I put in and what I leave out. If I write with somebody else, people reading it are never quite sure who said what, and very often it turns out to be a bit of a botch in terms of opinions. So yes, I have written a reasonable amount on my own. I don't mind, I enjoy writing actually, and of course one of my jobs now, which has been going on for years now, is co-authoring Rang and Dale's textbook [*Rang & Dale's Pharmacology*], which comes around every four years. It's a major effort. Next year is another writing year.

TT: How did you get involved with that?

RF: Well, John and I and Salvador Moncada and Sérgio Ferreira had written chapters for Goodman & Gilman's textbook [*Goodman & Gilman's The Pharmacological Basis of Therapeutics*] before, and we'd done three or four years of that. And we'd also written another couple of textbook chunks and so I'd got into the frame of mind, really. And then one day, I've forgotten when it was, Humphrey Rang telephoned me and said, 'Can I take you out to lunch?' Over lunch he said 'We're looking for another author for *Rang & Dale's Pharmacology* and I think your writing's okay, I've read some of the stuff you've written. Would you be interested in joining?' I said 'Yes.'

TT: When did you first get involved?

RF: This is my fourth edition now.

TT: So 2007, the sixth edition?

RF: Yes, sixth edition, yes, probably. It came out in 2007, that must have been 2002 that Humphrey contacted me. Because it takes a year to write and a year to edit before it is published. But it's an enormously influential textbook, and it's very important to have these types of textbooks, knowing how textbooks influenced me when I was an undergraduate. I think they're very important as teaching aids and I already mentioned Steven Rose's books on the chemistry of life and how influential they were. And you think of the other physiological books we had, [of] Guyton, Samson Wright etc. They were enormously influential. So *Rang & Dale's Pharmacology*, it's a nice project to do, it's very demanding, but Humphrey and Maureen Dale set a tone for a book, which is a bit unique. It has jokes in it for one thing!

TT: It's much chattier, isn't it?

RF: It's much chattier, deliberately so, to engage students. And also, although it's notionally a pharmacology book, it also deals with basic physiology and biochemistry as well and so lots of students say, 'I go to it because it's got everything in it. If I want to know about the heart there'll be a bit about heart biochemistry, bit about heart structure and so on.' So it's very nice. As I say it's a lot of work, but on the other hand it's very rewarding. And I might add, parenthetically, that one of the absurdities of the Research Assessment Exercise is that people who write books never get credit for them. It takes a year of writing to do that, but if I can't put it on my return, people will think, 'Flower hasn't done anything this year.' And so it's just not right, it's just not fair. It's not fair on authors.

[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 a video interview (14-Apr-2016)*. History of Modern Biomedicine Interviews (Digital Collection), item e2016069. London: Queen Mary University of London.