

AUDIO INTERVIEW TRANSCRIPT

Green, Richard: transcript of an audio interview (17-Dec-2015)

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Green, Richard: transcript of an audio interview (17-Dec-2015)*

Biography: Professor Richard Green PhD DSc (b. 1944) completed his PhD (1969) with Gerald Curzon and following two years at the National Institute of Mental Health (NIMH), Washington, DC, with Erminio Costa, he joined David Grahame-Smith at the Medical Research Council (MRC) Clinical Pharmacology Unit in Oxford becoming Assistant Unit Director in 1981. In 1986 he was appointed Director of the new Astra Neuroscience Research Unit in London. In 1996 he was appointed Director, Global Discovery CNS & Pain Control, for Astra. After retiring from AstraZeneca in 2007, he has continued psychopharmacology research in Nottingham, and is currently Honorary Professor of Neuropharmacology at Nottingham University. He was awarded the DSc by London University in 1988 and in 2010 was given the Lifetime Achievement Award by the British Association for Psychopharmacology. He is a President Emeritus of the British Pharmacological Society and a former President of the Serotonin Club.

TT: Tilli Tansey

RG: Richard Green

TT: What I thought we would do, Richard, would be to go through your career largely chronologically, a little bit about your background, where you come from, your education and how you became interested in pharmacology.

RG: I had a father who was an entomologist, with the Department of Scientific and Industrial Research in Slough. He was interested in pest control, basically. They were called the 'Pest Infestation Control Laboratory'. I don't think I ever thought of doing anything other than a biological subject and at A level I was aiming, I guess, to think about biochemistry, which I have to say, in those days, you know, 1962/63 time, was more biological chemistry than it is now. It tended to be more into what we think of as pharmacology now, because it was often whole animal biochemical mechanisms. I have to say I blew my A level physics and so I worked for a year at the Aspro-Nicholas labs before going to university.

TT: Which labs?

RG: Well, if you remember, Aspro was the premier branded aspirin. They were manufacturing everything from pharmaceuticals to household products in a way that some of those companies were then. I worked in analysis of raw materials. Then I went to Chelsea College and my degree was, chemistry and physiology. They'd started a physiology course there. Up until that year, 1963, physiology had been a Part 2 subject, you couldn't do it for Part 1. And that year they started doing Part 1. I absolutely loved it. That was the part I really enjoyed more than anything else.

TT: Who taught you? Who taught you physiology?

* Interview conducted by Professor Tilli Tansey, for the History of Modern Biomedicine Research Group, 17 December 2015, 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.

RG: In physiology there was a wonderful guy called John Dimsdale, who was a physiologist and he then went off to Hatfield Poly and became Head of Physiology as they got going on that. The Head of Physiology was someone called Dicker, who worked on the kidney. I think he was another German immigrant. And biochemistry was taught by David Plummer, a good teacher. I don't know why, I just thought of carrying on doing a PhD at that stage and saw this advert for work at the Institute of Neurology with Gerald Curzon and as luck would have it I think a lot of my career happened by chance. Someone came in during the interview who also worked at the Institute and who'd been doing the degree that I'd been doing, but part time, and greeted me and that gave Gerald a chance to say, 'What is he like?' after I'd had my interview. And I think that probably helped. And Gerald wanted me to work on an idea of how giving - there had recently been an indication that people with depression had raised corticosteroids - steroids, corticosteroids, which would raise the levels of an enzyme called 'tryptophan pyrrolase' in the liver. And Gerald's idea was, 'Well, tryptophan comes into the body, it's made into serotonin in the periphery and in the brain. If you increase the activity of this enzyme then even more tryptophan, would go down the pyrrolase pathway,' it was metabolised to niacin, 'so there'd be less available for 5-HT [5-hydroxytryptamine] to be made in the brain.' That's what I started on, and it was hugely successful. I mean basically we took rats and we injected them with steroids and brain 5-HT decreased, so my second paper was actually in *Nature* and it was a full paper, not you know a 'Letter', and that was my second paper ever actually [laughter]. And Gerald generously put me as the first author on that. And the reason, to answer your question, which I haven't done, the reason that my PhD degree was Biochemistry, was because at that stage in the University of London as I remember, you couldn't actually have a PhD in Pharmacology unless your first degree was in Pharmacy. It had to be Biochemistry. So, my degree was *via* the Faculty of Biochemistry.

TT: And which college, because you were at the Institute of Neurology, where was that affiliated? Where did you get your degree from?

RG: They were part of what then existed, which was the British Postgraduate Medical Federation; this included the Institute of Neurology, Institute of Child Health, Institute of Rheumatology, whatever. I was also lucky. There wasn't a grant for that investigation at that stage. Gerald had a 3-year MRC grant, he had money from them and I was actually employed as a graduate technical assistant or something. So actually I got a surrogate role in the grant, and then I think the second and third year got money from the Mental Health Research Fund as they were then called, because they were still giving money for pre-clinical research.

TT: So that you got really hooked on doing research?

RG: Absolutely. I mean giving drugs to an animal and changing brain biochemistry. Most of research obviously was on that. Then a paper by Roger Maickel in the States came out on a new method of measuring 5-HT, where you reacted 5-HT with *o*-phthalaldehyde and it produces a hugely fluorescent derivative. And I'd been using a method by Sol Snyder where you reacted it with ninhydrin but this took it to another level and Gerald noticed this paper and said, 'We ought to try this.' And Maickel's paper was only for measuring 5-HT and Gerald had said to me, 'Okay, well you extract 5-HT back into acid it should mean that the 5-HIAA [5-hydroxyindoleacetic acid], the main metabolite, is still in the solvent. If we now shake that solvent up with,' and I can't remember now, you know, 'an aqueous solution of such and such pH, I would have thought the 5-HIAA would have come back out.' Did that and it did. And the method worked. The method was so sensitive that we realised that we could measure in small regions of the brain. And as a result of that, we put the method in for publication for measuring small regions of the brain for 5-HT and 5-HIAA. It was only a three-page method in the *British Journal of Pharmacology* [BJP]. And until HPLC came along, high pressure liquid chromatography, about 10 years afterwards, it turned out to be, you know, one of the most important methods. We got something like a thousand citations of that method, this is the next 10 years.

TT: This was all in rat brain?

RG: That was all in rat brain, yes.

TT: How did you do the dissections? How did you get your discrete areas?

RG: Oh, just by learning how to dissect. Again I think there was a method by a couple of the neuroscience greats, Les Iversen and Jacques Glowinski, on how to divide up into, it was only six regions of the brain, I mean we're not talking discrete nuclei; striatum, hippocampus, cortex. But you know, up until that time people had tended, it's amazing we tended to think we might learn something, you just took the whole brain. As Les said to me one day, he said, 'My God, we take a whole brain, we mash it up, we measure something and think we can understand how the brain works.' So that was that. And it was actually work with Gerald that then influenced my future career in that I thought I'd like to go to the States, because a lot of really good stuff was going on in the States in neuroscience in the late 60s. I tried to get into Ted Sourkes' lab at McGill, who was doing some really interesting things, again on pyrrolase and that sort of area, and the Canadian authorities, Canadian MRC, would only give grants if you were a landed immigrant, and I didn't want to do that. I wrote to a friend I knew in Omaha at the University of Nebraska in Omaha, who had a neuroscience friend, and who's called Mike Ebadi, and he said, 'Yes, you can come and work with me.'

And then I then had another letter from him saying, 'I've got a year's sabbatical to go and work with Eminio (Mimo) Costa at NIMH, you should come here, it's fantastic. I'll give your name to him.' Well, I would never have dared even apply to Costa, you know. To me he was sort of near God, like Brodie and some of the others. I met Costa in what was then I suppose thought to be an offshoot of the American Embassy, the Hilton in Park Lane. And he said, 'Oh yeah, you know, I can take you.' Wow! At that point by the time I got to Costa's lab, Ebadi had gone back to Nebraska, so that was fine, you know, because I had a fantastic time there. And just before this, while I was wrapping up my PhD, I wanted to measure tryptophan hydroxylase, which had only recently been actually identified and measured by David Grahame-Smith at St. Mary's Hospital. I had got his thesis out from Senate House Library, copied the method down, read it, and if you wanted to quote a thesis you actually had to ask permission of the author. So I wrote to him and he wrote to me back and said, 'Oh, you're interested in this, come along and see me.' So off I trotted to St. Mary's and we had a long chat and I told him what my plans were and he said, 'Oh well, you know, I'm hoping to expand here. You know we must keep in touch because I hope I might have something for you when I come back.'

Fine. I'd been in NIMH for about a year and in those days *Nature* had news, so it was much more parochial, it used to have UK Science News. It reported that David Grahame-Smith had been appointed the first Director of the MRC Clinical Pharmacology Unit in Oxford and Professor of Clinical Pharmacology, so I wrote and said, 'Well done, David. Do you think there will be a job for me?' And I ended up in Oxford [laughs]. And as I say, things happened without plans, by chance. I've generally let my career sort of go the way it follows because it seems to have done okay doing it that way.

TT: And at that point, when you went to work with David, did you have any particular project? Because David had a very, much more clinical approach.

RG: Well, what David always was very keen on, or what these days we'd always call translational. His big interest was biomarkers of drug action, and it didn't matter whether it was preclinical or clinical. If you get preclinical markers and they go onto clinical, then do it. The lab was always 50-50, that's for sure.

TT: So you'd been with Costa, you came back, did you bring with you some special techniques?

RG: Again it was luck. I had been working in Costa's lab, in the second year I was there, on something Costa was really keen on which was a technique called 'mass fragmentography', which is where you used a gas chromatograph to separate compounds and then, using the mass spectrometer focussed just on one particular ion that was selective for your specific compound and you ran your scan very, very slowly and used it as the detector. Hugely expensive, really difficult to do particularly with the equipment then. And I was going to come back to use not that, but to set up probably gas chromatography in the lab to measure monoamines and things like that. And equipment, thankfully, didn't arrive and David wanted me to get going on something and he recently had been looking at the way of measuring function of 5-HT by giving tryptophan, a 5-HT precursor and a monoamine oxidase inhibitor, and that builds up the concentration of

5-HT in the brain and the animals show very distinct hyperactivity syndrome. It's generally called the 'serotonin syndrome' and you can see it in humans as well. And he said, 'Well, you know, I've got a couple of things on this. I think you know it's a way into showing how drugs can alter 5-HT function in the brain.' And so I started working on that and that actually hooked me the whole time I was at Oxford. I did lots of other things as well, but that was always the background, and we looked at all sorts of drugs like tricyclics, like lithium and then onto ECT [electroconvulsive therapy] as well.

And you know, yes I got involved in lots of other things because of other really good people I've got involved with, but that's what I started working on.

TT: And this was all neurological. Because you used the platelet at one point...

RG: We did platelets once, but that wasn't really a huge success. We used the platelet as a model of a neuron but you know it doesn't actually, it doesn't actually make 5-HT, so it turned out to be very limited.

TT: And where did that idea come from?

RG: That started off in my first year at NIMH because I worked with a guy called David Boullin, who is also British. He'd worked in Brodie's lab and looked at various compounds and their effects on platelets and I did some work on that. It was just the time that some of the amino acids had been shown to be neurotransmitters and so we tried to see if we could understand more about their pharmacology using the platelet it was okay but...

TT: You just mentioned there, Richard, that you got involved in lots of other things, with other interesting people. Can you say a little more about those?

RG: In the States?

TT: I think you were talking about Oxford.

RG: In Oxford. Well, David was an inspirational person to work with. Sometimes, I mean I heard on the wards, that, now, some of the young clinicians would think, 'God, this guy's a Professor but that is a silly idea,' because he would throw out ideas, often quite a lot of ideas, and perhaps, of 10 ideas, five or six might be silly. And it's easy for anyone to see that and think, 'Hmm.' But two or three would be viable, and one or two might be really great, and I used to have wonderful times sitting with him in his office where he would start off with, 'Well, let's imagine, and I don't know exactly what I mean by this but...' And he and I would often do it, sometimes without other people there, because sometimes others would pick out the fine detail and he didn't want that, you know. They would start criticizing things before it was worked through. But I understood him and you would just do, I suppose it's called 'brain storming' now, you sketch out in broad detail and I loved working with him for that, because he'd have some fantastic ideas. But he was also terrific for me in that he after a while said, 'For goodness sake, you don't need to have my name on this,' even though we'd often discuss things. I mean he'd let me establish my own place in science and that's just generous. Even more generous and I'm coming to the answer, is that he had some terrific young clinicians, usually psychiatrists, or getting to be psychiatrists, who wanted often to come in and do some preclinical work, whilst continuing some clinical work, and he essentially handed them over to me and my group.

So I had David Nutt. I did say at one stage that I felt that might be an indication of how clever David Grahame-Smith was in delegating him to me, you know. David Nutt was just like an over-excited Labrador. He wanted to do everything. Occasionally Grahame-Smith would say to him, you know, 'David, David, everything takes time. If you do that, you've got less time for that.' 'Righto, Prof!' and off he'd go. Nothing phased David Nutt, still doesn't. So I had him and of course he's become a mega-personality. Phil Cowen, Professor of Psychopharmacology at Oxford now, and we did a lot of work together. And he worked quite a lot with me again on the interface between preclinical/clinical and he's carried that right through his career. Dave Nutt has done the same. Guy Goodwin, Professor of Psychiatry at Oxford, who I did a lot of work

with on the 5-HT receptor. So all of those, but you know there were others in that I did work with Bill Deakin while he was at Mill Hill, and who is now in Manchester and a big name. So you know there were a lot of people who I interacted with, and it was always an exciting period because I never found in psychiatry that there was a big barrier between preclinical and clinical. I mean it didn't matter whether it was the BAP [British Association for Psychopharmacology] or the international meetings. When I look back now, I met a lot of big name people who I didn't realise until subsequently how big they were because they treated you as 'you know your area and I know mine' and you spoke on equal level. I mean people like Hermann van Praag and people like that, and Fridolin Sulser, there were a lot of important international scientists that you met. Ray Fuller at Lilly who developed fluoxetine, they were just all nice people.

The other person in the early days in Oxford who I worked with was Moussa Youdim, who went off to Israel, of course, working then on MAO [monoamine oxidase] but then he and I got involved in L-DOPA and deprenil, and that area. But then you know obviously the domestic people, people like Merton Sandler and so on, all of them were around and all of them were sociable and pleasant. I have to say, it became a change when I moved to Astra and, as we'll probably go into, got involved in stroke. And I didn't find that same openness, interaction and bonhomie with neurologists. Psychiatrists are much less: 'Well, you may say that but I know I'm the one that's right.' And I found neurologists, with the exception of one or two people like David Marsden, who was a delight, not to be anywhere near as pleasant to deal with as psychiatrists.

TT: Interesting comment. Can we just go back, when you arrived you went to work in Oxford with David Grahame-Smith and you mentioned earlier about these young psychiatrists in training almost, coming to your group. So you had a group. What was the situation? When you went to work with David Grahame-Smith you went as a scientist, a member of MRC scientific staff, and you set up your own lab?

RG: Oh no, it really wasn't the way it worked. I mean David had a full clinical programme. His other peak interest was digoxin. So very early on Jeff Aronson came into the lab and worked on digoxin. Grahame-Smith was always an on-take physician, because he said he didn't think you could do proper clinical pharmacology without being a hands on physician as well. And so he tended to cover those people and his clinicians and what I mean by having my own group: what I had was a couple of technicians, and often these scientists, psychiatrists in training. Well, in training, they were generally registrars to senior registrars. And we just worked in the lab still within the general umbrella but all the day to day running was with me and then we would meet with David every so often and review things. Because of the structure of the MRC, there wasn't separate money as such. Money was still fairly available in those days, we just worked.

TT: So we're talking about when, '73?

RG: '73 to about '85. And David had a sabbatical and made me assistant director. So you know I suppose a little bit more kudos but it didn't mean anything in very important terms other than it taught you a little bit more about trying to manage. I mean I've always maintained that Gerald Curzon taught me how to do research, Erminio Costa in his true Italian way taught me one had to be passionate about science. You know Mimo, even into his eighties, when I met him a few years ago, could get highly excited about everything. And David taught me that science has to be managed, people can't go off in every direction, you've got to have management of it. And so they all were a big influence on me, but David taught me a huge amount scientifically, but he also taught me that, I think.

TT: So how big was the unit when you joined it?

RG: The unit was around 27-28 people altogether, I guess, it may have been a bit smaller. Because you had people coming and going, we had visitors from South Africa and Australia and things like that. It wasn't that big, but it was always hugely exciting.

TT: This would be the time Les Iversen would be running the Cambridge unit?

RG: It was, it was. I went over and spent a week in his lab to learn how to measure GABA in the 70s.

TT: Because in the early 80s I was working for the MRC in Edinburgh, for the MRC Brain Metabolism Unit which was very tiny really compared with yours. Interestingly Guy Goodwin came just as I was leaving, our clinical attachment there was to psychiatry. I'm diverting a little from your story but did Les Iversen's unit have a clinical commitment?

RG: No, other than, they had clinicians there and they had of course they started the brain bank there.

TT: Oh, was that from Les' unit?

RG: Yes. That was Gavin Reynolds, he was involved in that.

TT: Of course he was, how stupid of me. Yes, yes, I do know that.

RG: But there were others. So a guy, Scottish guy, Angus Mackay was there. He went off then to Scotland to be I think a physician superintendent.

TT: Yes, he did didn't he? Going back to your years in Oxford, what would you think that a main achievement of that period would be?

RG: Well, I'll tell you two main things: one was we started looking in about late 1970s at ECT. We'd been looking at various other antidepressant drugs and how they might work, and I managed to get hold of an old ECT machine, clinical ECT machine, very crude. Oh no, it was earlier than that, it was about '75, it was fairly early on. First paper was 1976 in *British Journal of Pharmacology*. The first name, because *BJP* was then, alphabetical, was actually a student doing her project called Jane Evans. That's the one. And we gave daily electroconvulsive shots to rats and found it totally changed their 5-HT responses in the direction you expected antidepressant drugs to do. And oddly enough, we were beaten by about three months by a guy in Gothenburg in Arvid Carlsson's lab, called Kjell Modigh, who'd shown much the same thing, but with dopamine. And I kept in contact with Kjell and I had a British Council award very briefly, and spent about 10 days over there with them meeting Arvid Carlsson. Again, when you think of it, oh yes, he got the Nobel Prize didn't he? At the time he was just a very delightful Head of Department, and I have to say I used him when I applied for my tenure at MRC staff position. It wasn't a bad name to choose, was it?

And we then kept working on that and did all sorts of things on the mechanism, but I think the thing that was important about it was that it showed, because ECT was going out of favour by then, and the work proved it didn't 'just shake the brain up'. You know, you'd hear all of these phrases. And I think what we showed, which I think excited psychiatrists, was that it seemed to have a defined pharmacological-like mode of action. There were things it changed, there were things it didn't and those changes were consistent with some other antidepressant drugs. And then that led onto the fact that when we were working on, we were very early onto the fact that the 5-HT_{1A} agonist, 8-hydroxy-DPAT [8-OH-DPAT] had come long, and we wanted to look at that and it produced behavioural changes. And, again, we thought we would look at electroconvulsive shock on 8-OH-DPAT effects, because by then we'd shown that even if you only gave 5 shocks over 10 days in a more clinical way, it still had the same effect. And we'd even shown that it wasn't the electricity that was important. Actually if you just produced a chemically-induced convulsion. I managed to get hold of a drug called 'flurothyl' which was used briefly. It looks very much like ether, but it has a fluorine group on it and it produces convulsions. And I found a very elderly psychiatrist called Louis Rose in Harley Street who was still using it but they'd stopped making it years before. He gave me a pack. It's liquid, it came in ampules. When you broke it, it vaporised and if you breathed it in it produced convulsions. And we used that and showed again that it had the same effects.

But we then went on with the 5-HT_{1A} behavioural response and showed that actually if we gave ECT, electrical convulsive shock, over 10 days, the change response, which was exactly the same that we saw with antidepressant drugs, with the 5-HT_{1A} response, lasted for about a month. It was truly amazing and we got

that published in *Nature*. You know, David admits that he was amazed at this because I said, 'It's still there—the changed behavioural response.' 'Well, why don't you leave it a few more days and then have another look.' And it was still there. So we got a long-lasting, you know, should we say, antidepressant-like response.

TT: And these were in patients?

RG: No, these were all in rats. But as I say, I think it then gave the clinicians a chance to say, 'Well, you know, this does have a clearly defined mechanism of action.' Whether it actually has any relationship with how the drug actually works or the treatment works, I don't know, but it was consistent at any rate. And that was an exciting thing to find actually.

TT: Can I just ask, one thing intrigues me there: how did you find this elderly psychiatrist?

RG: Because I asked another big name who had another MRC unit, Tim Crow. He was interested in our ECT work, he'd also been in Edinburgh of course. And he came down to start, to found the Psychiatry Unit at the Clinical Research Centre. And I'm not sure whether I'd given a talk there and he said, 'Oh, you know, there's Louis Rose who still uses flurothyl, you ought to get in contact with him and see if he's got any left,' and he had.

TT: It's interesting, these juxtapositions, how you find these people. It's always intriguing.

RG: These days I guess, you know, you use the internet. In those days you talked to people.

TT: You did. And somebody like Tim Crow, having that bit of information, and you actually raising it in the situation where Tim could say it. Those little byways of history intrigue me greatly.

RG: You know, I guess, in the end you know if you know, it just seems to me science has expanded so much, but it was a smaller community then I think, and that helped a lot.

TT: So can we just go back to Oxford. You said there were two really big...

RG: Well, related. The ECT work, which I thought was really important, and in general the work on 5-HT but leading onto, I mean we were very early involved in the 5-HT_{1A} receptor, which is behaviour but it also produced a clearly-defined hypothermia in rats and mice. And we were very early involved in that and that was the marker that we used for the ECT work, and for some of the antidepressants, was actually looking, does it modify this temperature response, and it did. So I think that ECT and the work on trying to measure 5-HT function leading onto then the 5-HT_{1A} receptor and using that as a marker, are the two things that I'm most pleased with.

TT: Why did you decide to leave the MRC?

RG: Hah! Well again, chance. What happened was, again David looked after his own staff very well and in about 1984, I guess it was, an advert appeared for the Professor of Pharmacology at University of Bath. And I seem to remember David pointed this out to me and he said, 'Well, you know, you're just getting to 40 and this unit has only got a defined life until 1992,' I think, which was when he was 60, 'You should think about flying the nest and that would be an interesting job I would think.' And I went down to Bath, and I was shortlisted and interviewed, and Rod Flower got it! Which we have laughed about subsequently. And I thought, 'Oh well.' And I came back and then I got a letter totally out of the blue from Hans Selander, the then Research Director of Astra Södertälje, because Astra then had three centres. It had Astra at Södertälje, which is just south of Stockholm; it had what was then called 'Astra Hässle', which was at Gothenburg, and Astra Draco, which was down at Lund. And they did CNS in Södertälje, gastrointestinal/hypertension at Gothenburg, and respiratory down at Lund. Hans Selander was Head of Research, I think, at Södertälje, Head of CNS, and with Sune Rosell who was the overall Research Director of the whole group, a delightful

man. Pretty well all the people I met at Astra were pleasant people, I have to say, and mostly I admired because they were really good scientists as well.

It was before you had perhaps more bean counters in very senior positions, you had scientists. And this letter came and said, 'We're thinking of setting up a new unit in England to examine possible approaches to dementia/Alzheimer's, and if you think you might be interested in this, come and have a talk to me.' So I came up to London, met him. When I think of all the interviews and psychometric testing these days, and we went out for a meal together. So we had a long chat and after a while, I said, 'It does sound quite interesting.' I assumed he wanted a pharmacologist. 'Who are you thinking of heading this unit?' The usual sort of laid back Swede, he said, 'That's why I'm talking to you.' And I went, 'Oh! I don't think I know anything very much about Alzheimer's' and classic response he said, 'Well, here's your chance to learn.' I did ask him subsequently, I said, 'Well, what would have happened if it hadn't worked out between us?' And he said, 'Well, that's easy, I would have said I don't think this is working out and we'd have ended it.' And from then on, he didn't actually formally offer me a job but he just seemed to keep saying, 'Well, you know, how do we do this?' And they settled on the old Royal Free School of Medicine labs in Wakefield Street, just north of, The Institute of Neurology.

Astra were going to rent floors in this old building and part of the Institute of Neurology, where I'd done my PhD, were going to also move in there. And Gerald Curzon was then on the second floor, and we were on the third and fourth. And David Bowen, who was of course the big dementia expert, was in the building as well, and the idea was very much something that the Swedes had done for years, which was interact closely between universities and industry, which I might say almost sarcastically of course went out of favour for these new 'centres of excellence' which were huge, and 15 years after they found it doesn't work out so well at all and industry have all come back to saying, 'What a good idea this is, why don't we do this?' So everything goes in circles I guess, doesn't it? And I started to be asked to go up and help design the labs and everything. I did suggest in the end perhaps Astra might offer me a full contract, so I knew exactly where I was. So again it came quite out of the blue and I talked to one or two other people in industry, I talked to David, David Grahame-Smith, who said you know it's a really good company, with scientists like Svante Ross and Tommy Lewander. There were some really good neuroscientists in that company at that stage, but they'd felt that they were rather enclosed in Sweden with their own groups, and they wanted to get different ideas in. They wanted to go outside of Sweden.

I remember sort of, going back home and thinking, 'Can I do it? I'm not sure but no one is ever going to offer me the chance to set up something again, choosing my own staff from scratch, you know.' Normally you go into a department with probably someone who tried for the same job, a couple more who might resent you or are set in their ways. The chance to set up something from new, just as David Grahame-Smith had in Oxford, and so I thought, 'Well, I'm going to go for this.' And so that's how it happened.

TT: Was there any sense that you were letting the side down by going to industry?

RG: No, it was just at the time of course, 1985, Les has just gone off to Merck, Humphrey Rang was setting up the Sandoz unit, John Hughes was setting up the Parke-Davis unit. I mean the only thing I met was, at the beginning, on something, I think it might have been the Mental Health Foundation, I was on their Research Committee looking at grants, and it came up, as to whether should I be there as I was going to industry, and a couple of others members said, 'Oh, for goodness sake.' And it was about the time that whole attitudes changed. The MRC was starting to say to the units, you know, if you want to interact with industry you can, and there was much more openness. So I was just on the wave when an attitude of 'them and us' was dying actually fairly quickly. So no, I don't think anyone really was difficult about it.

TT: Ten years earlier it might have been different.

RG: I think that was so, I think that is so. And industry was beginning to publish as well, so it was a big change.

TT: How did you, I mean this was a tremendous opportunity but an awful challenge as well. So you walked in to set up these labs and hire staff in a field that you hadn't really worked in before. So this is all still dementia?

RG: I hadn't worked in dementia nor did I really understand, I have to admit, exactly how industry worked. I was used to MRC funding. I remember moving all my office from Oxford, and all my journals and everything, piling them in my car over two journeys and carrying them all into my own office, you know. It never occurred to me that one would be allowed to actually just employ someone to do that. Money was also tight. This was just before Astra's world changed totally with what became omeprazole, Losec, which totally altered their funding base. And CNS had suffered two very severe delays and setbacks. I mean they had with zimelidine actually, the first SSRI [selective serotonin reuptake inhibitor], and this went onto the market and the sales went through the roof in 18 months, and then it was withdrawn.

TT: When was that?

RG: Ooh, very early 1980s. And in about 1984 it was producing a rare but a problematic peripheral adverse effect, whose name I've forgotten now, and the drug was withdrawn. And then they had remoxipride, which was a D₂ [dopamine D₂ receptor] selective drug, which again very successful for about 18 months, and then again they got some rare but severe adverse effects. From nothing in 18 months they suddenly got about six reports and Astra were very concerned about this and withdrew it. In fact, those adverse events can be seen with other drugs like chlorpromazine. I think if they'd been perhaps a little less rapid in withdrawing it, I think it might have continued. But they, they didn't like the idea of marketing a drug with severe adverse events, so they pulled it. CNS had gone through I think two very ground-breaking drugs and they then saw, follow up drugs from other companies then reaching new heights. I mean the sales of fluoxetine, the next SSRI, went through the roof. So money was tight for our first couple of years setting up the unit, then it eased up a bit as the new drugs came along.

TT: What was your remit?

RG: We started with, well again, things changed. We started with the idea of running two to three projects. The first thing I did was get in as Head of Pharmacology, someone I already knew who had done his PhD with Bill Deakin in Tim Crow's lab, and that's Alan Cross, who is still with AstraZeneca and in the States now, and had only fairly recently gone up to Manchester, left and came back down to me. And I got a very good chemist called Robin Boar, who had been with Janssen in Belgium. And we set up with the idea of doing work on a cholinesterase drug, fairly straight forward, but it was an obvious way to go. I had the idea because I'd been working on GABA_B [gamma aminobutyric acid B] receptor when I was in Oxford, and I thought that looked an interesting way to produce a GABA_B antagonist. Only subsequently talking to Norman Bowerly and others, I discovered that he tried to do much the same at Merck when he was there, and no one's ever been very successful at that because there were no good *in vitro* tests for it. And Astra had, which is what finally defined our projects, had an old drug called 'clomethiazole', which was a sedative and hypnotic. It's also used for alcohol withdrawal, and it's an Astra drug. And it works a bit like a benzodiazepine, it works at the GABA receptor.

One of the problems with dementia patients is often, that they're more active and aggressive, so settling them down and getting them to sleep is important. Benzodiazepines, at that stage, were felt to produce memory impairment. And I said, 'Well, you know, there's no reports of that on clomethiazole, let's try and produce a new clomethiazole-like drug with a defined mechanism which will provide symptomatic treatment for dementia.' Because even if we can't treat a lot of things, if we can get that, that will be a good idea. We did produce one drug on the cholinergic side, I think, a very good cholinesterase inhibitor. Unfortunately, Astra had licensed one a little earlier, and in the end our drug was dropped still at the preclinical stage, but it looked very good and the Eisai drug eventually came, which was very related, came to the market and it's done reasonably well. I think we could have had something there, but companies only have so much money to push things forward.

The GABA_B we dropped after a while, because it just wasn't going anywhere. And the clomethiazole, we were looking into the mechanism of action and we found that it altered calcium flux into cells, and this was just at the time that Les Iversen was coming along with MK-801, altering calcium flux. And stroke was a really big thing. Brian Meldrum of course had, I think Brian is often not given enough credit for this - he was down at the Institute of Psychiatry - he had been doing some beautiful work on calcium and glutamate and that whole area, and so we thought, 'Well gosh, that's interesting, clomethiazole seems to be working a bit like MK-801, I wonder if it's a neuroprotective drug?' And so we set up and in those days one of, the main person I had in for the more behavioural side was Jackie Hunter, she'd come to me at the start. So I had, you know, bright young people with me and one can always [laughs] bask in reflected glory. And we set up a stroke model and clomethiazole was protective in it. And so we thought, 'Let's see if we can produce new clomethiazole derivatives that also were protective.' And we did, but the problem is - I don't think one has to be obsessive as some companies are - that you've always got to have a biochemical, *in vitro* biochemical mark of drug action. It does improve the speed of things. The only way we could test out new drugs coming along was to put them in animal models of stroke. And the company supported this because a lot of companies were working on stroke in the late 1980s and said, 'Go with it.' So we dropped dementia basically and got on to being a stroke unit more than anything else.

TT: What kind of animal models did you use?

RG: Well, again we've learnt so much, it's really clever going back and saying, 'That's the reason this changed, this failed and this failed.' At that stage we were predominantly using the rat transient ischemia model. I would never use a transient model now, I think you've got to use permanent ischaemia models, in fact I would probably question all of the animal models. I was a huge defender of animal models of stroke but when I think back on it now, people have got it wrong. It was Eng Lo from Harvard who said a few years ago, and I think it sums it up, 'What we have forgotten is that stroke is primarily a vascular effect with a neurological outcome.' And he showed a graph - I ran a symposium at the *BJP* and had him come over - he showed a graph of the number of papers looking at vasculature research versus neurological approaches and neurological studies just went up and up and up with no one looking at the vasculature. And now people talk about the neurovascular unit. I don't think we really understood that the vasculature and glia talked to the neurons and back again. As the then CEO of our company said at one stage, when we were saying, 'Well, we know that's failed but you know we know much more now,' he said. 'Yes, you know, I can give you a lot more money and when that fails you can tell me why that one's failed.'

We've learnt and learnt but at that time looking at a neuroprotective drug was where it was at and I don't have to defend it too strongly in that it just seemed very logical. You give something straight after the stroke, or as soon as you can within six hours, whatever, that will protect the neurons from dying. And we could do that in animal models so why shouldn't we be able to do it in humans. After all I'd come from psychiatry where we had the mostly nonsense animal models but were nevertheless predictive. But you can only do that prediction backwards and forwards if you've got a drug that works. Once you've got a drug that works in humans then you can go back and say it worked in that model, that's the model we'll use. But we didn't have that.

TT: When you were doing this work, Richard, did you then get involved in the other kind of aspects like regulatory affairs and clinical trials or was that passed onto somebody else?

RG: Not at that stage, no. We developed up clomethiazole and that was moving forward and went into clinical trial in about 1994/95, and then in 1995 I guess it was, yes, we suddenly heard out of the blue that Astra had bought Fisons at Loughborough. And the first thing that happened with that was that, of course, buying Fisons at Loughborough also meant that they had bought Fisons CNS Research Unit in Rochester, in upper New York state, who were also interested in stroke, because they had glutamate antagonists because they were interested in epilepsy. Fisons had bought Rochester, from 'Pennwalt' before that, which is an old American small company. And whilst you can do CNS research at two sites, three is too much. And we immediately knew we were at risk. We were about 27-28 people strong, I guess, and covering everything from behaviour through to neurochemistry through to medicinal chemistry. We had everything, we were a

nice little unit. Astra announced fairly quickly they were closing us, they were very generous, quite a few of the staff went to Sweden in fact. And then, they gave everyone Swedish lessons while they were still in England, paid for them to go over, quite generous in paying off staff that didn't want to go. I then had Gösta Jonsson who was Head of Astra Södertälje saying, 'Well you know, what would you like to do because I've got an opening for someone to oversee projects.' And I thought, 'Well, that sounds quite interesting though I know I'd miss the lab.' So I didn't particularly want to go to Sweden to do that, and so I actually moved up to Loughborough which provided an office, library, you know, e-mail and everything, and then started flying once a month really to Sweden to oversee the preclinical control of the project, because clomethiazole was then in clinical trial.

TT: So you continued overseeing the same project?

RG: I did at that stage, yes. I mean I might also mention, as we move to this stage in my life, it was Gösta Jonsson that got me involved in a new area. He had been interested when he was at the Karolinska in the way that amphetamines produce damage in the brain. Gösta had worked with all the big people, you know, Fuxe, Hökfelt, and Hans Corrodi and that big group of neuroscience people, he was part of that group. He came to me, I mean he's a bit like David Grahame-Smith in that he had this, 'I wonder what happens if,' the sort of thinking that got frowned on in industry. You couldn't just do 'I wonder if...' sort of experiments or wander off track. But he sent me a paper from the States which said that MK-801 protected against methamphetamine-induced damage to dopamine neurons, and sending a fax as we did in those days those days, 'I wonder what clomethiazole does to methamphetamine-induced damage?' And we tested it and it protected. But methamphetamine is a difficult thing to produce brain damage, and so we moved to thinking about MDMA [3,4-methylenedioxy-methamphetamine]; it was just at the time when MDMA (ecstasy) was shown to produce damage to 5-HT neurons.

So I thought, 'Well, I'm going to try MDMA,' and clomethiazole protected against that. And I was then lucky enough to have someone that had done a little bit of work within the States in Costa's lab in the late 1970s, when I'd gone back there to do a short project, writing to me saying, 'I'm coming over to do some work at the Natural History Museum,' he'd moved areas tremendously. He said, 'My wife is a neuropharmacologist, could she come and work with you?' And I thought, 'I don't know, I've no idea who she is.' So I said, 'Well come and meet me.' And this was a lady called María Isabel (Maribel) Colado, who turned out to be the most fantastic scientist. She's Professor and Head at Complutense University in Pharmacology and is, you know, on government committees and goodness knows what, so she was then a young, very bright scientist who came to me. She started working on MDMA as well, and we carried on that collaboration between Astra, who let me continue to work on MDMA even though it was nothing to do with them strictly, but it was just that the damage produced by MDMA is almost certainly free radical produced. Stroke-induced damage is probably free radical-induced. So you know there was a link, but it was loose.

And the collaboration with Maribel carried on for years, even when I went up to Loughborough, even though I didn't have a lab there.

TT: That was just what I was going to ask you because you said you were going into this more managerial role in Loughborough, so where was the lab, how were you doing this collaborative work?

RG: But then I was again lucky, I mean you know, I think you're going to find my whole career was luck; was that Alan Cuthbert was a governor at De Montfort University [DMU], because I think he'd done a degree there. Alan had been of course when I was with the BPS [British Pharmacological Society], when I was Meeting Secretary and General Secretary, he was Chairman of the Board. He'd been the Editor-in-Chief when I was in Editorial Board. Alan was always above me with whatever I did with the BPS, and he wrote to me and said almost 'bet you're missing the lab. I know they need people down at De Montfort to sort of perhaps boost their research a bit. Why don't you go and talk to the Vice Chancellor?' So I did and he offered me a PhD-student, which I got, and half of another one but who worked on a different area.

TT: Who was the Vice Chancellor then?

RG: Professor Kenneth Barker, he was into music, it was nothing to do with science but he was incredibly supportive. So I then had a very successful PhD-student at De Montfort. I mentioned this to Astra because you know DMU wanted me down there half a day a week or so. And Christer Köhler who became Head of CNS Research in Astra, said, 'Fine with me, you're going around talking, getting the stroke projects going, you know, new things set up in universities. It's always good I think that they feel they're talking with someone who is still an active publishing scientist, you can do it with our blessing.' So Astra continued to give me time to become an Adjunct Professor at De Montfort and continue on with that work. So I started work with clomethiazole, and then just at the time that the whole unit was closing down in London, Astra licensed in a drug from a company called 'Centaur', who were a venture capital company in San Francisco, with their stroke drug, which had only been discovered, again mostly in animal models. But it looked so good in the animal models, and Bö Seisjö who was a Professor of Stroke Medicine at Lund and huge name in stroke research, a Swede who was really powerful in the world stroke community, was really impressed with this drug, which I think probably helped as well. And we licensed it in. And I then became, as we watched clomethiazole fail in Phase 2, the preclinical project leader for what then became coded as 'NXY-059'.

And so my main job was 'overseeing', I guess you would say, any new preclinical work that needed to be done, and getting it done externally because we didn't have anything done internally by then, right through to things like when the FDA [Food and Drug Administration] wanted evidence that it didn't alter clotting time and things like that, and wanted models that our general pharmacologists didn't do, we collaborated with Nuala Booth up in Aberdeen, who had a really good system. So I was involved in going and seeing these people in different universities saying, 'Will you do work on our drug?'

TT: Yes, almost commissioning? It's quite a shift, isn't it, from you being in the lab?

RG: Yes, it was but it was very exciting because I saw a whole new world that I didn't know anything of, and I was part of - one might say it was then the trendy word 'global' - I was part of the global project team, and that meant I was sitting in monthly with everyone from the regulatory to marketing, to patents, to pharmaceuticals, everything. There were about 10 or 12 of us sitting around the table updating every month where we were to try to bring everything through. And it was a very exciting time because we got it through into clinical trial, it was incredibly safe, it was said to work by being a free radical trapping agent. NXY-059 is a nitron and chemists have used them for years to trap free radicals. But it was hard to really say that was how it was working, but it was a nice story. It went on to Phase 3 and the first Phase 3 trial, which was about 1,700 patients, was positive. Published in *New England Journal of Medicine*. You can't do really good Phase 2 trials in stroke because there's such a wide variation, and people who look almost dead recover totally and ones that keep coming not too badly, then just go down and down. So you have to have huge trials, it's not like giving something for local anaesthetic where you can tell in 40 patients that all is well.

So the first, it had to be two Phase 3 trials, the first one was 1,700 patients and it was positive. But you know when you worked out the power of it, we needed another even bigger trial which already started. But you can imagine the excitement. Most companies had pulled out of neuroprotection, and several of them said to us, 'Well, we think you're doing it right.' There had been published, in about 1999, something called the 'STAIR Criteria', which was 'Stroke Trial Academic Industry Roundtable'. Because there had been so many failures, a group of academic and industry people working on stroke, had got together and said, 'We shouldn't go into clinical trials unless we meet all these criteria. You know, we should look at functional outcomes.' By that, I mean most preclinical work on stroke had been on just looking at histology. You've got to look at function, because finally, in patients, we measure arm movement. It doesn't matter what's gone on in the brain finally, unless they can lift their arm and leg up; again we haven't got a successful drug. The FDA won't accept scanning techniques as an outcome measure.

You've got to look and show that the drug works several hours after you give it, because we don't get patients coming in immediately and so on. And these were criteria, and we had worked out that we wanted all our preclinical work to meet, including the fact - which again most people hadn't done - which shows that the doses that we gave our animals, or the exposure at plasma levels, should be at least equivalent in animals and humans. Again, lots of people hadn't done that. And we found we could exceed in our humans without adverse effects the plasma levels produced maximum protection in our animals. I'd always joke with my students subsequently that we should have worried by the fact that the result of the trial resulted in the *Daily Express* calling it 'a new wonder drug' [laughs]. If anything is going to be the kiss of death it's going to be the *Daily Express* telling you you've got a wonder drug. And it went into the second Phase 3, and it failed totally. No indication of effect. And the company stopped. I was then setting up projects to look at head trauma and things like that, where it worked, and the company, a day after the results said, 'That's it, the end.'

I found it's almost like a death in the family. If you've worked on something for the best part of 10 years, you wake up in the middle of the night thinking, 'Why do I feel so depressed? Oh yes, I remember.' It was awful actually. We did really feel, everyone talks about the industry looking for money and that, but what motivated people I knew, the scientists and clinicians in the company, was we felt we could produce benefit to patients and no one was helping very much, because very few people at that stage were giving thrombolytics, because they were considered to be unsafe. We really felt we got something. That was really very hard. I had stayed on, I mean at that stage - in general Astra retired you at 62 - and I had actually, I was then 63½ because they said, 'Hang on, we want to get this through. And of course even if you retire we'd probably want you to come back for this, that and the other.' And so I then moved onwards to retirement, as I emphasize, not because the drug failed but you know that was the time to go anyway. And I had moved on from De Montfort to Nottingham University, where I was working with Charles Marsden and Kevin Fone particularly. And had moved on, we were still doing some work on MDMA, which I was still doing there instead, because the DMU got much less enthusiastic about any lab work there. You know, they'd got limited funds and it's frankly finally cheaper to teach nurses and social students than it is to do animal studies.

And Charles said, 'Well, come here,' so I went there. And I then, at the time I got, this is the end of the stroke story really. I then got involved with Philip Bath, who is Professor of Stroke Medicine there.

TT: In Nottingham?

RG: In Nottingham. And had been on our data monitoring, I'd never been able to meet him before. He'd been on the Data Monitoring Committee, the independent committee that oversees the projects, because he's not only a very good stroke physician, but he's an expert on statistics and all that sort of stuff. And he said, 'I'd like to take all the preclinical data, because you know preclinical data is usually these rather small studies, which we'd never tolerate clinically.' And he said, 'I'd like to do a meta-analysis to see if it really works.' And this happened just as I was about to retire from AstraZeneca, so I said, 'Well, how about...?' I said to the company, 'How about I provide him with all this data?' Because I've got three files at the moment in my office. Every single study, whether it's been published or not published, the numbers, most of the raw data, every report with it of course, we'd been getting ready to file with the FDA. The amount of work! You know the view was once the second Phase 3 was positive, we were going to register almost immediately. I had spent two years writing and making sure the reports were right. All that got scrapped.

And to the company's total credit they let us do the meta-analysis, because it could be of course that finally we were going to show that the preclinical data didn't look very good at all, in which case they were going to have people coming down on them saying, 'Well, you know, why did you go and put this drug into all these patients? Your preclinical data isn't very good.' But they said, 'Yes, go ahead.' So he and I and his PhD-student, I don't fully understand what they do because of course most of it then goes into a computer, we did what I think was probably the first individual animal meta-analysis that's actually even been done, not only in stroke, in anything. Because we had it all together. So we fed all the data from every single animal. It didn't matter, a few with mice, some marmosets, and mostly rats. And all of this was fed in. I did say to

him, not understanding necessarily meta-analysis, 'Well, why are we putting the mice in?' Because they gave the drug intraperitoneally and I said, 'I know it's not absorbed that way.' He said, 'You can't make decisions like that, it will come out in the wash.' And the drug worked in the animal studies. No doubt about that.

It showed weaknesses. There was one animal model that we undoubtedly should have done much more, because it was one of the models where the drug didn't work, but overall data statistically, whether it was a transient model, it was a permanent mode where we were looking in the cortex, whether we were looking sub-cortically, it worked. There's no doubt. Which then makes you say, 'Well, there is a real problem in translation here.' As I say I think a lot of the companies had been standing back saying, 'We think you're doing it right. If you get a positive result we'll probably start up stroke research again.' And I went to a lecture on stroke yesterday using mechanical extraction of the clots, and they've got really good positive data coming out. There are different ways of going forwards now from preventing, giving statins, giving thrombolytics, mechanical clot extraction, but apart from a couple of Japanese companies, and I don't know where they are now, no one's working on neuroprotection in stroke anymore.

TT: So you've retired from Astra, you have the honorary chair at Nottingham.

RG: I'm still at Nottingham. I still do a little bit of teaching there, but not very much. I had, who I regard as my last PhD-student through, who worked with Kevin Fone and Maddy King and I, where we've moved on from ecstasy, we did a little bit on that, but we moved through and looked at the drug mephedrone to see whether it was the same sort of drug. And it's not, it's different. It's related in its mood altering effects, but it doesn't have the same profile. But there's no way you're carrying through on that. For 20 years MDMA was the recreational drug of choice. Mephedrone came along partly because I think it became much more difficult to get ecstasy for a while, so people moved onto other things. But there is so much coming onto the market. Hah! You know every week something new, quite horrendous actually, because you know these kids are taking things where we have actually no idea about their pharmacology at all. And so what is the point? With ecstasy there was, 'Well, let's learn more about this because it's continuing to be used.' Now if we went to any grant-giving body and said, 'We want to do some more work on mephedrone,' they'd say, 'Why bother? You know, there's 30 new cathinone-like drugs come along and on the street in the last six months. Why study just one in-depth?' And I wouldn't argue with that.

TT: Who funds your research?

RG: Well, the study done at Nottingham was actually funded by the university. It was a grant for a PhD-student Kevin found, which was very nice of them. You know I think she's paid them back, we've had three or four very quick papers out of it. We've written quite a big review on mephedrone and we wrote one on MDMA as well that she was involved in. Because I used to be fairly convinced, again from the animal work, that ecstasy probably in high doses produces brain damage in humans. I am now totally unconvinced by that, and that's mainly because when you actually look at the kinetics, pharmacokinetics of MDMA in rats versus humans, it is totally different. In rats it's metabolised extremely rapidly, it produces very high temperature in rats, which you know, they can get over, and it does in humans as well. But it's fairly short-acting, and then of course it's metabolised through to these other derivatives that probably produce the free radicals and the damage. Its half-life is about 40 minutes in rats. In humans it's about 8 hours. So yes, you get the temperature effect, and that's what can kill people, because it goes up and it stays up for a long time, but it feeds through, it's metabolised very slowly, but it is metabolised. And I think the free radical scavenging, trapping activity, that we have naturally in the brain can mop these up normally.

I have to say Andy Parrott at Swansea would argue with me strongly against that, but most of the data on brain damage in humans is reasonably anecdotal, it's small groups, and the thing that worries me, I think ecstasy can produce damage but that's because few people just take MDMA. They take often several other recreational drugs and we found, and others have found, and it's true of mephedrone and it's true of ecstasy, that caffeine, so many people are taking, particularly if they're partying with Red Bull and things like that, caffeine alters the MDMA responses. So, you know, I think if you could take pure ecstasy and nothing else as a human, you would be relatively safe. I'm not sure whether I should say that but, yes, I've pretty well

said that in print, so I don't see why I shouldn't say it here. But, immediately, you start mixing with other things, then there may be problems. It's just when people say, 'Ecstasy is MDMA,' which it often isn't, then I'm not sure in humans it's that dangerous.

TT: Yes, interesting. One of the things I noticed, Richard, looking through your CV is how enormously productive you've been. Some years you're publishing 10, 11 papers and a book chapter. It's just staggering.

RG: I think, generally we've had nice projects to work on. I'm not sure it wasn't Brodie, he was very much Costa's mentor and Brodie's view was very much that one should almost do, shall we say, the easy things that start to produce results. You know if things look bad there are plenty of other things, go on and look at something else then. But I think there's a certain luck element in these things, certainly on one or two things, like the GABA_B drug. We worked on that for a while but there came a point of saying, 'Why are we doing this? There has to be other things to do. Don't just keep hitting your head.' I've also worked, as I say, with some really good people. I mean you know people like Phil Cowen, Dave Nutt, Guy Goodwin, obviously David Grahame-Smith. I had Dave Heal who went on to work with Boots when they were Boots in Nottingham, and then became Knoll for a while, and then when it closed down he set up a company called 'RenaSci', and Dave was a very good, you know, active scientist. Maribel Colado and then her student Esther O'Shea in MDMA area was really, I mean she was amazing. Maribel has the, what I think of as the scientific equivalent of green fingers. She didn't work enormously long hours, she wasn't one of these people who was there until 10 o'clock at night, but almost anything she did seemed to work.

So you know I've had some great people to work with. And then sometimes people come to you, people like say Bill Deakin. We just had a joint area of interest, we did it, it worked, move onto something else.

TT: One thing you've mentioned and started talking about with the BAP, scientific societies. Could you say something about the importance of societies and which ones?

RG: Well, my two are Pharmacol Soc, BPS, more than anything else, and then BAP. I helped organise the 50th anniversary meeting in 1983 of the BPS in Oxford. It was a committee of four of us, which was Bill Paton, John Walker from Pharmacology and David Grahame-Smith and myself, from Clinical Pharmacology. Well, you can work out: the two professors oversaw, John Walker was extremely senior and organised the dinners, and I did everything else. That's not a complaint, it's just a statement of what happened. Tony Birmingham was the Meeting Secretary at the time, so I interacted with him a lot. Shall we say, democracy came reasonably late to, I think, all the major societies. Committees, Councils, tended to suggest names and it was pretty well the expectation that no one else would ever stand against them. So Tony worked well with, the meeting was hugely successful. Tony obviously said, 'Ah Richard Green did a good job there. I think he could be the next Meeting Secretary.' So my name came forward, I suggested to David Grahame-Smith, I said, 'You know, can I do this? It's going to take time.' 'Well, it would be great, wouldn't it? We'll find space for the secretary somewhere, you know.' We were pretty crowded. And then Astra came along and I said, 'Well, I've been offered this job and accepted it and I would quite like to do it.' And they said, 'Well, it'll look very good for our company, won't it, that you're doing it. I guess the Astra name will go on all the note paper and everything as your address. Well, do it.' When I think about it, because the Meeting Secretary in those days, did most things with the help of the local host organising their team. All the abstracts came into you, you got them in the right format. Whether I should have really done it, I don't know.

Luckily the first year or so, when I was really finding my feet, was when the lab was getting going and perhaps a little less science than I might have had. And I then went on obviously to be General Secretary. In some ways, as Meeting Secretary, I enjoyed it the most because you met everybody. You know, everyone comes up to you 'about my abstract,' so you got to know a huge number of members. But it was enormous fun, and again, the way these things link up.

TT: How many years did you do that?

RG: Well, in those days you did three years as Meeting Secretary, three years as General Secretary. As I've mocked Tom Blackburn subsequently, I think it was Tom that converted the name because a lot of international societies didn't understand the term 'General Secretary', and converted it to 'President'. And I said 'The name General Secretary wasn't good enough for you.' And it was an enormous amount of work, but you know you got to know so many people, and people I might not have met, like from John Vane onwards. I mean John, if I may divert, was marvellous because he was just setting up the William Harvey Institute at the time, and we were so busy, we used to run four meetings a year, and everyone used to present because it used to take so long to get stuff into print in those days, for a full paper. So if you wanted to establish primacy, it was by presenting at BPS, which published your abstract. And I'd said, 'Well, we might only manage to have a paper submitted, one paper submitted from each author,' because we were getting up to 400 abstracts.

John Vane phoned, I'd never talked to him then at that stage, I don't think. 'Ah, it's John here.' 'Hello, Sir John.' 'I've just sent some abstracts into you. I hope you'll be kind to me because we're just setting up the Institute, you know. We do need to make a bit of a splash.' 'Yes, Sir John, I'll do my best' thinking to myself, 'Well, I'm bound to do something here other than accepting everything from our most senior member and Nobel laureate.' Anyway so we put them all in and a few days later, 'Ah, John here again. A few more if you could squeeze them in!' I thought, 'I am being manipulated here.' But how nice, not, you know, 'I am John Vane and I want these in.' Then, when subsequently he wanted one of his meetings sent out and we had a nice machine that would label, which was really temperamental, and I seemed to be the only one that could make the damn thing work and not stick six labels on one envelope. So I set this whole thing up, ran all the labels through and then these huge bunches of flowers came to my two secretaries for helping him out!

So yes, it was a fantastic time and a couple of years ago they were looking for a Trustee and I thought, 'Well, I don't mind.' So I put my name forward, there was supposed to be going to be an election, I'd heard, and then I had Jono Brüün phone me up and said, 'Well, someone else wants to stand. Do you have a problem with that?' And I said, 'No, not at all, you know. If I get it, it will be lovely, if I don't, I'm not going to be upset about it.' And about an hour later he phoned up and said, 'The other person's withdrawn.' I've no idea who it was, but you know when I say that I've had a lucky career; moved into being a Councillor, a Trustee, without even an election. I've got another year of that.

TT: And when were you elected to the Pharm Soc?

RG: When was I elected? 1973. Because it was just after I'd come back from the States, and certainly in those days you know once you'd done your post-doc and you'd got a few papers it was a career move, you know. You'd got your degree, you joined the Pharm Soc.

TT: Yes. Same with me in physiology and the Phys Soc [Physiological Society]. But what were the criteria because for Phys Soc you'd have to have given at least one Communication.

RG: As I remember, normally something like two abstracts to the Society, one of which you should have presented. And three papers.

TT: Is it still like that?

RG: No, not at all because, basically they take anyone with some pharmacological interest. You know, because we've got undergraduate members, graduate members, post-docs, so you can move through. When I was, I can't remember, I think General Secretary, we wanted to make Harry Holt a member. Harry was then, and for years had been, in charge of our journal while he was on the staff of MacMillan Press; it became Stockton Press. And, you know, we just thought it would be nice to let him join. I think he asked. He said, 'I wouldn't mind being a member.' And there were one or two people saying, 'I've worked my way through the Society, why are we letting this non-scientist join?'

TT: What a shame.

RG: But we pushed it through without any trouble. I think Jimmy Mitchell was then the Editor-in-Chief of the journal, and no one would argue with Jimmy either, so it went through. But I do remember a couple on Committee being a little less generous about it.

TT: Can you remember your first communication to the Pharm Soc?

RG: I suppose I can, to Pharm Soc. The very first communication I gave actually was down at the Institute of Psychiatry to the Biochemical Society, because Gerald was a member of the Biochem Soc. And I presented our work down there and someone asked me about, I think, CSF [cerebrospinal fluid] changes in depression and I said, 'No, you know, we haven't looked at that. But Ashcroft and Eccleston,' I said, 'at the Edinburgh unit have looked at serotonin this and that.' And he said, 'Thank you very much.' And I came off and Gerald said, 'That was good. And do you know who asked that question?' I said, 'No idea.' He said, 'That was George Ashcroft,' [laughter]. So I went, 'Oh!' He said, 'Everyone is delighted when you quote their own work back at them.' So that was my first experience.

TT: What about other societies?

RG: Well, the BAP. As you know I've just written a history of it. I wrote to Alec Copen because it had been an odd thing that the name of the BAP changed from 'Academy' to 'Association'. But then, 'of' and 'for' got mixed up a bit in there [i.e. 'of Psychopharmacology, or 'for' Psychopharmacology]. So I wrote to Alec Copen, who must be 90, and who was what, the second President, and I said, 'You know, was this because it legally was that or because someone typed it wrong?' And he came back, just shows still bright as anything, and he said, 'Well, it's a bit like Lord Palmerston said of the Schleswig-Holstein question: only three people ever understood this. One is mad, one is dead, and I've forgotten.' So I'm going to quote that to you.

TT: We can come onto the BAP because I think the BAP encapsulates a lot of the problems between scientists and clinicians and the different turf wars, as it were, because there was, when it was first started there was an idea, because the first letter was in *The Lancet*, I think, and it was just going to be medical people.

RG: Did it actually say that? But no, it's interesting, it's something that's gone through it the whole time and people have always tried to be very careful. Actually, the original aims did talk about both clinical and pre-clinical, but over 60% of the founders and people involved were clinical. If they had called it the 'Academy of Biological Psychiatrists' there wouldn't have been a problem. It was because they called it 'Psychopharmacology'. But in fact they've worked very hard ever since to make sure it's not dominated by one side or the other, and just by the best efforts, whatever, it's remained roughly 60-40 clinical ever since. But it's very translational and it's done well actually to avoid sort of becoming cliquey, and I do think the first President, Max Hamilton, worked hard to make it inclusive. Because they'd chosen someone very high up, you know, in the early 60s and onto the 70s, everyone knew the Hamilton rating scale for depression and he wasn't part of the original founding group, but they needed a big name. And so he had no particular axe to grind, and I think he did a lot. I mean I did talk to Eugene Paykel who was what, about fifth President, and he said Max was fantastic in helping to pull the whole thing and keep it together.

When there was this fuss to make it more open and I joined immediately after that. I was on Council in the early 80s. I was an Editor when the journal started, and that had incredibly rocky start. And then, when Dave Nutt came back from the States, he took over the editorship and I left soon after, because you know by then I was so involved, more in stroke, and I thought I can't keep going on that. But I remained a member and, of course, once the MDMA work started getting going, I was back much more actively in psychopharmacology and I got more involved, and then, I have to say, a complete shock that I got a letter in 2010 from Susan Chandler, the Executive Officer of the BAP, and it said, you know, 'Dear Richard, hope you're well. Attached is a letter for your attention.' And I thought, 'Oh God. I must have forgotten to pay my membership fees.' And I opened it up and it said, 'We're delighted to offer you the Lifetime Achievement Award.' It really strikes home in so many ways, I had absolutely no idea. I also opened it up when I was

staying in a hotel in Dundee, just about to go up the road to see my then 7-day old granddaughter who had just been born. Everything happened in the last week of April or whenever [laughs]. It was quite amazing, actually.

TT: Wonderful, wonderful.

RG: But you know that again takes one back to David Grahame-Smith. It wasn't that big a unit. Out of that came, David and I got second prize in the Anna-Monika Prize for depression. He got another, the Paul-Martini Prize with Jeff Aronson; an international award for their digoxin work. Jeff and I from that unit have both been Presidents of the BPS. David Nutt and Guy Goodwin have been Presidents of BAP. Phil Cowen and I have both got the Lifetime Achievement Award of the BAP. You know, for a not very big unit, it had an incredible influence, I think, on British pharmacology and psychopharmacology. And you know, I think, it's one of the great sadnesses to me that when one or two good things have happened and I've thought I would like to have told David that. I mean you know he was such a big influence and he just rejoiced when things happened well for people, and you know, lovely man actually.

TT: And you don't have the chance to tell them.

RG: Exactly.

TT: What about international societies. Have you been very involved?

RG: I gave a talk at the 1972 IUPHAR [International Union of Pharmacology], I remember that. That was an outstanding thing in its way because I gave a talk, Costa loved that for all his international students, and he had a large number, mostly from Italy I have to say [laughs] to travel in the USA. And he always tried to find a meeting on the West coast that they could go to, because you were only allowed to travel domestically and so he spent a lot of his budget one year sending us over, because IUPHAR was there and I gave a talk with Costa's name on as well. And Gerald Curzon asked me a question and to Costa, you were his family - you really were - so Costa immediately jumped up, and started shouting at Curzon, defending me. And immediately after Costa came up to me and said, 'I had no idea,' he said, 'that was Curzon. I would never have done it.' And I thought, 'You shouldn't have done it to anyone, but we'll let that one pass.' But Gerald laughed, he said, because Costa came up to apologise and said, 'Ah, you are the father of Green.' And that's how Costa saw himself. And so, years later some of my other more inhibited Swedish colleagues would wonder, because I'd be going through some international meeting when some Italian who didn't even have to work at the same time you were in the lab, would come up, hug me and kiss me on both cheeks. And I remember Alan Cross saying, "I had a couple of our Swedes saying, 'Who is that kissing Richard over there?'" You know, but you were family, and it was fantastic.

So that certainly is notable. I became an IUPHAR rep for the BPS when it was in, when it was in Amsterdam. All us representatives went to a dinner, and it was when England was playing someone in the World Cup, which was on at the same time. And the waiter kept coming up, whispering to Alasdair Breckenridge who was next to me, who was the other representative, what the score was. And after a while the dinner went on interminably, I suddenly realised that several people, including Alasdair, had disappeared and I asked the waiter. He said, 'Go downstairs.' And there was a café downstairs and everyone was watching us lose the penalty shootout. And I was EPHAR [Federation of European Pharmacological Societies] representative for the BPS. Going to international meetings was less easy, as you know, when you were at the MRC, because there wasn't necessarily the money as much. But Sol Langer, who was then Head of Synthélabo got me to speak at the Barbican Centre, where the World Pharmacology Congress was in 1984. That was quite fun, you know, such a huge audience then.

TT: Yes, I remember being at the BNA there, the British Neuroscience Association.

RG: I've never really been involved with the BNA. I've stayed just really on the sort of two main pharmacology societies. There was a small group in the 60s when I was doing my PhD, which was I think the forerunner

of British Neuroscience Association. And we used to meet occasionally at a pub called the 'White Horse', which was in an alley off Tottenham Court Road. You went from Tottenham Court Road and went down a little bit, I suppose, possibly the start of Oxford Street, and there was an alley. And you used to get people like Steven Rose attending.

TT: Steven Rose has just written a history of the BRA, the 'Brain Research Association' as it was originally called, which starts with that pub.

RG: And people like that going, and you know, it was quite an active group that there was a lecture each time and a few beers. And I think the whole thing grew up from that. I'm not sure this wasn't even before the BRA. I think the BRA might have grown out from it.

TT: One thing I haven't asked you is about family. You mentioned a granddaughter. So there's wife and children, yes?

RG: I'm onto my second marriage. I got married in 1967, when I was doing my PhD. And we separated in 1995. My second wife was my PA [personal assistant] with Astra, which the company were quite kind about because we were moving up to Loughborough and they said, 'Fine but she should go and work for another section.' When we were in New Zealand, one of the daughters is in New Zealand, and we were travelling round. Geraldine and I were arguing a little about something about where we would go, and the woman behind the desk in the hotel said, 'You've got to remember, mate, the woman's always right.' And I said, 'Tell me, I've got five daughters.' 'You poor bastard!' It's alright actually. I have two daughters and Geraldine has three. They all get on fine. Well, they're all grown up, but you know.

TT: And how many grandchildren do you have?

RG: As my daughter would say, 'You've got one that's a blood relation and several that are not.' I have two other step-granddaughters and two step-grandsons. Actually, because my older daughter married a guy who had been divorced and so she has two stepchildren and so, it's quite a large lot, but few of them are related to me and I have no brothers and sisters. Geraldine has a lot, she has a lot of cousins and everything, and Jude, my older daughter once said, 'It's slightly weird. You know, we're not used to this, are we, because we don't have that.'

TT: Now is there anything else you want to tell me that I haven't asked you?

RG: When I printed that out [a copy of his CV] I thought, gosh, there are lots of papers. But, for example, I published with Sue Iversen, but that was because Nick Tye who went on to actually be Head for a while of Lilly, this is about 1977. Nick was doing a PhD on 5-HT and punish-responding; doing his PhD with Sue Iversen. And Sue wanted 5-HT measured in the brain of the animals that he'd been doing things to, I think it was lesioning and stuff like that. I gather she asked Les, who just said, 'Well, we don't do it here. Go and ask Richard.' So, you know, my involvement with that being on with a prestigious name like Sue, was because I did measurements on their brains of their animals for them, and they put me on the paper. I wasn't the initiator of that.

TT: There are some very familiar names. I also notice Mike Minchin, because I knew him in Sheffield.

RG: Ah, Mike came to us as, I think, the replacement for Moussa Youdim, as more of a neurochemist then, and we worked together on GABA because Mike knew that. And then he left and went to Wyeth actually down at Taplow when the Wyeth labs were there. He went to Australia, and worked with Phil Beart in Melbourne. Of course the Wyeth unit closed, and then the whole site closed apart from marketing, and he then joined, and I've forgotten what their name was, a Japanese company that was setting up labs at the old Littlemore Hospital in Oxford, which was the county asylum as opposed to the city asylum, which is the Warneford. And I can't remember, and that company then closed that research down but kept him on. The company is now called 'Astellas'. And you know they're one of, a bit like Novartis, they're one of these combinations

of two or three Japanese companies. And I haven't seen, we exchanged Christmas cards, I haven't seen him for a couple of years. I saw him a couple of years ago at the BPS. He has a much more of a roving job. I mean not only CNS, almost, he goes to meetings listening to what's going on and might be exciting in almost any therapeutic area, which always seems to me to be a very challenging thing to do. I love listening about things I understand, I don't like learning these days about things I don't understand.

TT: Well it's been great listening to you, Richard. Thank you very much.

[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. Tansey E M (intvr); Tansey E M, Zarros A (eds) (2016) *Green, Richard: transcript of a video interview (17-Dec-2015)*. History of Modern Biomedicine Interviews (Digital Collection), item e2016035. London: Queen Mary University of London.