History of Modern Biomedicine Research Group
School of History, Queen Mary University of London
Mile End Road, London E1 4NS
website: www.histmodbiomed.org

AUDIO INTERVIEW TRANSCRIPT

Humphrey, Patrick: transcript of an audio interview (08-Feb-2016)

Interviewer: Tilli Tansey

Transcriber: Debra Gee

Editors: Tilli Tansey, Apostolos Zarros

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Humphrey, Patrick: transcript of an audio interview (08-Feb-2016)*

Biography: Professor Patrick Humphrey OBE DSc PhD HonFBPhS (b. 1946) was born in South Africa and graduated from the School of Pharmacy, University of London, in 1968, with a strong interest in drug receptor theory. After obtaining a PhD in Pharmacology at St. Mary's Hospital Medical School and briefly working as a Lecturer in the Department of Physiology there, he joined Allen & Hanburys at Ware to initiate a project on migraine. His work on cerebrovascular pharmacology led directly to the development of sumatriptan, the prototype of a new drug class (the triptans) for the treatment of migraine. During this time, he became the overall Director of the Glaxo Division of Pharmacology that was not only instrumental in the discovery of sumatriptan, but also naratriptan, alosetron, ondansetron, vapiprost, and salmeterol, covering a broad spectrum of therapeutic areas. He has received many important academic honours, including an honorary Professorship from the University of Cambridge, as well as the Royal Society's Mullard medal. In 1999, he was awarded the OBE for 'services to migraine research'. He maintains a passion for research aimed at drug discovery and was latterly the successful Head of Research and Executive Vice President at Theravance in South San Francisco from 2001 to 2008. He has over 300 published scientific papers and book chapters to his name and was ranked fourth in the list of total literature citations in Pharmacology and Toxicology from 1994 to 2004. He is currently consulting for a number of new, innovative pharmaceutical companies and is a non-executive Director on the Board of Verona Pharma plc.

TT: Tilli Tansey

PH: Patrick Humphrey

TT: First of all, thanks very much for coming, Pat. As we were saying before I switched the recorder on, I thought it would be sensible to try and do this in a mainly chronological framework to begin with. So would you like to say something about your background and which part of the country you come from and your schooling?

PH: Oh right, okay, that really is going back. I was actually born in South Africa. My mother's an Afrikaner and my dad was in the Royal Air Force (RAF), and that's where he was during the war. And I was born in South Africa, came back, left South Africa when I was 10 months old, so I'll never forgive my mother for not teaching me Afrikaans. But I did realise later that it wasn't actually that useful a language, I don't think, because, I think, it's not exactly Dutch either, so it has its limitations. Nevertheless until I was 10, I think, I supported the South African cricket team. Now being 70 years old, I've long supported the English cricket team.

TT: You pass the Tebbit test.

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* Interview conducted by Professor Tilli Tansey, for the History of Modern Biomedicine Research Group, 08 February 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.

PH: Yes, definitely. But, though I was very keen, very proud of being of Afrikaans background, or Afrikaner background. I must admit none of our family and friends supported apartheid and many left to go to Australia many, many decades ago. So I've really got nobody left over there. But the only other thing I can think of that links with what we're about to say, is that many that emigrated were doctors and so, I think from quite an early age, I quite liked the idea of being a doctor. In school I went to grammar schools and my first one was the Beckett School in Nottingham. By the way, I went to 13 schools because my father was in the RAF, we moved every year or so [laughs].

TT: It wasn't as if you were expelled for bad behaviour?

PH: Well, maybe a bit of that. But my first senior school was a grammar school at 11, and I went to the Becket School which, in those days, was a terrific school. We were taught by Augustinian Brothers and I really was very excited by Latin, I loved maths, and I became a bit of a chess guru, so I was probably a pretty good scholar. I always remember, in the second year, I started on ancient Greek as I was good at Latin, I was really excited about that and then two weeks later Dad said, 'We're moving.' So… [laughs]

TT: That must have been so disruptive for you.

PH: Well, a lot of people say that, and it was to some extent. I remember, you kept changing schools and you ended up doing the same bit of the curriculum you'd done before, and not the new bit. So I had to learn a lot on my own, I guess, but as I joked to people, my geography was pretty good [laughter].

TT: It must have been quite difficult on the social front as well, always leaving, making and leaving friends?

PH: In some ways it was, and that was interesting too. Many schools you went to you were sat at the front as the new person and you could feel all these eyes boring into your back, and it took quite a while to get familiar with people, but it didn't take long. But I always remember, though, Lancashire was a place I loved and I went to school at one stage in Lytham St. Anne's, and all the kids rushed to the front and say, 'Who are you? Where have you come from?' So I have a soft spot for Lancastrians, I must admit. But then, my second senior school was at Chippenham, so we lived in Wiltshire for a while and I really liked that school. I actually won the Wiltshire Chess Championship, under 15s, and my favourite subjects I suppose were maths and Latin and zoology.

TT: Certainly maths and Latin and the chess, there's a very logical structure to them?

PH: Yes, that's right.

TT: Were you aware of that or do you think that's in retrospect?

PH: Yes, to an extent, although I must admit most of my friends went and did the arts, and I was quite interested in languages and other things as well. But no, I am very logical I think.

TT: And then you would have done O levels and A levels.

PH: Well, at Chippenham Grammar we actually, that was strange too, I was in the top of the top class and I think it must have been about half a dozen of us actually did O levels a year early, and then we didn't go into the Fifth form, we went straight into the Sixth form, which again I didn't mind that. In fact my subjects then were pure and applied maths, two subjects, and physics and biology.

TT: What encouraged that choice of subjects?

PH: Well, I liked the maths for the reason we just heard. Physics just seemed a natural follow-on from applied mathematics. And biology, I was always interested in biology. The first book I ever read myself was Enid

Blyton's book of garden birds, which wasn't a book on bird species. It was about a little boy and his sister who live in the city and all they ever see is pigeons, and then they go to stay with their auntie and uncle in the countryside and they suddenly hear all these noises they've never heard before. And so it goes through bird species but it's always part of a little novel. I just recently found the book, I lost my copy and just recently found the book in a Cambridge book shop. It was printed in 1947 and I've got a copy of it again.

TT: It's amazing what you can find on eBay and AbeBooks and things like that, and thrilling to find books that were really influential as a child.

PH: That's right, it is, yes.

TT: You mentioned that you had an uncle who was an eminent doctor. Were you still thinking of medicine?

PH: Well, not quite at that stage because a funny thing, you will laugh at this, but I was going to be, I decided I was going to be a biophysicist and sort of invented that. I almost made it up, and then when I found out there was no such thing as a biophysicist, and I wouldn't get a job. I just thought I'd better think about something else. But of course there are, today it's an obvious thing but in those days I don't think it was. We're talking about, I was at school in the late 50s.

TT: It would just be about the time the word was coming into usage.

PH: Yes, precisely. But only just, it wasn't on most people's radar. I'm sure my science teacher didn't know anything about it. And then that influence of family: one of my uncles worked on the polio virus in South Africa and so I thought about medicine. But then I had to change schools again, so I went to another grammar school, my father went out to Singapore and he said, 'Do you want to come to Singapore or do you want to go to boarding school?' Oh, what a choice. Singapore would have been great because we'd have been sailing every day but I would have done no work, because by then I was starting to grow up and get older and…

TT: You would be about 16 at this stage?

PH: Yes, that's right. And there's all sorts of other activities like, well, I won't go into that but anyway.

TT: We all remember what it's like to be 16.

PH: So I decided I'd better go the boarding school route so I went to a boarding school called 'St. Peter's' in Bournemouth, Southport. That was run by the De La Salle Brothers, it was a bit of a sort of prison type of boarding school.

Anyway, so when I went there, I don't know what happened, so in going there, in transit, as it were, I decided I was going to do medicine and not biophysics. So I decided I was going to do, just do a single maths, they didn't do biology, so I did zoology, which I preferred anyway. And I decided to do chemistry in one year.

TT: Quite tough.

PH: Yes. Anyway, I spent most of my time climbing down a drainpipe as far as I remember at that school so suddenly I went a bit off the rails [laughs]. And I didn't get particularly good A-levels, was having trouble in fact. I think I went to 16 Medical School interviews and didn't get a single place. I didn't even get offered a place. That was before I got my A levels and my A levels weren't brilliant. My parents were abroad and so I didn't get much support, I think. In fact I really do, even to this day, and I don't want to make a big deal about it, but I don't think I was awarded the right grades, actually.

TT: Nowadays I suppose your school would be busy challenging those things.

PH: Yes, well that's it, for instance in zoology, I'm sure I wrote sort of PhD level stuff and it was over the head of the examiners [laughs]. Although funnily I got a B in chemistry in one year. But anyway, that's all water under the bridge. So this sudden idea about doing medicine was sort of a bit of a problem. I ended up doing pharmacy, and I was very fortunate that I was good at maths because my parents were abroad and I was out there with them for a while, and all the vacancies were all going. So when I got to the School of Pharmacy, University of London, I had heard that was the best School of Pharmacy and might as well go for the best rather than the worst. It was claimed to be the best almost in the world in those days. I got there and the Dean interviewed me, he was quite a character and, Hartley his name was, Professor Hartley, and he interviewed me. I am sure it was only because I could answer his questions on calculus that he gave me a place.

I've actually missed out a bit here. I actually, because I was too late to apply to start with, or I was trying to get into Medical School, I ended up going to do an apprenticeship with Boots. Because in those days you could do the pharmacy apprenticeship before university, and not after. Now you have to do it after. And I think I was probably the last person in England ever to do the pre-university year.

TT: Where did you do that?

PH: That was Boots in Dover. I did pretty well there and so when I turned up to the School of Pharmacy I thought I knew it all and in fact, I remember, I got in in the end. I'm just jumping ahead a little bit here and I remember we had a big practical and I remember the pharmaceutics guy came across and he gave me 95 instead of 100 and he said, 'I'm taking five off because you've got a dirty lab coat.' But anyway, the interview with Frank Hartley was quite tough and he was obviously throwing out a lot of people, and he asked me a lot of pharmacy questions, which I knew for the reasons you've now discovered, and then he asked me to do some calculus, some maths. And he was getting, apparently he was getting everybody to do the maths, because he believed you had to have maths as well as the chemistry, the physics and the biology. And I was able to do all the calculus for him straight off, so I got in and I was so lucky because it was a brilliant School of Pharmacy, I learnt so much. I did medicinal chemistry to a very high level and, but more particularly, they had a fantastic Pharmacology Department and I was just hooked on pharmacology, absolutely hooked.

TT: Can I just interrupt and ask you why pharmacy, which is almost an implied vocational training to become a pharmaceutical pharmacist, as opposed to say a degree in pharmacology or physiology?

PH: Well, there wasn't a degree in pharmacology in those days. That shows you how long ago it was. There literally wasn't. There may have been one in the whole of Britain, at Chelsea. And that had only just started. So to me I didn't really know what pharmacology was as such.

TT: But you then came across pharmacology in the School of Pharmacy?

PH: Precisely.

TT: Who were your teachers?

PH: Well, this is really interesting. In those days the Professor of Pharmacology at 'The Square', as it was known, had to be medically qualified and so the Professor at the time was Gladwin Buttle.

TT: Ex-Wellcome Foundation.

PH: Yes. He was an amazing sort of guy. Apparently he'd been in the Second World War in the desert in Africa, and he came up with this idea of using milk bottles to take blood around for people injured on the battlefield - that was his contribution. He was a strange sort of, not strange, he was a real character, and he would always walk around with a big cigar in his mouth and he was really funny. Because it was always the butt

end and it was always splayed out. It looked as though he'd walked into the wall with it and got crushed. But I don't think he was a great pharmacologist, but he was the medic that they wanted. He was a great character and greatly motivational but the key pharmacologists were Bowman, Rand and West, who wrote their textbook at the time. So we were being told what was in their textbook and if you missed the lecture you just bought the textbook at the end of the year [laughs].

TT: You said you got hooked on pharmacology, was there anything in particular?

PH: Yeah, there were two things; one is the mathematical side of it. I still very proudly proclaim that pharmacology is the only biological discipline that involves mathematics and numbers, and you treat numbers seriously and they mean something. So obviously drug receptor theory and all that sort of thing appealed to my mathematical inclinations. But not only that, but it was the medicinal chemistry and designer drugs, so we were learning about Ehrlich and people like that, who spotted the opportunities. I don't know whether people know, but Ehrlich was very fascinated by the fact that drugs could get into bacterial cells and not into human cells, such as dyes so you could actually see the colour. He talked about the 'magic bullet', so that you could design chemicals that actually target a particular cell. Subsequently, you could extrapolate that to a receptor, and he did actually talk about receptors, so that if you put together the medicinal chemistry that I'd done and that we were doing in pharmacy, the mathematics and then the discovery side, you get my career! I was always interested in people who had achieved things, and that went beyond even medical things. Think about Shackleton in the Antarctic and Hillary climbing Mount Everest. I always liked the idea of doing something that nobody else had done before. So it just seemed it was all there really.

TT: Well, it just seems an amazing confluence that you have these three things almost coming together in pharmacy. So that inspired you, encouraged you to think of becoming a professional scientist and doing a PhD?

PH: Well, it did and it didn't. I was really excited about it, but I was so determined to become a doctor in my early days that I went to see the Dean about getting a place at the Royal Free Medical School next door. I played rugby for them, so I might as well go and be a student there, because the Royal Free at that time had very few men, so I think in the first 15 there were 9 pharmacists. But of course, bit by bit, it took on more and more men and it became 50-50. And so he looked into it and he said he could get me a place because he said my pharmacology was particularly good because by then, from the exams, they could see that. But I decided that I've done a year as a pharmacist apprentice, I've done two years almost, I might as well finish it. I don't know why, but I do like to finish things, I guess, and it seemed silly to walk away from it. So I decided I'd do medicine at the end of it but do all those exams and things I thought, 'To go back to Medical School I've got to learn every bone in the body and this, that and the other. I think I'd rather do a PhD and use my brain.' So I did eventually get offered a place at the Royal Free, I've still got the letter that says, 'You've got a place,' but I did not take it up.

TT: They're probably still expecting you [laughter]!

PH: I actually wrote to the Royal Free Dean and said, 'Maybe if you'd have given it to me before I did pharmacy I'd have been there like a shot.' But anyway, but I had a place at St. Mary's Medical School to do a PhD and that really appealed because the Professor there was Richard Creese, quite a well-known physiologist, and it was a Physiology Department, not a Pharmacology Department I went to. Creese purposely went to The Square, he said, 'I want somebody who can actually use analytical techniques and mathematics,' because he was into dose-response curves and understanding them, so it was right for me, right for him, I guess.

TT: So Richard recruited you?

PH: Yes, he went to The Square.

TT: Trying to find somebody with your particular skills and interests? How very fortunate. So did Richard supervise your PhD?

PH: Yes.

TT: And what was your PhD on?

PH: It actually was on the neuromuscular junction, which is quite interesting because obviously from a medical point of view, diseases of the neuromuscular junction, problems of locomotion and everything else are very important. But it was also the physiology of it, in terms of neuromuscular transmission.

TT: And this was?

PH: This was actually on decamethonium.

TT: So it's very much the Paton and Zaimis era?

PH: Precisely, yes, Eleanor Zaimis. The electrophysiology, neurophysiology appealed. It was a medical condition, which also appealed, and we were going to work out, we were looking at decamethonium and it was taken up into skeletal muscle. We were trying to work out how it got taken up and why it got taken up, and so I was excited to go there. And funnily enough, Richard Creese took me on as what they call the, what did they call them in those days? I can't think at the moment but I was, I'll think of it in a minute, but I had to do some teaching, rather than just get a grant.

TT: So you were more like a research assistant?

PH: No, there was a term in those days, I can't think of it. But anyway, Richard said to me, because I'd only been there the first day, and he said, 'You're going to do my teaching, Pat.' 'Hang on, okay,' I thought. He said, 'Tomorrow we've got the first lot of students coming in, you're going to teach the ophthalmoscope.' I hadn't got a clue how to use the ophthalmoscope, but he showed me how to use it and the next day there's me with my lab coat on, showing them how to use an ophthalmoscope. Anyway all these students were very impressed, thought I was a doctor, which was interesting. But I said, 'No, I'm a pharmacologist,' [laughs]. But anyway, that was fun because we did lots of studies on students in those days so, you would never have been able to do that today, it would be impossible.

TT: These were studies as part of their course?

PH: Part of the second MB course, yes. I used to take blood out of students and all sorts of things and they never knew, I'd taken blood out of plenty of rats and rabbits, but I'd never taken from a student before, but they didn't know and I was pretty good at it [laughs]. And one of the experiments I actually loved was I used to put a Ryles tube down the nose of the student into their stomach and then they had a syringe on the end so they could take out stomach secretion, acid and everything, and measure it. And every time I put that down their nose they said, they were quite frightened because it's not particularly pleasant, but they said 'Have you had this done to yourself?' And I said confidently, 'Yes.' I think it was one of the few times that I told a lie, but I thought it was appropriate to tell a lie [laughs].

TT: To encourage them, yes.

PH: But then, this is the amazing thing, I used to inject them with histamine to stimulate acid secretion, and obviously it was very effective but they had to take an antihistamine in order to stop the systemic side effects that you get. So the thought of doing that, they would not allow that today.

TT: I'm trying to think how you would get ethical committee approval nowadays to do something like that.

PH: Precisely, precisely. So that's in '68-'69. Oh, by the way, I was in sole charge, nobody around, and I think I was one of the few or almost the only non-medically qualified person on the staff at that time.

TT: Good Lord. So you were on the staff whilst you were still doing your PhD?

PH: Yes, yes.

TT: And then when you stayed?

PH: Well, I stayed for year after my PhD, when they made me a Lecturer then. Yes, prior to that I was paid as a demonstrator. I think that's what I was during my PhD years.

TT: Oh yes, demonstrator - that would be the right expression, wouldn't it?

PH: Demonstrator, yes.

TT: And then you decided to leave?

PH: Well, I'd taught students and I'd done a PhD which I really enjoyed, it was more pharmacology than physiology, but I'd interacted with all the physiologists and knew them pretty well, knew what they did, and I knew that if I stayed on as a Lecturer I'd be teaching physiology to medical students. So okay, I'd have some research and maybe I'd have a line or two in a textbook one day, but it didn't seem to me to be a very attractive sort of end target. And given all the things I've just said, I was interested in medicine, interested in pharmacology to a great degree, could see what it could do, and I wanted to discover a drug. That's what I wanted to do. I wanted to discover a drug. And it was overriding, and I thought that that way, that's how I could fulfil my interest in medicine, that if you could make drugs that make people better and change their lives, that would be it. And funnily enough, many years later I got to know Jim Black very well and he said in a book he wrote, but he also said it to me several times, that he was medically qualified, he was a pharmacologist as we all know, but he said, 'I've done more for patients by being in a laboratory than I could ever have done in a clinic.' So I had foreseen that, getting that sort of satisfaction, so I wanted to find a drug.

Now this is the next step, I've been so lucky it's unbelievable, because David Jack, Sir David Jack, was a head of Allen & Hanburys in Ware in Hertfordshire, and he was looking for somebody to start a migraine project. He was looking for what he used to call 'bright young things' because, funnily enough, he'd taken over Allen & Hanburys but they hardly had anybody who had a PhD. Even the Head of Department, Roy Brittain, didn't have a PhD when he started. So David Jack was looking around and the School of Pharmacy was the obvious place. So he went there and I think people sort of knew me at St. Mary's, and I think that's how he offered me the job.

TT: Why were Allen & Hanburys looking for a migraine drug?

PH: A very good point. David Jack had this maxim that we, and I'll say it, the people who work for Allen & Hanburys, had to find better drugs for diseases that were poorly treated. But then he had another addition to this. If you spoke to him about it he said, 'Ah, it's also got to be a common disease, there's got to be lots of people who have it, because we're a pharmaceutical company, needing to make money. It's no good if one person in the world has got the disease.' So he said, 'How do we know it's common, laddie?' And the answer you had to give him was, 'I know somebody who's got it' [laughter]. And the one person that he knew, or several people who had got it, and his daughter I believe had migraine, and he obviously read about it and he realised that it was a disease that was very poorly treated and it was very common.

TT: So you've got your PhD, you've done some teaching and now you go to Allen & Hanburys, Ware. Was there any tension from your academic colleagues that you were going into industry from academe?

PH: Not really. I think, as I said, in physiology they were all medically qualified anyway, and I was well accepted and I had no problems like that. I think they always thought that people like me would go into industry because it was the perceived thing. Today I think more obviously somebody like me would have been in an academic department of pharmacology or bioscience or whatever.

TT: You have spoken about this before, but it would be good to have it on this record as well, about you arriving at Allen & Hanburys.

PH: Yes. Well, that was interesting because I'd already met Roy Brittain who was the Head of Department, I'd met David Jack several times, all this was through the interview process and other things. I actually went, even when I was at the School of Pharmacy, to Allen & Hanburys to look around, and in fact David Jack had told me, 'You're too bright, laddie, come back when you've got a PhD' sort of thing [laughs]. So I did, I took him at his word in a sense, and he approached me as well so that was a meeting of minds. But I was really looking forward to going to Allen & Hanburys, and when I got there and met everybody it was really nice. And then they said, 'This is your lab' and I walked in there and there was a lab and there was nothing in there. And then I found out there was really nobody going to work with me except one person that they'd assigned and that was Eira Apperley. She was a young graduate and she's sitting there on the bench and says to me, 'What are we going to do?' [laughs]. And it was interesting, nobody told me what to do because the Head of Department was away, and somebody else was away, and David Jack was somewhere else, so it was pretty clear that it was down to me to find something to do. And I think I was quite pleased about it then. Retrospectively, I think it was fantastic because nobody would have that opportunity anymore, now you'd be told what you're going to do and it was probably the wrong thing, and you couldn't do much about it anyway [laughs]. I think industry has got itself into a pretty abominable state now. But anyway, at the time that was the best place to be without a doubt and to have that freedom was fantastic.

TT: And how did you deal with that challenge? You walk into an empty lab and…

PH: Well, the first thing I said to Eira, 'We're going to find out about the disease. And how are we going to find out about the disease? We're going to talk to clinicians.' So it was obviously a question of doing a lot of reading but also contacting various clinicians and going to see them. And, I'd already decided from what I'd read, and this was the teachings of Harold Wolff that migraines seemed to be a vascular disease of the cranial blood vessels. So we ordered a whole lot of stuff to look at isolated blood vessels and what we started on doing was the rabbit ear artery, because ostensibly that's a cranial vessel, extracranial, it was easy to get out and it was easy to put a catheter into it. You could, in isolation, you just took it out of the animal, you didn't use the animal itself, you could look at a whole vessel, which was quite good because you could look at contraction and you could measure blood flow through it and so on and so on. So we ordered that equipment while we went to various places. But the one place that we particularly went to was the City Migraine Clinic, which was a place where migraineurs in the City could actually ring them up and they'd even get a taxi to bring them into the clinic, and they'd try and treat them.

TT: And that was a private foundation, wasn't it?

PH: I'm not sure what the basis of it was. I think there was private money in there but it must have been part of the link to the NHS [National Health Service]. Anyway, the person in charge was Marcia Wilkinson, who is quite a famous person in her own right, and she was charming really because she didn't know me from Adam, and I was just someone who sort of turned up from Allen & Hanburys, which was hardly a well-known pharmaceutical company. But she took me around and showed me what they did and gave me a lot of information on how she treated people. She was a bit anti-drugs, which was ironic given what I was going to do. They liked to get people in a dark room and let them rest and in the end it can go away although some people can be in bed for 24 hours or more, so it's not overly helpful.

TT: Was there sweet tea involved as well? Didn't she always give people tea?

PH: Yes, I think tea was involved. I can't think what that was. There's obviously always been this link with caffeine. I don't remember that being obligatory, but it may well have been.

TT: You say that Marcia Wilkinson was against drugs? Was that common?

PH: I don't mean that in a pejorative way, I just think there was that typical sort of conservatism that the medical profession had at that time. And it was also actually, funnily enough, the one thing I learnt at the School of Pharmacy from all our medically qualified Pharmacology Lecturers, that drugs are dangerous, that most people in hospital were there because of wrongly prescribed or overdosed drugs. Iatrogenic sort of problems were manifest about that time in a big way.

TT: And as far as migraine was concerned, what about ergotamine?

PH: That's the one thing that I got out of Marcia Wilkinson, that ergotamine worked. She didn't like giving it but it worked. And if people had a severe condition she would use it. And so this was one of the key parts of my hypothesis that I put together, which was that ergotamine works and we can talk about that a bit later if you like.

TT: Well, do you want to carry on now to say a little bit about it?

PH: Okay, well the question why does ergotamine work? I might think about it but I think it's pretty obvious that it was probably a vasoconstrictor. And that coincided with Wolff's teachings that vessels in a migraine attack were dilated, distended, inflamed, and therefore if you shut them down, then that would be beneficial. This was, Marcia Wilkinson telling me that ergotamine works, so this is in what period '72-'73? '72 we'll say. But Wolff, in 1938 I would think it was, had shown that ergotamine would actually constrict extracranial vessels in humans and correlated the constriction with injected ergotamine that was also causing the ablation of the headache. I used to float this around when I used to talk about migraine in the very early days, trying to convince people about my ideas and they did tend to pooh pooh them a bit and the reason is, I think, that Wolff had a selected subset of migraineurs where you got this extracranial vasodilation, they were red, but most migraineurs go pale, totally white, so that extracranial vessels are not obviously dilated. But nevertheless, he'd done it and I think, I suppose the key thing is just the dynamics that the ergotamine's constricting and at the same time it's doing something else; i.e. removing the headache or making the headache get better.

TT: You've talked to clinicians, you're developing some ideas, and you've got the ear vessel preparation. How does this develop, Pat? Could you talk us through the next stage of your career?

PH: Yeah, okay. Well, if I could just finish off on the ergotamine and the constriction. Marcia Wilkinson's views helped, Wolff's hypothesis or mechanistic sort of ideas were still there in my mind, but the question is whether they were real, and I started to firmly believe them when James Lance told me that ergotamine really did work, and James Lance was a very famous neurologist in Sydney. And I really respected him as a clinician. If he said it worked, it worked. And he said ergotamine worked, he thought it was a vasoconstrictor. So that's where we were in terms of the vasoconstriction concept, so I decided that we would really start to work heavily on the migraine vasoconstriction hypothesis as a treatment. The logic of that then is that blood vessels somewhere are dilated and the distension causes pain. Now we can talk later on about why that might be so in migraineurs and not in normal subjects, because again it's well known that people who, say, drink alcohol, who are migraineurs, get a headache, a migrainous headache. But I think normal people don't get a headache unless they have ridiculous amounts. So again this idea of dilation by alcohol, constriction by ergotamine, seemed to fit quite nicely, although I think already people were going off the Wolff ideas and not many people really accepted the idea actually that I was trying to push, if you like, in terms of trying to come up with a mechanism that I could pursue to find a new drug.

But the other thing about this constriction is 5-HT [5-hydroxy-tryptamine]. 5-HT had been injected in migraineurs and that would abort an attack as well. So you have to say, 'What's 5-HT doing?' Now we all know that 'serotonin', as 5-HT is more commonly called, at least on the other side of the Atlantic, is a brain neurotransmitter and of course a lot of people don't appreciate that 95% of the serotonin is in the gut. But it is a very important neurotransmitter in the brain. 5-HT is also a vasoconstrictor, but that turned out to be a real can of worms because when we started investigating it, we found that as had been proved earlier by Irvine Page, who discovered serotonin, 5-HT would also dilate. So it's got dilator actions, constrictor actions, and so on. I later got the Vane Prize for Neuropharmacology, I did actually get into the 'neuro' in a big way later on, but at that time I was hard-core cardiovascular with regard to the cranial blood vessels as opposed to anywhere else.

TT: You were talking about Wolff's ideas not being so popular when you were developing your own ideas. How were you own ideas accepted by Allen & Hanburys? How were you regarded?

PH: Well, I think they were fine there because internally I developed my hypothesis, which I'll get to in a minute, fairly quickly. And they could see that there was some rationality in it, and David Jack was prepared to go along with it because I had an idea that seemed plausible. And that was it, it was a risk. But, interestingly, they were quite wedded to vasoconstriction anyway in the company, because the only help they gave me was a big pile of books about what they'd done in the previous three or four years, and what they'd done is taken rabbit ear artery, like I was doing, putting lots of different ergotamine, ergot alkaloids on there, and I more or less said, 'Well, that's rubbish, we're not doing that' because ergotamine is a dirty drug and what are we going to do?' We could make another ergotamine but that's not very good. But they were open to the idea of vasoconstriction, but the question is which blood vessels, how do you explain it, and I think the salvation for me being able to really put the idea forward of wanting a vasoconstrictor was Pramod Saxena who had been working in Rotterdam on this idea of shunts. It wasn't his idea but he was developing it beautifully in animal models in relation to migraine, and he'd shown that in animals at least, if you took a cat or a dog or even a pig, you can dilate the vessels or even, they may actually even dilate under anaesthetic conditions, and then if you constrict them you find that most of the constriction is not the arterial supply but it's these what are called 'carotid arteriovenous anastomoses', which is very strange but in a sense because basically what you're saying is that a lot of the blood is just diverted away from the normal brain circulation.

But I think that, as I said, it's a somewhat artificial model in an anaesthetised animal, but the animals have these shunts and I don't think to this day people believe that big shunting mechanisms occur in humans. But there was a German Professor Heyck who put forward the hypothesis that in migraine there are carotid arterial shunts that open up, and when they open up you actually can show in the jugular venous blood that oxygenated arterial blood that should be going to the brain is being diverted on the jugular side. Nobody really was able to confirm that hypothesis and nobody seemed to really want to believe it. But I argued that maybe, whether they believed it or not, I just said he'd shown it, he'd claimed it, and in animals these shunts are real and, lo and behold, 5-HT which will abort an attack - constricts these shunts. Ergotamine constricts these shunts, why couldn't we try and constrict these shunts selectively? And so that was the sort of idea, but at the same time we were working on peripheral blood vessels and we discovered that this is one of the reasons that many people never really understood the hypothesis I had, because we discovered a new 5-HT receptor on blood vessels in the dog saphenous vein. And we used to take dog saphenous veins out because they were handy and we could get them, and we discovered this new receptor in the saphenous vein but it was predominantly in these carotid arterial shunt vessels, predominantly in certain cranial vessels, and nowhere else. And so that allowed us to find a new agonist for this 'dog saphenous vein receptor', as we called it then, but now really a '5-HT_{1B} receptor'.

And we actually went to Pramod Saxena's lab in Rotterdam to take one of our prototypical agonists and we were just euphoric when we saw that all it did was constrict the shunt blood vessels, cranial shunt vessels, and no other vessels in the head, no other vessels in the rest of the body. Just amazing. But the reason, well, the way we actually discovered the new receptor in the dog saphenous vein was, again, because of the migraine and it was again because of James Lance. The whole thing is very complex and what I was able to

do is drive through the complexity and get simplicity. Some people believe 5-HT caused migraine, some people thought it didn't. But one of the problems that I had was that if 5-HT causes migraine, why don't the 5-HT blockers really work? They were used as prophylactics but they were, and still are, pretty poor. And methysergide was one of those 'used as blockers', which was quite good. But James Lance told me that he, on occasions, had people in his office have a migraine attack, he gave them a dose of methysergide as given prophylactically, and the headache went away, within 20 minutes in his office. That was the only one that did it. So if 5-HT blockers are all the same potency as inhibitors, what's different about methysergide? And we discovered in our laboratory experiments that methysergide constricted the dog saphenous vein, and we showed it was at this new receptor.

So why wouldn't you use methysergide? Well, methysergide is another ergot derivative, it's got other actions; in fact, you can't even give it prophylactically for long periods because it causes retroperitoneal fibrosis and it's got other actions, and it turned out to be a partial agonist. Now again this is another thing about pharmacology, understanding what a partial agonist is, or a full agonist, or whatever. So we decided we needed a full agonist, not a partial agonist like methysergide, because it only worked in some patients, not all, and so on. So there we were. We had this vascular hypothesis put together, we discovered a new receptor. Now it was amazing that we called it 5-HT_1-like receptor, because they were talking now about binding sites in the brain, called them 5-HT_1 etc. But we actually got it right. We found a receptor in the pre-molecular age, before molecular biology could isolate all these things.

TT: You've just used a very elegant phrase: driving though the complexity towards simplicity, which I really like. I may claim that for myself at some stage. And I just wondered whether we could now talk a little more about, I'm aware we're still carrying on with your career chronology, but just divert into 5-HT, into the 5-HT receptors, and that whole morass that you got very involved in sorting that out.

PH: Yes. Right, okay, that's interesting in itself. By the way the complexity phrase just came out, off the tip of my tongue. I didn't practice it before I came here. But the one thing I'm very proud of is - David Jack put it in another way. He, in his interview at Oxford Brookes that you sent me the transcript of, he said it more than once actually, he said, 'Pat, that was the most amazing pharmacological jigsaw puzzle that you solved, that I've ever seen.' And he said that more than once. He was very excited about the fact, so it's just another way of looking at it. No, actually, he didn't call it a 'jigsaw', he called it a 'detective story'.

TT: Would you like to say something about that detective story?

PH: Well, in a sense I sort of wandered into it. But I think again the reason it all came together, we'd got to find a migraine drug but we'd got to solve the pharmacology. One thing I didn't mention was, when I first started, there was just Eira and I working, so we didn't have hands in the lab, we were both working on these things. At one stage we said, well it could be 5-HT that's important, but it could also be prostaglandins, because when prostaglandins infused into people it has been shown to cause a headache. And so for a while we actually worked, crazy but this is me, we did six months on 5-HT and six months on prostaglandins with the idea that we're not sure what it is at the moment. Within two years we'd switched completely to 5-HT. But as far as prostaglandins were concerned, we actually had a clinician who was prepared to take jugular venous blood during a migraine attack and we were going to try to link it with the Heyck hypothesis and whether we could find out whether it was prostaglandins coming out in the jugular venous blood during a migraine attack. Now, to some extent, I'm glad we didn't do it because it sounds a bit hairy and you have to have the right clinician and everything. But we were working on that and we even developed a bioassay to measure prostaglandins. Again, that was a bit crazy because later on you realised you needed mass spec[trophotometry] and all sorts of other things to get proper readings.

But then, the 5-HT story was the other story, and there we were approaching it through the vascular approach, but were also asking questions about how many receptors are there? And at the time we only knew, from the day we started and up until our discovery, we only knew of two receptors: Gaddum and Piccarelli's receptors, one was the 'M receptor' and the other was the 'D receptor'. And the M receptor was,

funnily enough it wasn't the one on the muscle, because it was actually the one on the nerves, but it was called 'M' because it was blocked by morphine or the effect of the activation of the receptor was blocked by morphine, and the 'D' receptor was blocked by dibenzyline, and that was the muscle receptor, which we now know is the 5-HT_2.

So that really intrigued me because of my background in zoology and I thought, 'We've got to get some proper classification here' or as James Black used to call it, 'taxonomy'. I'm not quite sure of the difference between that. But anyway, at the end of the day 'receptor classification' became a strong theme for me in all my work and all my career, and I didn't like the idea of 'M' and 'D' because they were just named after two very poor drugs, they were lousy drugs to name the receptors after. So I thought, 'Well, why don't we have 'S receptors', we can have 'S_1' and 'S_2', that would be a good start,' and even that was frowned up by some of my colleagues. Well, Americans call it 'serotonin', we call it '5-HT', so that one rumbled on for a while too. And in fact, ultimately, when we did get the nomenclature sorted out it did actually remain at 5-HT, which was quite nice. But anyway, we were just looking at how many receptor types there are and when we discovered this dog saphenous vein receptor, we called it the 'S_3 receptor'. We had S_1 and S_2, why not have S_3 [laughs]?

But then it got a little bit complicated when, it was Steve Peroutka published his paper on binding. He came up with S_1 and S_2, but they didn't correlate with our receptors, so that was when I started to really talk to a lot of people at a sort of, beyond the realm of drug discovery and beyond the realms of partisan politics within companies, to see if we, the scientific fraternity, could intellectually get together and come up with a sensible classification. So we did.

TT: I think I have to stop you there. 'So we did.' Now come on, Pat, it was much more than that.

PH: Well, it was a long road in a sense, and some people just hate it when they've named their receptor and felt we were going to change it. I was not interested in that sort of thing. I don't think people would necessarily call me diplomatic, but I had to be pretty diplomatic in those early days. I actually, the start of it all really was at Birmingham, because I had a PhD student with Philip Bradley, I think Philip knew, I don't know whether Richard Green was there as well actually, at Birmingham at the time, or had been. He'd been a student of Philip Bradley's I think. But anyway, Philip had approached Roy Brittain and said, 'How about a PhD student?' So I had a PhD student there and got talking to Philip about my ideas, and he got me up to give a lecture and in the end he became quite interested, the student was obviously becoming interested in classification, so we had our first meeting in Birmingham where I invited a lot of people. Funnily enough, most of them were working on migraine or something like that, because they were interested in 5-HT.

But there were other people like Steve Peroutka who was a neurologist, he was at Johns Hopkins and we had a really good meeting. People got to like each other and I broached some of my ideas a bit tentatively, not because I was trying to hide them but because I didn't want to say, 'This is what I think' and frighten people away. But the Bradley paper was really quite definite, and always in those early days I was very keen to have alphabetical authorship and all that sort of stuff, and that first paper, to this day, Bradley *et al.* because I think I'm probably, I don't know whether that was alphabetical or just because it was at Birmingham, Philip being the Head of Department there. But that was the beginning I think of an amazing fraternity of people who did share a lot of things. They did, keep a lot of things to themselves, because they were company things, but ultimately led to this meeting on Heron Island, which was amazing because of such good interaction. It was so exciting, people were really excited about the idea of sorting all these things out. And it was a beginning of a whole era where people realised there were multiple receptors for a single neurotransmitter.

As I told you when we started in '72 there were two 5-HT receptors, well earlier than that there had been two receptors for noradrenaline, adrenaline, alpha [α] and beta [β]. And then they found there was α1, α2, β1, β2 and of course that's now extended. So suddenly we realised there were more 5-HT receptors than we'd realised because at Heron Island, that was in '87. I think people like Michael Gershon who was a GI [gastrointestinal] physiologist really of some eminence, but he was talking about 5-HT_{1P} receptors. Well, he

was very annoyed when we said, 'We don't think that's a real receptor, it could be this or it could be that.' To this day he still believes in 5-HT_{1P}, but the 'P' the nomenclature committee has never accepted and never will, because there's not enough rigour in terms of the classification around it, in terms of having selective agonists, antagonists, knowing what the coupling mechanisms are and ultimately even molecular structure now you have to have.

TT: The whole work, this work on 5-HT receptor nomenclature, this just started from the scientists themselves?

PH: Yes.

TT: This was bottom up?

PH: Definitely bottom up, yes.

TT: So you were working together, talking together, you set up or became the international nomenclature commission?

PH: Well, I was certainly a founder but by being diplomatic and talking to people, people were coming in so in the end you couldn't really identify any one person but it was born out of the 5-HT set up, if you like. So in '86, I think, Paul Vanhoutte decided that 5-HT was the next up and coming neurotransmitter and he decided in his very American way to have the Serotonin Club. And so quite a few people joined that and then we had this meeting in Heron Island, which was a sub-conference from the IUPHAR meeting in Australia, and Paul was very instrumental in getting money together, though by now I knew we had a migraine drug which was based on 5-HT, so Glaxo Australia put in quite a bit of money and so we had this amazing meeting. It was a small conference hall on a small island but there were about, I don't know, 50, 60, 70 people there and everybody was talking and I was one of the chairmen and the other chairman was a good friend of mine, Brian Richardson, who worked for Novartis, so I had to be a bit careful there because they were working on 5-HT_3 blockers and things like that.

By the way, that was the alternative strategy to migraine: 5-HT_3 blockers would be anti-migraine, and I said all along they never would but everybody who had a 5-HT_3 blocker put it in migraine, it never worked but they never told anybody. It took me years to get somebody to own up and publish it.

TT: Oh how frustrating are negative results.

PH: Yes. But that's an aside. So this meeting was phenomenal and it was in, I think it was a book, I may have given you a copy actually, anyway there's a chapter in there that Brian Richardson and I wrote, which was a compilation of all the thoughts, all the ideas that people had. And that was the beginning really. So we moved on from that meeting in '87 to, actually the same year I went back to the main conference in Melbourne and Paul Vanhoutte had a meeting of the Serotonin Club. And I was made Chairman of the Nomenclature sub-Committee, because I was the only one who had any over-arching ideas and I had all the slides and everything all ready and so I was Chairman for a very long time, and we eventually wrote this big tome, it was an official IUPHAR thing really when it came out in *Pharmacological Reviews*.

TT: Yes, it's a tremendous document.

PH: Yes, and that was amazing because again it was a lot of people with different views, they're all very alpha people, but I think we did come to some really good decisions. But what's amazing is that now you look back on it and there are 13, 14 5-HT receptors, and even today people say to me, 'How could you have discovered, a selective drug for migraine out of 14 receptors?' Or they probably ask it the other way. They say, 'If you had to do it today would you discover it?' And my answer is 'no' because you have to start with physiology, you have to start with medicine, and you have to understand mechanisms and you have to understand the whole body and you have to understand how blood vessels work and nerves work. If you

looked even at that article I described, molecular biologists just put these things in cells, that's all they can do. They can't tell you what they do in the body. They certainly can't tell you what disease they're relevant to.

TT: We've jumped ahead and you've talked about this wonderful meeting on Heron Island. And Glaxo, because by this stage, Allen & Hanburys had moved to become Glaxo.

PH: Yes, it went from Glaxo to Glaxo Allen & Hanburys, Glaxo Group Research to Glaxo [laughs].

TT: And you stayed there. You now had a drug?

PH: Now we did actually have a prototype, 25068. 25068 or 0568. Anyway, those numbers are right, whether they're in the right order or not doesn't matter [actually AH 25086]. And that worked. We had a couple of clinicians in Germany who injected people with it and it worked, and quite dramatically. Migraine is mainly female disease of course, we've discussed before, as at least three to one, women to men. And they had women come in, they had migraine, a bit like Marcia Wilkinson's clinic. They were lying on a bed and being looked after, but they were being injected and they just jumped up and went home. It was amazing. We knew therefore that we had a drug, but that drug was not quite suitable in terms of duration of action and there were some other issues. And, funnily enough, we then got in some silly issues that we shouldn't have done in terms of toxicity, because of the screening for oncological (mutagenicity) potential; some of these drugs turned out positive, and we had to carry on screening until we found one that didn't affect it. So it took us another four years to find sumatriptan just to avoid this. Now that screen is defunct and nobody uses it, it's not thought to be relevant. So that was a bit annoying.

But it didn't really matter because I think, because we had the prototype, we knew what we were doing. But the other thing is we had to set up the clinical trials in the appropriate way. One of the problems with migraine is the very high placebo effect, and many of these drugs now that are given as prophylactic pills, they're really good but the fact is that 50% of people get a placebo response. So you don't really know how good they are at all. And even on our trial with the first drug we had somebody in which the drug didn't work: seven out of eight it worked fantastically and in the eighth it didn't and two days later they found out that, I think it was a man actually, he had a broken jaw. So diagnosis and getting the right patient population, doing the right sort of studies, was critical. Another thing that I got very positive about and encouraging other people was to think about the clinical trials, and there again was as stroke of luck, because Jes Olesen in Denmark is a brilliant neurologist clinician type, who is more logically and rationally organised than some medical people at that time, and he was thinking seriously about clinical trials and designs and statistics and all that sort of stuff.

TT: How much influence did you have on the organisation of the clinical trials?

PH: I can't claim any of it at all, any credit for it, other than the fact that I encouraged Glaxo to fund Jes and he got quite a lot of funding from Glaxo. I went to a lot of his meetings and talked about our drug and I think he saw that as an opportunity in itself (a) to find out if it really was as good as was claimed, and (b) to do a proper clinical trial, which we needed to do anyway. So in many ways I think the trial of sumatriptan was the first proper trial on migraine, although people might sue me for that. But that's the way, and that was down to Jes Olesen. He must take an enormous amount of credit because in the same way, I wasn't on the committees or anything, I probably could have been, I was the sort of person that could have probably talked my way onto them but I left it to him. I knew he could do it, and he did a very similar job to what I've done in the nomenclature side of things. He just got in loads of people and heard everybody's views and then led the thing to a satisfactory conclusion.

TT: How do you feel as a drug discover, your baby being passed on and going into other people's hands?

PH: Well, in a sense this really was more like saying, 'We want the doctors to know everything there is to know about bringing up a baby, here's my baby, make sure you look after it.' There was a selfish sort of desire to make sure the drug was properly tested and that when we got the answer, we knew if it worked or it didn't work. But yes, I felt good about it, and again, because of my interest in medicine, which we've heard about, quite a few times now, I liked the idea of being involved with people who are doing medical things so even though I wasn't doing it, and in a way I'm a bit of an ideas person, pass it on and make sure somebody else does it, you don't have to do it [laughs].

TT: And what about the rest of the paraphernalia about a drug company, you mentioned the toxicity tests and stuff like that, but marketing also comes into it. Did you get involved?

PH: Yes. Because I ended up being Head of a Division of Pharmacology and was effectively sort of second in command at Ware, I had to be involved with that sort of thing. I always felt a bit uncomfortable in marketing but I think rationalised it to myself that, 'Look, if we're going to find drugs we need money. If we're going to need money, we've got to find drugs.' And so there's this virtuous circle, if you can call it that, because if we don't find drugs the company is not going to be here and we're not going to be able to find anymore. So let's make sure we do it properly. And I think, again I think one spends a lot of time in the industry trying to make sure that we didn't say anything that we shouldn't, and that the marketing people knew what they were talking about and that they didn't go off half-cock on some other angle. I think we were quite lucky, we had some pretty good people in marketing so as far as Glaxo were concerned, I always considered them very highly in that respect. I didn't really have a problem. There were always interactions but I don't think there were any fights. In fact, certainly in the days when sumatriptan was being developed, I spent quite a lot of time with the marketing people and got on with them well and respected them quite a lot.

TT: Throughout this period, you've moved on from just you and one person in an empty room, so you're now head of the division?

PH: Yes, so at one stage I had nearly 200 people working for me and in fact it's probably not well known and I don't mind saying it, but it was decided by David Jack that I would take over from Roy Brittain when he retired and I remember Roy saying to me, 'Do you want to write the next Ware site report?' And I said, 'No, because I've got to go here and there, I've got this lecture to do, I've got this book to write, I'll do it in three months' time.' Well, three months' time never materialised because Richard Sykes had arrived and he decided to reorganise the whole company. So I never became Roy's, well, took Roy's place. And to be quite honest, I don't know whether I would have wanted to necessarily, because I wouldn't have wanted someone more senior in a fast growing, politicised, international organisation telling me what to do. But it wasn't the sort of thing, I'd rather be at the bench. I've always been like that, I'd rather be at the bench. Now that doesn't mean necessarily doing lots of experiments, it means being at the bench side by side with people who are doing the experiments.

TT: Yes, having that constant interaction and knowing what's going on.

PH: That's right. So if you want the end game, the end game was that when I didn't like a lot of the things that Richard Sykes was implementing, I didn't like the company becoming highly political, I didn't like the fact most people were no longer altruistic but only interested in themselves and what they could get out of it, and people weren't being developed properly, there was no team work. So I said to Richard Sykes, basically, I wasn't very happy. So he said he would set up a research centre, he said I could have some money and go off and do my own thing basically [laughs].

TT: So this was the institute in Cambridge?

PH: Yes, that's right. But he didn't specifically recommend Cambridge. I think at one stage he was talking about a sort of warehouse somewhere or something like that. Anyway we had discussions about it and in the end, his idea was that the only way we're going to discover drugs in the future was we had a ton of molecular biologists, we didn't need any chemists because they were all redundant. I envisaged some sort of machine,

like a coffee machine, you just press buttons and, hey presto, a drug. And I said, 'Look, Richard, pharmacology is always going to be number one in drug discovery. It's never, ever going to change. In medicine and everything you need pharmacology, you need to understand the doses, you need to understand pharmacodynamics, pharmacokinetics, how they relate. Toxicology is arguably a branch of pharmacology and so on and so on.' Anyway he didn't seem to see it at the time. Nevertheless, he respected me and entrusted me to keep 'pharmacology alive within the company.'

TT: Quite clearly or he never would have done that?

PH: Precisely. He respected me but we did disagree, is that okay? His idea was that if pharmacology is so great, you keep it hot and we'll do what we're going to do and if we need it you can come back and sort us all out again, which was fine. But then I was talking to Alan Cuthbert at Cambridge, realised that he had a whole floor he wanted to sell to a pharmaceutical company. So in fact yesterday I found, I was going through all my files before I came here, and found a newspaper cutting Cambridge Evening News saying 'Cambridge University gets £16 million' and all about all the drugs we were going to discover and I can talk about that in a minute if you like, but yes - it was great. It worked out fantastically, I really worked well with Alan Cuthbert and it turned out to be a very valuable time for us. The annoying thing was that we had some brilliant ideas and Glaxo would just not take them on because again, the people running it were molecular biologists and they just couldn't see the point of some of them. The irony is I'm now on a scientific board of a company called 'Afferent Pharmaceuticals' in America, and they're doing exactly what I urged Glaxo to do 20 years ago.

TT: When you moved to Cambridge, you moved some of your group?

PH: Well, that was the other interesting thing. Richard said, 'You can take 15-20 people from Glaxo and you can have so much money and we'll give you 10 years.' Great! But I only took five people because I didn't need tons of people from Glaxo. I took two absolutely brilliant scientists with me. One was Dr Wasyl Feniuk, who, you talk about me being unsung, but Wasyl is unbelievably unsung because he was such a good pharmacologist and a terrific man.

TT: We tried very hard to get him along to our meeting, he really was not at all willing.

PH: Yes. But he really understands tissue pharmacology and functional pharmacology. And Anton Michel was the other guy, who was a bit of a mathematical genius, he could write all sorts of algorithms for computers, his stats were brilliant, he was really hot on radioligand binding stuff and we did a lot of molecular biology through him as well, because he was the sort of guy who said, 'Oh, I'll do that.' He'd never done it before, but he'd do it. So they were the only two people really and then there was a technician, and there was a chap called Ian Kennedy who worked with me and Bob Coleman on all the prostaglandin receptor classification work. And he was an ideas man, definitely not a do man, but an ideas man and so there were only five of us. And I ended up with about 30, and half were PhD students and the rest postdocs.

TT: And what was your remit from Glaxo? Did you have any? They were very generous too, from what you're saying, giving that level of support.

PH: No remit really. I had to report to the, this is another irony, I had to report to the R&D director in the UK and that changed seven times in 9 years. That shows you something? And they couldn't care less what I was doing, so that was fine by me, so back to Allen & Hanburys again. Richard said at the time that I was the top non-managerial scientist in the whole Glaxo worldwide, so he did respect me and thought I could do something.

TT: Quite clearly.

PH: We did some pretty pioneering work in terms of ATP receptors which now Afferent Pharmaceuticals are pursuing, a lot of other people have been looking into with not much success for a variety of reasons,

because I think, technically, getting the right drugs is difficult and again, maybe people aren't pursuing it in the right way.

TT: Are you doing it with a particular clinical entity in mind?

PH: There are quite a number of things actually. But what they've shown, and I can say it because it's been published, they've shown a P2X3 receptor that blocks cough. And this is in patients that have been coughing for a year and they're coughing 60 times an hour. And it's remarkably effective. So that's pretty exciting. And then somatostatin we worked on. That's been a difficult nut to crack because it's a big peptide, and trying to find ligands for the receptors has not been easy. But again there are still people working on somatostatin, I think there's potential there as well.

TT: One of the things is, when you say somatostatin, immediately what comes to mind is something you said in passing almost about the gut and 5-HT in the gut. Because one of the things you have also been interested in is migraine in the gut.

PH: Yes, that's right.

TT: Which almost goes back to Langley and the third nervous system.

PH: Yes.

TT: Did you do very much on that? Because that's where your career came from with migraine?

PH: Yes, I did actually because, as I said, I was Head of a Division in Ware and I started up a GI Pharmacology Department with a view to finding new drugs for gastrointestinal diseases, for which there's still great need. One of the ones I was interested in was irritable bowel syndrome [IBS], which is the one I've claimed to be migraine of the gut. Just to give you an idea because I think the thing about IBS, it is a malfunction of normal gut function but it's also associated with pain and sensory perceptions, very analogous to migraine, it's also a female condition, not quite as profoundly as migraine, but it's certainly two to one women to men. And I still believe that's an unmet medical need in a huge population. So I think that that's interesting. But in fact, actually led to alosetron, which was the 5-HT_3 antagonist, while actually that was marketed for IBS but it was diarrhoea-predominant IBS. I think people don't realise, or we do now, but even the medical profession didn't realise that IBS can have different sorts of bowel motility dysfunctions in different patients, so it can either be diarrhoea-predominant or it can be constipation-predominant. In some people it can be alternating.

TT: Terribly debilitating.

PH: It is. We heard stories in the US of people actually buying a second house on the way to work in case they got caught short when they were driving to work. And alosetron turned out to be amazingly effective in diarrhoea-predominant people.

TT: And that was marketed by Glaxo?

PH: It was marketed by Glaxo, it was hailed as big blockbuster and I think that was where it went wrong. I think by then, you asked me about dealing with the marketing people, well by the time we got to the alosetron years, which would have been when I was at Cambridge, so it would be '92 onwards, the company had been taken over by the Americans and the American marketeers were very pushy. And they wanted to sell it to everybody and anybody, if you had a bit of diarrhoea, take it, sort of thing; whereas it should have been for the people who had this profound condition of IBS associated with diarrhoea. Anyway it turned out that some bowel ischaemia occurred in several patients, it was very, very severe, and so the drug was withdrawn. It's now back on the market because it's so important for certain patients that, under certain conditions, given by an expert clinician, it can still be prescribed.

TT: Going back to your Cambridge years, you've got your own institute almost. And you're not really accountable very much to Glaxo, it seems to me. What happens as you're going through those 10 years?

PH: Well, me being me, I felt, whether they felt I was responsible or not, I did feel responsible to them. They were providing the money and I felt what I needed to do was provide drugs for them. But at the same time, because I'd set up this GI Pharmacology Department, I was the only one who really knew GI pharmacology, so I remained the head of GI drug development even though I was at Cambridge. So I used to go in for those meetings and I had a lot of influence over people within the company still, even back at home, because of that role and other roles that I had. So for instance in the migraine area, I was still helping them out and at one stage I actually managed to get an adenosine agonist into man through a back door, they didn't even know about it. I managed to persuade some of our clinicians to do it.

TT: What was that for?

PH: It was an adenosine A_1 receptor agonist, which again I argued would have been, because we haven't really talked about the full mechanisms of sumatriptan, but I think there is a neural inhibitory effect on the nerves that are innervating the very blood vessels that are being constricted. I'd argued adenosine was quite a powerful inhibitor of neuronal function and the coupling of the A_1 receptor was very similar to the coupling of the 5-$HT_{1B/1D}$ receptors, and that it should work. In fact it did work pretty well. But there were some side effects in terms of heart rate effects, and it could have been a new drug type, but they just didn't study it enough. I think I proved that it was a mechanism worth exploring to my satisfaction and, eventually, ended up talking about it to the American Headache Society. So I was involved with the GI, I was involved with the migraine work, but my main role was discovering mechanisms and one of them was the ATP receptors. We were the first people to show the functionality of ATP receptors on neurons in live neurons, and propose that a blocker would be actually analgesic.

TT: Was that taken forward?

PH: No, nothing was taken forward properly. What I ended up doing was training people and so many of them have gone onto phenomenal jobs. There are so many people that did PhDs with me or started second postdocs with me that now are Vice Presidents in companies all over the world and I still get letters from them saying they'll never forget the days they spent with us and what they learnt. It wasn't just me, it was people like Was [Wasyl] and Anton, who spent so much time with the students and they were learning so much on the job, as it were. And my only regret that with training for all these phenomenal people, they're not getting jobs at Glaxo because at the time they were shutting the door, and they certainly didn't want pharmacologists. I remember some of my students, PhD students, coming to me and saying, 'We're never going to get a job.' And I said, 'Just don't worry about it. Just do a brilliant PhD and you'll be fine.' I said, 'If anybody is any good they'll get a job.' And they've all got fantastic jobs.

TT: That must give you a great deal of satisfaction.

PH: It does, and it's one of the most satisfying aspects of that time. But we also published a huge number of papers, and a lot of people did well on it and went to meetings and it was a real fun time. I used to give lectures to undergraduates as well in pharmacology, so that was good.

TT: And then after 10 years, time was up.

PH: Yes. Alan Cuthbert was quite keen that I should stay on and become an academic professor in the Department, but I'm not a great one on politics or mundane management, all that sort of stuff, so I wasn't that keen on that. And I decided I might just try and see if I could get GSK [GlaxoSmithKline] to fund it for a further period, because we still had lots to do and an intermediate period of that 10 years, we were starting to make compounds, so there would have been rationale for another 10 year period. But they didn't

want to do it so fine, they didn't want to do it. So I was effectively made redundant when they become 'GlaxoSmithKline' and I thought, I could have had a big job in that organisation but I don't know why I ever even thought I would want that because I'd left, gone to Cambridge because I didn't like the organisation so why would I? So I decided I really wanted to find one more drug, and I searched the world for a company I thought could do it, and unfortunately there wasn't a single start-up in England that I could find that that was worth its salt, and even if it was they didn't have any money. So I started looking in the States though I didn't like the idea of biotech companies really, because I think my motivation has always been altruism. I wasn't really bothered for myself or even necessarily the money as long as I could look after my family. And I just felt the Americans had it too materialistically and were too much rampant capitalists, and I didn't really want to do that. But I was approached by a company called 'Advanced Medicine' and I don't quite know how they got hold of my name but I found them as well because one of the guys I worked with, David Beatty, at Ware. He was a nice young chap, a Scotsman, he'd gone out there and I didn't know how he'd got on, but it sounded as though the company was doing quite well. We had a look at each other and I thought, 'Well, this is the only company in the whole world I can find that I think could discover a drug in the next 5 or 10 years.' And I went out there and I was interviewed by Roy Vagelos, who was an ex-CEO of Merck (Merck, Sharp & Dohme), and a very famous man in his own right for all the things he's done as a clinician and a drug discoverer, I suppose, rather than as a pharmacologist.

And he paid for my wife and I to go out there to, we went out to Martha's Vineyard, where he lives, and stayed in a hotel and he sent a car to collect me, and that was amazing because we went through this wood and then suddenly there was this sign saying 'Vagelos Residence' and we turned in and another three miles through this wood before we got to his house. And it's on a cliff overlooking the bay there, just amazing. Anyway, I spent three hours just talking solid medicine pharmacology with him and I was so excited when I came back to my wife, I said, 'He's another David Jack! Another David Jack!' I just was so excited because he seemed to have ethics and he was a clinician, he was a medic, he wasn't just in it for money, he was in it to find better medicines. So I was sold. So it was a big move for us, my wife and I, because she was a Headmistress in Cambridge, and she had to give up her job and we were leaving all our children behind so it was a big move, but I never regretted it for a second. And that was really fantastic and Mary said, 'We'll go for five years.' And I said, 'Right, dear,' but it ended up being seven because, again, for altruistic reason, I didn't want to leave them in the lurch, because they wanted me to stay even though I'd said five years, they knew it was five years. But when the five years was up they didn't want me to go and so I spent the next two years finding my successor who, funnily enough, turned out to be a guy in the organisation who I had been mentoring for the whole five years. So that was a phenomenal ending to my career.

TT: And did you discover another drug?

PH: We discovered quite a number of drugs actually. It's really amazing. The guy I took over from as Head of Research, he was a chemist and he'd been in the antibiotic area for a long time and they had this antibiotic there, and they weren't quite sure what to do with it and weren't sure whether to develop it. And when I took over Roy said, 'Do you think we should do anything with this?' And I said, 'Well, it has some development issues, but it's an interesting compound.' And I said, 'I think it could be a medicine and I think we should develop it, because if we're going to become a pharmaceutical company, we need research and development. We need to show we can develop it.' Anyway, we carried on and in the end we got it to the clinic, and it turned out that it was not only anti-MRSA [methicillin-resistant *Staphylococcus aureus*], as we thought, but it was actually effective in individuals who had MRSA that were resistant to vancomycin, which was the compound of choice at the time, and to some extent, still is. So I didn't do anything except say 'yes' every year or so to the development programme, and Burt Christensen really is the man who invented it and was my predecessor, so all credit to Burt.

But what I did, which was amazing, for me it was amazing and I take great pride in it, was I found that the guy who was the Head Microbiologist was not a pharmacologist, he didn't understand numbers and they'd got all sorts of weird and wonderful numerical data that didn't mean anything or were inaccurate. So I said, 'Look, we need to find out how this drug works because clinicians are not going to buy this unless we tell.' I actually asked him to find another job, I'm afraid to say, and temporarily I became Head of Microbiology,

which I'd never done in my life, and with some of the very competent biochemists we had there, published three mechanistic papers on how this drug has got a new mechanism of action that other drugs haven't, which explains why it was effective in vancomycin resistance. So that's one thing I thought, as you can see, I'm a bit of a generalist [laughs], but it was fun. It was fun. But the other things I was involved in, right at the beginning, I said that we needed to develop a 5-HT_4 agonist for, again, potentially for IBS, but also very effective in constipation-predominant conditions and we have a fantastic drug, and we published on it, but unfortunately that class of compound has got a bit tarnished, because the compound that Novartis developed, tegaserod, was found to cause heart effects. I won't elaborate on what they were, because I'm not sure how real they were to some extent, but in a miniscule number of patients. As a result, the drug class has been somewhat tarnished. But nevertheless this drug, velusetrag, is in development at the moment and I think it's quite an interesting compound.

But I think the thing that's probably most well-known is the β agonist programme that we prosecuted there. When I arrived they had some very interesting chemistry, completely novel. One of the things that attracted me to 'Advanced Medicine' was the name, which by the way later became 'Theravance', because once we got the antibiotic, we were about to launch it, the company decided they couldn't possibly talk to the FDA about it as a company called 'Advanced Medicine', because it was advertising almost in terms of the drug company name. So we had a competition within the company to change the name. So everybody put their ideas in, there were some really funny ones, but that was a place where we worked hard and laughed all the time and it was just like Allen & Hanburys was in the very early days. Some funny names, I can't remember any of them, but we ended up as 'Theravance' which was probably a play on therapeutic advance. So that became 'Theravance'. But anyway, when I joined Advanced Medicine, which became Theravance, now this was another interesting thing. The company was about 200 fold when I arrived, 190 of them were in research and I was Head of Research. And they decided, they'd just lost their CEO, and they asked all the people in the company, 'which do you want first, a CEO or Head of Research?'

They said they wanted a Head of Research. So I turn up and I didn't know that the old CEO had just left, so I'm sort of CEO and Head of Research, but only for about a month I think or two months, three months. But Roy Vagelos was saying to me, 'Should we be in respiratory, Pat? Do we need a β2 agonist?' 'Roy, we need a β2 agonist.' Three days later he'd ring me up, 'Do we need a β2 agonist?' 'Yes, Roy, we need a β2 agonist' [laughter]. And the argument was that we'd gone through salbutamol, which was a brilliant drug, short acting. We then went onto serevent, which was salmeterol, that stops you waking up in the middle of the night with bronchoconstriction, 12 hours max. But the thing is, obviously subsequently the world finds out you really must have a background of a steroid, an inhaled steroid, which is now the drug of choice, so it's superseded a β2 agonist, but for safety reasons you need the steroid. So you had 12 hour. So Advair, which was Glaxo's biggest drug, was of course a 12 hour β agonist and a 12-hour steroid. But now you've got 24 hour steroids, one dose will last for 24 hours by inhalation. So you need a 24 hour β2 agonist. And a lot of people, even pharmacologists, theoretical pharmacologists, were saying, 'Well, it can't sit on the receptor all that time, it'll cause desensitisation, it won't work.' We very quickly found one that did work. And then we did a deal with Glaxo, which was a very interesting deal, which I probably can't even now say too much about, but basically we pooled our β agonists and we said we'll go with your steroid and we ended up with a perfect compound and again, I've got a paper cutting where they were saying, 'How is it that Theravance is getting $500 million and promises of millions, millions more when the guy who is running the company in research has just left GSK?' Because we did this, the deal was with GSK. So I suppose if I did anything, that changed Theravance, it's now a phenomenal company, it's still got phenomenal people in it and it's going places.

TT: And you came back to the UK and by this stage you've left being directly involved in research?

PH: It's sort of a difficult thing really, I didn't really know whether I should continue, but I'd said I was going to go from pharmacology to ornithology and study my love of birds. And I see my bird surveys for the BTO, which is the British Trust for Ornithology, as my new labs, the fields. And it's analytical and it's numerical and so I'm pretty happy with doing that. But on the other hand I keep being asked by people about this, that or the other, and you realise you do know quite a lot about pharmacology. At first I was a bit reticent

because I'm not as close to science as I was, I'm not in the lab anymore, but I just find that still people, even really clever people, don't always seem to know what they're doing. I found that at Theravance even, these bright young people who are terrific, unbelievably good, but because they didn't have the experience they didn't always know quite what to do. There were people there from Oxbridge, there were Canadians, people from Harvard, there were people from all the Californian universities, Berkeley, all that sort of thing, really, really clever, but when I went there all of them, to a man, or a woman - because there were quite a few ladies there - said, 'What are we going to do?'

It was just like Allen & Hanburys again, 'What are we going to do?' I said, 'The first thing we're going to do is pick the right projects, because if we pick the wrong projects, five years down the road, we're going to find out it was the wrong project, we're going to come back again and we won't have a company by then.' And I still just tell people what they should be doing and leave them to do it [laughs].

TT: We've run through your career, Pat, but there's one thing we talked about to begin with, before I switched the recorder on, and that is this question of recognition. It always shocks me when I come across fabulous people who have done amazing things and they're not known, they're not really recognised. Yes, you've got an OBE, you've got the Royal Society medal, you got a Queen's Award, but not the Nobel, not even an FRS.

PH: A lot of people say, 'Have you not?'

TT: That's astonishing. Have you ever been put up for the RS, do you know?

PH: I was. You can have the long story or the short story, but I was. Alan Cuthbert, David Jack, with support from John Vane and James Black, they put me up and I remember Alan saying, 'Well, you're going to be hanging there' or whatever they call it, but he said, 'you shouldn't be disappointed if you don't get it.' I think that was not that he didn't think I was going to get it, because all the other things that he said implied that I probably would. I have analysed it, because it would have been nice [laughs].

TT: And entirely appropriate.

PH: And David Jack certainly thought so, so supportive and so disappointed that I didn't get it, but anyway, one of the things is I never, well, at the beginning my only raison d'être for doing anything was sort of altruistic, coming back to this medical thing about wanting to do things for people. So I never worried too much about publications. And it was only later that I realised that if you don't publish, nobody knows who you are, and if they don't know who you are, they're not going to come and talk to you, you're not going to learn things. So I thought, 'I should start publishing.' And I think of three, what I think are really seminal papers, all sent to *Nature* and all refused. It was sort of bad luck having the wrong people refereeing it at the time, I think. The one that really, really does hang a little bit in my mind is the sumatriptan story. I wrote a paper, *Nature* style, and it should have been accepted. And of the two referees, one of them said it was outstanding, and one of them said, 'Load of rubbish, this is just another ergotamine.' Now, I'm pretty sure I know who it is, and I know it's a competitor, and I also know it's somebody who doesn't really understand the pharmacology, because it is complex. I think I did complain but they said, 'Well, if we get a referee who doesn't like it, our policy at the moment is just to reject it.' So I think if that had gone in and then I was hanging in the whatever at the Royal Society, with a *Nature* paper on sumatriptan, that probably would have been the difference, I suspect.

TT: Well, these things do happen and some excellent people don't get in, and it's like any of these kind of things, some people who don't deserve them, get them, and some people who do, don't.

PH: Precisely. So the second paper was the prostaglandin receptor paper, and that was Bob Coleman and Ian Kennedy and myself, and another one of our close colleagues, Phil Lumley. I think it was brilliant, it was so incisive, nobody had ever even thought it, and we gave all these receptors, we had all the receptors sorted out, all from tissue bath work. We gave them all names, and everything has come right with the molecular

biology. They've had to use our terminologies and we even point out to them when they got the molecular biology wrong, because we'd already worked out the functionality of it. And so that was probably a brilliant paper and that was rejected.

TT: Where did you publish it?

PH: That was published in bits of *British Journal of Pharmacology*, and it didn't get into any higher level things anywhere near equivalent to *Nature*. By the way, I could have published the 5-HT classification stuff all on my own, but I told you that there were two things: one is I didn't want to give away the company secrets in the very early days, and secondly, I could see it was moving at a pace and I didn't really want to publish stuff that wasn't right. There was so much information from other people over the world, so I took the diplomacy route and invited colleagues from all over the world, and to me again maybe that's a slightly altruistic perspective, but that's what I took.

TT: It's also highly ethical, I think, in many ways.

PH: Yes, well I'd like to think…

TT: It's an old fashioned scientist way which perhaps nowadays people wouldn't take, they'd be scrabbling to the top.

PH: Precisely, precisely. And then the third one was, we were the first people in the world to have a really good thromboxane antagonist that would go into man, did go into man. It went into a lot of different indications. And I wrote again a *Nature* paper and it sat on David Jack's desk for at least a year. I didn't really mind because again, why was I there? I was just, we wanted to find out if a drug was a drug, and could bear a little bit of frustration or not. I didn't bear any ill will towards David. But anyway by the time he agreed with the publication, somebody published on a really weak compound that wasn't anywhere near as good as ours, and so *Nature* rejected it on the basis, well, somebody else has got a thromboxane antagonist already. So those are three papers which would all have made superb *Nature* papers and my CV would look somewhat different with those [laughs].

TT: The other thing I wanted to ask you was about relationships wherever you have been, because you've been an academic, you've been in a drug company, you've dealt very closely with clinicians. You talked about going to see Marcia Wilkinson. Would a lot of pharmacologists have gone and talked to the clinicians?

PH: Not as it was in those days, because it wasn't like going to a meeting. I made the approach. But today the world is a bit different, I think you've got lots of clinical meetings, medical meetings that scientists do go along to, and I think they actually cultivate the medics these days with a view, not necessarily very altruistic, but just to get people on board with their approach and their drug, and maybe do their trial for them.

TT: One of the other strands of this grant is clinical genetics and I have had a number of people, particularly if they're clinicians, tell me for example, about meeting young postdocs or young lecturers who were working on such and such a receptor, but have never met a patient with the condition. I was just wondering if there were some parallels?

PH: Well, I don't know. Well, I think again you've got to want to do it. I think the reason I've been successful in drug discovery is because I was interested in medicine, I was interested in physiology. Pharmacology should always involve physiology and when I was taught pharmacology it did. But now, it's molecular, molecular, molecular. So medicine, physiology, pharmacology in the old fashioned sense, are absolutely critical, and if you want to discover a drug, chemistry, medicinal chemistry is critical too. But I haven't mentioned pharmacy. I'm on the board at the moment of Verona Pharma and I've been involved in getting the medicine into the right formulation, because if you can't give it, it's no good as a medicine, particularly with inhaled medicines, it's a real art in itself. So I think I'm very fortunate to have that background,

medicine, physiology, pharmacology, medicinal chemistry and pharmacy, and I think they're all critical. And I didn't learn them because I just wanted to learn them, I sort of picked them all up because I was interested in medicine in the first place, so the umbrella is medicine.

TT: Thank you so much Pat for sharing so many memories.

[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. Overy C, Tansey E M (eds) (2014) *Migraine: Diagnosis, treatment and understanding c.1960-2010*. Wellcome Witnesses to Contemporary Medicine, vol. 49. London: Queen Mary, University of London.
3. Tansey E M (intvr); Tansey E M, Zarros A (eds) (2016) *Humphrey, Patrick: transcript of a video interview (08-Feb-2016)*. History of Modern Biomedicine Interviews (Digital Collection), item e2016021. London: Queen Mary University of London.