

VIDEO INTERVIEW TRANSCRIPT

Humphrey, Patrick: transcript of a video interview (08-Feb-2016)

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Humphrey, Patrick: transcript of a video 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.

[1]. BECOMING A PHARMACOLOGIST: THE SCHOOL OF PHARMACY AND ST. MARY'S

Well, I think as we were talking earlier, I always, from quite a young age, was very interested in medicine and did want to pursue a career in medicine. But, on the other hand, because of various things that happened in my life, moving schools and so on, I ended up in pharmacy and I was incredibly lucky. I can't say how incredibly lucky I was to go to the School of Pharmacy in the University of London, which at the time was considered to be the best pharmacy school in the world. And it was called 'The Square'. Often you saw in papers 'The Square', that was enough to say where it came from. And there we had an incredible Pharmacology Department that was very medically orientated. Our pharmacology was taught on the basis of how drugs worked in patients but it was also very mechanistic because we had Bowman, Rand and West here, three very, very famous pharmacologists. And I'm indebted to them for really inspiring me to do that, to carry on, you know, pursuing a career in pharmacology.

But to me it was still medicine because of this fact that pharmacologists find drugs that make people better and improve their lives radically, even save lives. Interestingly at the time I was there, I went to the School of Pharmacy in '65, I joined them, and we were being taught very much about iatrogenic diseases where, you know, people were ending up in hospital because doctors had prescribed the wrong drug or the wrong dose or whatever. And this again made me very aware that people needed to understand how drugs worked. And later on it became very obvious to me that if you know how they work you can make even better drugs, and that's really what I've pursued the whole of my working life.

* 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.

Well, you know, I was very lucky that when I left the School of Pharmacy, I went to do a PhD at St. Mary's Hospital Medical School. And I was very lucky because Professor Richard Creese had actually gone to The Square and asked if they could have one of their good pharmacology students to come and do a PhD with him, because he was very interested in dose-response curves and the more mathematical side of pharmacology. And the great benefit for me was not just working with him but I learnt some electrophysiology, but I also had to do teaching as a demonstrator, and I learnt a massive amount of medical physiology teaching medical students, which was very inspiring. And again we even injected the students with drugs and saw drug effects *in vivo*, in a live human being. And that I thought was tremendous. And then I was lucky enough to be invited to become a Lecturer in the Medical School, in Physiology, but I decided that wasn't a very good career end, if that was where I was going to end, because I really felt I wanted to discover a drug. I really had that passion.

[2]. ALLEN & HANBURYS: THE BEGINNING OF MIGRAINE RESEARCH

I was so incredibly fortunate, I think I've had many occasions where I've been just tremendously lucky. But again I was somewhat headhunted because David Jack at Allen & Hanburys had a daughter who had migraine. He believed in finding drugs for common diseases that were poorly treated, and so he wanted somebody to come along and find an anti-migraine drug. And what an opportunity.

When I arrived there was nobody there. I was given an empty lab and shown through the door, 'That's your lab.' And there was a young lady, Eira Apperley, a young graduate sitting rather forlornly on a chair saying, 'What are we going to do?' Quite a few people said that to me over the years, 'What are we going to do?' And I quite enjoyed working out what we are going to do. I said, 'The first thing we are going to do is find out about migraine, understand the disease.' 'How are we going to do that then?' 'Oh, right, we'll go and talk to some doctors who treat it.' And so we did actually contact a number of clinicians who were treating migraine. I think the most notable for me in the first instance in this country was we went to the City Migraine Clinic that Marcia Wilkinson was running. There they were doing a great job for individual patients in London who were probably working in the City, have a terrible migraine attack that comes on when they're working, and they arrange for a taxi to bring them into the clinic and they did their best for them. But it was pretty clear there weren't many particularly good drugs, mainly bed rest and a dark room was the sort of thing that helped enormously, but obviously this could go on, they could be in bed for 24 hours even. But the one thing that Marcia did actually convince me was that ergotamine was used and it did work. She didn't like using it because it had lots of side effects, but it did work and that was one of the sort of seminal sort of clues we had in starting the migraine project at Ware.

[3]. MIGRAINE MEDICATION: THE DISCOVERY OF SUMATRIPTAN

So I mean thinking about my achievements, one of my proudest, I think it has to be the migraine one. And, in many ways, that's what people know me for. I was given the task of finding an anti-migraine drug, no clues, get on with it. So from nothing, I did discover this drug. I led a tremendous team. I think I did discover it because it was my idea but it could never have been done without a tremendous team that included particularly I've mentioned, Wasył Feniuk, a close colleague of mine. I recruited him about four years into the project and he made tremendous contributions. And many others. But I won't elaborate on that. But also chemists, the chemists were fantastic. Some of the clinicians I worked with, we'd never have discovered that drug without the team but I still feel that it was my baby, my idea without a doubt. And then along the road were a number of issues. We found one drug that actually didn't do what I'd predicted on the basis of my hypothesis and we had to go away and think again, and that was really because there were so many 5-HT [5-hydroxy-tryptamine] receptor types that we hadn't appreciated, what we were discovering along the way. And then I think later on there were safety issues, worries about the drug being a vasoconstrictor and what other blood vessels might it constrict other than those that were involved in the migraine aetiology. And you know in many ways, I remember when the drug came on the market, people said, 'You must be very, very pleased with yourself,' and I said, 'I will be in five years' time.' Five years' time people said, 'Oh, you must be very pleased with yourself.' And I said, 'I will be in another five years' time.' And I must admit I got really euphoric 10 years after it had been on the market, because I think many of the safety issues had

passed by and I think the drug was being used sensibly in the right patients and I still get letters from patients, even my wife kisses me every morning because her migraine's a lot better than it ever was and so on and so on. So I'm very pleased with what I achieved.

[4]. SUMATRIPTAN: SAFETY ISSUES

Okay, so I think it's worth saying a little bit more about the safety issues and what they were because when we first had the drug we weren't sure about the dose and the question of route of administration and in the very early days the drug was 'sumatriptan', as it was called chemically, and later on it got the trade name 'Imigran', and 'Imitrex' in America. But the safety issues were such that in the very early studies a lady had a cardiac event when she was given the drug intravenously, and I remember debating this with the clinical people and Sir David Jack. And obviously this was disturbing but we realised that by giving the drug intravenously, that a bolus dose was being injected and the concentration, the local concentration at the receptor and at other sites, would have been much higher than you would anticipate if the drug was given by a more normal means. But we didn't want to just say, 'Theoretically it would be better if we give it by a lower dose or a different route,' we actually started studying every patient, measuring ECGs [electrocardiograms] and I actually came up with a proposal that we should get some human coronary arteries. And at that time it was very difficult to get human coronary arteries in England so we decided that we would liaise with an American clinician who could actually get human coronary arteries very fresh and we could do the study on.

And I had another young postdoc working with us, Helen Connor, who just joined the team and I said, 'Oh, by the way Helen, you don't mind going to America, do you?' And she did, she was very worried about going to America but she was very brave and we gave her all the support we could. She went out and did some studies on human coronary arteries and we found that there were small constrictions to sumatriptan but they were very small compared to 5-HT. So in other words, 5-HT constricts human coronary arteries massively through the common 5-HT₂ receptor but our new receptor, the 5-HT_{1B} had only a minimal effect. And later on studies were actually done in humans who volunteered to have sumatriptan injected into them and then they, the clinician actually measured the coronary artery diameter. And again the diameter was reduced by up to 14% in some individuals but that's the sort of level you would get far in excess of that even if you were exercising very heavily. So I think there is an issue and it's always been a contraindication not to give this drug to people who are cardiovascularly compromised. But now I think the drug, I mean I've spent 10 years of my life trying to show that the drug was safe and probably that's when I started smiling when I felt it was safe [when used properly], and now it's actually available over the counter in Britain, so I think that says something about the safety issues.

[5]. GLAXO RESEARCH GROUP AT CAMBRIDGE

So thinking about things I might have regretted. I don't think there are any because I've been very fortunate that when things had come to a sort of, not exactly a grinding halt, but less than satisfactory, I've been able to move on. So for instance, Allen & Hanburys, they were 20 fantastic years, I had fantastic colleagues, we were incredibly successful, at least four blockbuster drugs, lots of ideas. But I think that slowly but surely big pharma became big pharma, it got bigger and bigger, more and more corporate, more and more political, and I was really quite keen to get back to the bench and start thinking about new ideas. And I was very, very lucky that the new CEO, Richard Sykes, could see what I really felt and he was prepared to fund me to go and do some new things in another location. And it was fortunate that we found Cambridge University had a floor that they were prepared to vacate in their Department of Pharmacology to allow a drug company to come in, and Richard Sykes put significant money in and he said, 'Off you go, you can take 10-15 people with you and get on with it.' So I actually only took 5 but they were 5 fantastic people, in particular Wasyl Feniuk, such a close colleague of mine and worked with for many years already, and Anton Michel, both brilliant pharmacologists who well, I can't speak too highly of them.

And the three of us really led a group of about 30 people, postdocs, PhDs and all of them went on to do great things themselves. They learnt a huge amount about pharmacology, which I think is the biggest thing

that I was able to give people and one of the major benefits of the programme, although we did do lots of good research. We had ideas that could have been prosecuted but I think it was quite difficult working in an academic department to transfer these ideas into you know a big organisation that was already following down its own path. But I think the money was incredibly well spent and I think in many ways we did continue to show the importance of pharmacology in drug discovery which is really indisputable. And I think you know people very obsessed with genetics and molecular biology today, but I think people at last have seen the light that you cannot throw out pharmacology, it's always going to underpin drug discovery.

[6]. GLAXO RESEARCH GROUP IN CAMBRIDGE: SOMATOSTATIN AND ATP RECEPTORS

The second achievement, of which I am very proud too, I went to Cambridge in the Department of Pharmacology with some of my colleagues and started up a research group that was looking for fundamental new ideas for the company. I was fortunate that Richard Sykes had this idea that I might start up this group and he was prepared to put in at least £10 million into the effort and I was very pleased that Alan Cuthbert, who was the Professor of Pharmacology, was very keen to get some industrial people into his Department. And in fact he gave us a whole floor within the Department and we just got on with things and we had some amazing projects. I just took five people from Glaxo and we didn't need more, because the whole idea was we would get PhD students and postdocs in who would provide the lab work and the new ideas and everything else. And we set about some fundamental research which we hoped would lead us into new drugs. And in fact one of the areas we chose was somatostatin, which I think is still a very intriguing area but it's been chemically very difficult to master really. But the other area was ATP [adenosine triphosphate] receptors. They'd barely been thought of at the time. And we did some pioneering pharmacology which led us to a whole lot of ideas about how ATP antagonists might be beneficial in a variety of diseases. And more recently, I've actually been working with a company called 'Afferent Pharmaceuticals', who are actually pioneering some of the work we would have liked to have done at Glaxo. But I think it was quite difficult really working at Cambridge to come up with ideas and then transplant them into the bigger company, which already had its own projects and was not overly receptive.

So in a sense we had exciting times, we published lots of important papers. All the PhD students did terrific projects, I had some great postdocs. And we had a great time but we didn't actually discover drugs for Glaxo, which was probably would have been the ideal scenario. But what we did do was train some phenomenal people and these people have gone on to be Vice Presidents in a whole variety of companies, and in fact one of them is actually a very eminent Professor in UCLA [University of California, Los Angeles] in California at the moment doing some terrific electrophysiology.

[7]. 5-HT RECEPTORS

So one of the other things that I'm very proud about that I think I achieved during my career was to focus on receptor characterisation and classification, what Sir James Black called 'taxonomy', 'receptor taxonomy'. I think it's absolutely critical and clearly biologists long ago realised how critical it was, it even goes back to Linnaeus when he came up with a classification for plants and animals. And as somebody who is now studying ornithology, I'm aware how important it is that what you call a bird can be very confusing if you go from country to country, and I think it was exactly the same in the laboratories at one stage.

So for instance we cut our teeth in pharmacology on receptor classification with 5-HT receptors because when we started working on sumatriptan we only knew of two 5-HT receptors. At the time they were called 'M' and 'D', and later we reclassified them into '5-HT₃' and '5-HT₂'. But as it turned out there are at least 14 receptors or thereabouts for 5-HT and one of the problems when we were working on the sumatriptan project was my original hypothesis kept changing simply because we kept finding more and more receptor types, and it was quite confusing as things went on simply because different people were giving these new receptors different names. Fortunately, the ones we were interested in in relation to sumatriptan we discovered ourselves so we didn't have to worry about other people's names but talking about it in the scientific fraternity worldwide was quite a problem at times and that's why I was very keen to get people together and agree on some proper nomenclature that would stand the test of time. And that's really what

happened through the workings of IUPHAR [International Union of Pharmacology] and the receptor nomenclature group that I and others set up.

But in relation to the 5-HT receptor classification the other thing that is very pleasing is that, despite the problems we had as new receptors grew up in the project, we managed to keep our team together and the enthusiasm that, 'Okay, Pat's original hypothesis was wrong but we'll get there in the end' and we actually did. And I'm very proud that David Jack always said that this was a detective story of quite some significance and that he'd never seen anything quite like it. So I was pleased with that. But in terms of nomenclature, we did go on and do a lot of work in other areas so a group of us in pharmacology at Ware also worked very thoroughly and dedicatedly on trying to work out prostaglandin receptor classification, and we did publish a nomenclature very early on before any of the receptors were identified by molecular means, and it turned out we got them all right based on function, which again shows that structure's important, but function's important too, and you can classify things just as readily through that means. And subsequently many, many other receptor classification projects were set up under the auspices of IUPHAR, you know I was there in the beginning of all, of that wave of activity which has turned out to be incredibly important and will, I think, continue to go on now because it's imperative that we have proper nomenclature, proper names and proper agreement in terms of what differentiates one receptor from another.

[8]. 5-HT RECEPTORS: THE HERON ISLAND MEETING

So I think one of the seminal activities in starting up the 5-HT classification studies worldwide was definitely the Heron Island meeting in 1987, I would say. The Serotonin Club had been started by Paul Vanhoutte in 1986 and him and I talked a lot about classification and he was very keen on it and wanted to support it. In fact Paul found a lot of money to subsidise the Heron Island meeting but equally Glaxo Australia put quite a lot in because they knew obviously that we were about to launch sumatriptan in the not too distant future, and so that was the sort of means, the funding. Ewan Mylecharane was a prime mover in organising the meeting and asked me to help. And I said, 'Well, I don't mind as long as it's somewhere decent.' And he said, 'Is Heron Island decent?' I said, 'Right, you're on, I'm helping you.' So off we went and it was a very exciting meeting. We had a tremendous opportunity to go snorkelling and fishing and all those sorts of things but I can tell you that during the meeting periods everybody was in there because it was just one of those meetings where it was buzzing and everybody wanted to know how many 5-HT receptors there were and whether the name they'd given to their pet 5-HT receptor was the right one and, I mean it was just an amazing meeting. It was well organised and I think the climax in terms of classification was the round table discussion where everybody in the conference was involved and I and Brian Richardson chaired it, and everybody had their six pennyworth and in the end Brian and I wrote something up together.

And the whole point of that was that I wanted everybody to be involved, everybody to feel part of a scientific fraternity worldwide where they could have their views expressed. And you know some people were not totally happy with the outcome, I know Michael Gershon, who is a good friend of mine, I love him dearly but he was very upset that his 5-HT_{1P} receptor was not allowed, and it still isn't allowed so maybe we got it right? I don't know but we'll have to see. And it was rather funny that evening everybody was still very high and got in the bar and people were having a drink and then somebody decided they wanted to take a photograph of some of the key players and everybody had to put their hands up with how many receptors they thought there would eventually be. And so we all had to, right, now you go, and I put my hand up and I only had one finger up, some people had 10 up. And what I really meant was one finger meant we found the receptor that is going to provide a drug, and it's sumatriptan! So that was funny. Another thing that wasn't quite so funny was when we were leaving, we had three big boats, massive big launches to take us back to catch our planes. We had to cross the Coral Sea. And the one I was in with my wife and other people broke down. There we were in the middle of the Coral Sea. I can't really claim there were white sharks circling around but it was quite eerie being in this boat that was not going to go anywhere. So they had to get lots and lots of small boats to get us back to the island and then we had to have helicopters to take us to the airport before we missed our planes. That was all good fun, but a lot of people will remember that as well. But it was quite a meeting. I think it was very successful scientifically and it was great fun, and something I don't think anybody who was there will ever forget.

[9]. THERAVANCE

Theravance was a start-up company, a biotech company in California, they had lots of money, they had lots of really good people there but they needed a new Head of Research. And they got in touch with me and as it happened I was searching the world myself, because the Glaxo funding had run out after 10 years and I was looking for one more opportunity to discover another drug. And I was called over by the Chairman of the Board of Theravance, who turned out to be Roy Vagelos who is a very famous, incredibly famous, man in his own right as a scientist having discovered a number of things and also having been CEO of Merck.

And when I arrived I was so excited to find that Roy Vagelos was what I called 'an American David Jack', because he was very altruistic, very driven, very able, very knowledgeable and knew what was required to turn a lab idea into a medicine. Because I think a lot of people are pretty good at finding out new ideas, very few people are able to go the whole way and turn it into a medicine. And so I was so pleased to go out there and work there and I was not disappointed. In fact, for me it was just like going back to Allen & Hanburys except that it was in America, in California, which can't be bad either. They've got more sun and the light there and the sky there is always blue so the trouble is, if you're a scientist you want to be in the lab all the time so it didn't make that much difference except for the weekend.

[10]. REFLECTIONS ON A CAREER

Okay, so thinking about the changes to my career. I think my career has changed for a variety of reasons that I can describe and I think it's equally interesting to reflect on how the world had changed in relation to medicine and drug discovery. I think again I just consider myself incredibly lucky because from a very young age I was always very keen on the idea of becoming a doctor and medicine was important. But equally I was also very interested in mathematics, I was interested in zoology and a particularly keen bird watcher from about the age of 5. But having gone to a multiplicity of schools, because my father moved around in the Royal Air Force, I didn't manage to get into medicine at first try, and so I ended up doing an apprenticeship in pharmacy and I think I was incredibly lucky.

So the apprenticeship at Boots allowed me to get a place at The Square in London, which was an incredible opportunity and there I was able to learn not just about, more about dispensing and making medicines but particularly medicinal chemistry and pharmacology, which were absolutely critical to drug discovery. And not only that but we had such a Department of Pharmacology, many of them medically qualified, that we learned about you know the physiology, medical physiology and all these things were actually critical to understanding, and how one might go about making a drug. But then to have the opportunity to do a PhD in a Physiology Department and teach medical physiology was absolutely critical. So you know I went out into the world to discover a drug, equipped with a pharmacy background, medicinal chemistry background, particularly a pharmacology background, but I can't speak too highly of the medical physiology component.

And I remember when I went to Ware I thought the labs were good, you know, lots of good scientists around but I said to the Head of Department, Roy Brittain at the time, I said, 'This is a great place, but the only thing that's missing is a hospital.' But little by little, I think, we did actually recruit quite a lot of good medical people into the company and we had a tremendous volunteer panel there where a lot of experiments were done in volunteers like ourselves, and that sort of was linked in very much when I was teaching myself medical physiology to medical students, where again we actually did studies in human beings. That's very illuminating in terms of trying to understand how drugs work. So I think that was the starting point for me but then having discovered the drug sumatriptan with a fantastic team at Ware, in parallel there were many other projects going on that I was either involved in or partly, or understood, or was heading up in terms of development committees, and there the ability to learn about how to make drugs was you know inculcated into me. I could go on forever now thinking about how one designs drugs and I've had the opportunity to lead projects in a number of places since.

[11]. CHANGES WITHIN THE PHARMACEUTICAL INDUSTRY

So in parallel with what I've been talking about with my own career, there were massive changes within the industry. Some of them were very good, I think. I think a lot of lessons have been learnt over the years about how to make safer and safer drugs, and how to try to negate any potential risks. And I think there's a lot of refinement in chemistry and many other aspects of drug design and making and production, but I think there have been changes now, slowly but surely I think genetics have come in in a big way, and I think that's good because I think that allows one to be able to select patients more effectively for clinical trials and it may end up that the promise that is dangled in front of us, of designer drugs for individual patients, may come along one day, and I think this is a path we have to go down. I think molecular biology has turned out to be an invaluable tool. I think to some extent though it has been problematic because in the industry pharmacologists were let go and molecular biologists were brought in instead, and that's led to a loss of knowledge about functional pharmacology. And I think this is regrettable because molecular biologists don't really understand the medical physiology and other aspects that are so critical to drug design. But I think where molecular biology has really, really come into its own is being able to identify specific receptors in tissues and so we've got better ideas about distribution and specifics of the receptors. And in fact there are now some very nice computerised design of drugs becoming possible because we know so much about the receptor structure and this allows better chemical design. So I think there's, I think we've just got to continue to develop all these new techniques but equally I think it's very, very important that pharmacology is not lost because pharmacology overpins all these things. Pharmacology is about understanding how drugs work, and if you know how drugs work you are better able to make even better drugs in the future.

[12]. PHARMACOLOGY IN THE FUTURE

So, where do I see pharmacology in 30 or 40 years? Well, I hope that pharmacology is still a predominantly recognised discipline. I think because of funding problems and some of the issues that I've just talked about the danger is that pharmacology will be assumed into other disciplines under some generalised title like 'biosciences' or whatever. This is potentially a problem if we forget all the basics of pharmacology. So just to remind you, pharmacology is really about understanding how drugs work, so we have to understand the receptors, so molecular biology can teach us about this. But we also have to understand the functionality, which is very important. And functionality means understanding the pharmacodynamics; i.e. the doses, and routes of administration and everything else, and the accessibility to the receptor site. But it's also how it correlates with pharmacokinetics, that's understanding what the concentrations of drugs are in various parts of the body. Again this is really part of pharmacology. And then pharmacology is really going all the way from a receptor, through animals, through to humans and I think all these things are going to be, continue to be critical even in 40 years' time. So let's hope that pharmacology is still there and I think it's up to the various societies around the world to really show how imperative and how critical pharmacology is to all of us who are involved in drug design and development.

[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 an audio interview (08-Feb-2016)*. History of Modern Biomedicine Interviews (Digital Collection), item e2016020. London: Queen Mary University of London.