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VIDEO INTERVIEW TRANSCRIPT

Sanger, Gareth: transcript of a video interview (08-Dec-2016)

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Sanger, Gareth: transcript of a video interview (08-Dec-2016)*

Biography: Professor Gareth Sanger BSc PhD DSc FBPhS FRSB (b. 1953) received his BSc and PhD degrees in physiology from the Universities of Newcastle and Manchester (1974 and 1977), later returning to Manchester to be awarded his DSc in 1998. He worked as a postdoctoral fellow at King's College Hospital Medical School, London, where he was among the first to examine the functions of some of the newly discovered prostanoids on the human isolated gut. A move to industrial research led to his identification of a novel serotonin (5-HT) receptor-mediated function in the gut, later named by others as the 5-HT_4 receptor. Parallel research led to the identification of the role of the 5-HT_3 receptor in the mechanisms of emesis and to new drugs to treat severe emesis, for which he was jointly awarded the 1998 Discoverers Award by the Pharmaceutical Research and Manufacturers of America (PhRMA). Within industry he held various roles within the "discovery science" arm of the business, exploring multiple research areas and new drug targets, placing several novel compounds into development. In 2008 he was elected Fellow of the British Pharmacological Society (FBPhS), and in 2009 he joined Queen Mary, University of London as Professor of Neuropharmacology. He was elected Fellow of the Royal Society of Biology (FRSB) in 2013. His research focus is on the use of human gastrointestinal tissues for translational neuropharmacology, the consequences and mechanisms of advanced age on human bowel functions and on the mechanisms of disordered gastric movements during nausea. His first paper after establishing this new laboratory won a "highly commended" award from NC3Rs (National Centre for the Replacement, Refinement & Reduction of Animals in Research) for promoting a culture shift in the use of human tissues for functional research. He has published more than 150 peer-reviewed manuscripts, served on editorial boards, teaches on BSc, MSc and MBBS courses and sits on advisory boards for gastrointestinal (GI) research within the pharmaceutical industry.

[1]. A CHILD BY THE COAST; STUDYING MARINE ZOOLOGY AT NEWCASTLE

I had no intention of being a scientist. I just enjoyed life with a very open, simple, probably uncritical, unfocused mind. I lived in the country as a boy, it meant that I didn't really associate with all my friends who lived in town, and did things that teenagers do, and I couldn't, because we lived so far away. It meant that I spent my life with a great friend, mostly on the beach, fishing, swimming, always there. And I guess that helped nurture my enjoyment of beach life. I did biology projects on mussel beds, and one thing led to another I guess, and I wanted to continue enjoying that, hence an application to Newcastle University to study zoology, chosen in part because they had a great marine biology station and I thought, 'That will be fun.' I could imagine myself researching and understanding marine life, went to Newcastle, felt liberated because I no longer had to do subjects at A level like physics, which I couldn't do very well. And yes, there was a pleasure in learning; there was a liberation. Loved zoology, loved the discovery of the coelacanth at the time, the fossil now alive. It was a great time. But I had to do other courses. I had to do physical sciences, which I didn't really enjoy, and I had to pick another subject, chose physiology, which at school I'd never heard of before. By the end of the year realised I loved zoology, but kind of didn't know where that would go. But a feeling inside me told me that physiology was a bit more hardcore science, a bit more directed and might lead to different and better things. And I had no idea what that meant.

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

[2]. FROM ZOOLOGY TO PHYSIOLOGY, STUDYING THE GASTROINTESTINAL SYSTEM

So at the end of my first year at university, I loved the zoology but there was a feeling inside me that thought, 'I'd like that as a hobby. I don't quite see what I can do with it.' Whereas physiology spoke to me in some sort of way, maybe more hardcore science, maybe more of a clearer direction, I wasn't sure. Went to see my then zoology tutor, Dr Panshen who said, 'Look, whatever you choose will be right, because you'll never know what you gave up.' The wisest advice I've probably ever received, and I've said it to many people since. So I went to physiology, which I'd never heard of at school, no idea what that was. And spent a couple of enjoyable years with a small group, I think there were about seven of us doing the degree, so it was very close. We all became great friends and ended up with our degrees. It was a University Department that specialised a lot in gastrointestinal science.

Professor Harper used to run it, he was a joint discoverer of cholecystokinin. He retired, Professor Eric Blair took over, he did a lot of work on gastric secretion, and a lot of colleagues were there doing that, so my student project was on gastric secretion in anaesthetised cats, which you'd never do again. And I guess it became by default a career path for me to stay in GI. I was lucky enough to spot a PhD-student vacancy in Manchester, so without any planning, without any thought, I applied and I was lucky to be accepted, and there I was in Manchester.

[3]. BECOMING A PHARMACOLOGIST: PROSTAGLANDIN RESEARCH AT KING'S COLLEGE LONDON

So the PhD in my view was ordinary, and by the end of that I believed I needed training. I'd picked up papers by Alan Bennett, then in King's College Hospital, Surgery Department there, who wrote papers that kind of spoke to me as well. They were good papers, but they seemed to push the science a little bit forward in a place that I thought was creative, and I liked that for some reason. So I went down and saw Alan. We talked and a little later, and I said, 'Is there a possibility of working with you?' And he eventually came back to me and said, 'Yes, I can put the money together on provision you get your PhD first.' So I then promptly made him my external examiner, and got the PhD, and joined Alan. Of course my degree was physiology, my PhD was in the Physiology Department, but I was doing pharmacology. I was doing ligand receptor interaction studies in effect. Alan was a pharmacist but PhD pharmacology, and effectively trained me. So I would come into work and you had to walk past his office to get past the lab, and I eventually learnt to kind of creep by his office a little bit because once he realised I didn't know pharmacology and I needed training. So he would start leaping out of his office and saying, 'Define me a pA_2.' And the first time I thought, 'pA_2, what on earth is that?' So I screwed that up completely. And this would go on until eventually I could define a pA_2 verbatim; I'd learnt it. I knew a pA_2. Then he'd move onto pD_2, and eventually I kind of learnt. He would, which is no different to my father, going down to breakfast he'd say, 'What's six 8s?' '48.' I'd know that so well.

[4]. BECOMING A PHARMACOLOGIST: THE BRITISH PHARMACOLOGICAL SOCIETY

So, eventually, he would get me to prepare a talk, ten minute talk, for the British Pharmacological Society and I would prepare the talk. I would start off and I'd get about three words through and he'd say, 'No, no! What do you want to try and say?' We'd go through that. 'What you want to say is this. That's your first line. Learn your first line, get accustomed to where you are.' So right, you'd learnt your first line. I'd start my first line, I'd probably get through about three quarters of the way - 'No, no, no! Stop that. You should have done that, go back and do it again.' I'd get through the first line, I'd be on the second, 'No, no, no, you've got that wrong. Go back, do it again.' Third line, 'Go back, do it again. Stop waving your arms about, you're distracting me. Hold your arms like this. Go back and do it again. No, use your pointer properly. Point on, off, like that. Go back, do it again.'

But to cut it short, and it wasn't short, we would be rehearsing that ten minute talk for the vast proportion of that day, by which time I knew it worked perfectly. I knew when to wave my arms and when not to wave

them. I knew when to use the pointer, I'd learnt my first sentence, I'd learnt to say, 'Mr Chairman, ladies and gentlemen,' I'd learnt to say 'Thank you,' I'd learnt everything and it took most of the day on the first one. The subsequent ones we did were less, but we still had to rehearse it, and I still do the same to my students. So Alan taught me a lot, he took me demonstrating, he took me on consultancy where I sat like a little boy. And, eventually, made the right contacts for me to move onto the next job. So yes, good. Alan was good.

[5]. SATISFACTIONS OF PHARMACOLOGY: JOB CREATION, AND GRATITUDE

You asked me about greatest achievements, and there were loads in life, but within work, there are lots. I'm reminded of a quote by Winston Churchill, I won't remember properly, but it's basically when it comes to writing a manuscript, you begin with enthusiasm, excitement, passion, and then it becomes a bit of a dog. And then it becomes difficult. And by the time you submit your manuscript, you hate every second, you loathe that manuscript and you submit it and it's published. And looking back on some of the manuscripts I would think, 'Yes, that's pretty good actually,' but at the time you hate it, you want to get rid of it.

So if I go back perhaps over to the 5-HT_3 work we did, that led to the development of anti-emetic drugs, and I think revolutionised the care of cancer patients. You've got to remember I never saw these patients. I heard the stories of transformed lives and so on, and they were great. What I did see though were at the time of an economic depression, was the reality of the fact that that work created jobs. I saw teams of people coming in both to the lab work and development work. I saw nurses being employed. I actually saw job creation, and that for a long time gave me the greatest pride. I could see that, people had jobs. And that's what industry, it's not what it's about but it's one of the factors of industry, it employs people, gives good careers, or should do. So that was one. Other achievements, always when you see a couple of ideas come together and you think, 'Yes, I got it right.' That's a good moment and they can be little things like the design of an assay, to the Eureka moment on getting the link between 5-HT_3 and vomiting. There are lots of little achievements like that. I can remember great talks, I can remember bad talks, I can remember the pride at shaking Nobel Prize winners' hands. There are lots of special things. I remember some of the awards that were given. I remember in particular going to the Discoverers Award Dinner run by pharma in America, which I'd won a few years previously, and I went back. They invited me back to the dinner as all past winners did, and at the dinner all past winners were named and you stood up to have a clap. At the end of the dinner the person running the whole show just breezed over, stormed over to me and just gave me a mighty bear hug as I stood up. I thought, 'What's this?' He said, 'Thank you so much. I've just come off a course of chemotherapy, I took these drugs, didn't vomit, thank you so much.' That was a very public bear hug, which was quite moving, yes. And I have that on camera.

[6]. ANTI-EMETIC DRUGS: INVESTIGATING METOCLOPRAMIDE

The link between 5-HT_3 and vomiting was a process of biological discovery based on - by then I had quite an in-depth knowledge of what metoclopramide would do - based on my own work, which was trying to tease out particular mechanisms, in particular how the compound could stimulate gut movements. By a series of experiments I was able to show it had nothing to do with dopamine D_2 antagonism, which is what people believed it was. I linked it to 5-HT based on similarity of response to what other people had described for 5-HT. Tried to block it, tried to characterise it, couldn't do it, didn't have enough knowledge or the tools at hand, so published this 5-HT-like receptor that I claimed to have discovered within the nervous myenteric plexus of the gut. Published that, and then while I was doing an experiment another scientist from France, a guy called Joel Joel Bockaert, who I didn't know, phoned me up and said, in his very thick French accent, 'We've just found your receptor in the brain.' 'Whoa, in the brain? It's supposed to be in the gut.' So it was lovely. And he'd taken my work and reproduced it in mouse brain and phoned me up out of the blue; I didn't know him, I know him now, and said, 'We've just found this. We've discovered the same receptor, no, it's in brain.' He later went on and called it "5-HT_4", and the rest is kind of history.

During that process of trying to understand the actions of metoclopramide we had to kill the idea that, although it was a dopamine D_2 receptor antagonist, it had other actions. So the other actions were not due

to dopamine. This was one of them. We also realised that the concentrations of metoclopramide that stimulated movements of the gut were a lot lower than the concentrations which others, in particular John Fozard, then in France, were publishing, describing it's ability to antagonise at, 5-HT_3, which were known as 5-HT_M receptors in those days, so there was a clear concentration gap. One I could characterise, I knew what it did, or I proposed, I hypothesized and we were right, it became 5-HT_4. The other kind of lay there until my colleagues, in particular Wes Miner, were undertaking experiments, with the ultimate aim of getting a better D_2 receptor antagonist and anti-emetic. And he was testing different compounds, testing metoclopramide, testing others, finding effects which were clearly nothing to do with dopamine D_2, but clearly effective - clearly acting in some way that was different. It was a possibility they were being effective because they stimulated gut movements, and with hindsight, a 5-HT_4 agonist; we couldn't disprove that, but it seemed unlikely.

[7]. ANTI-EMETIC COMPOUNDS: 5-HT_3 RECEPTOR ANTAGONISTS

But another possibility was that it was these compounds with unknown pharmacology were working, were being effective by antagonising at the 5-HT end, or 5-HT_3 receptors. So when Wes was doing his work I was able to - if you like, I knew I understood the literature, I'd created the literature but I understood what I hadn't created - and was able to put that two together, predict this was, this anti-emetic activity against the really tough form of vomiting that cancer patients were then experiencing. To put it into context, this is almost 100% response; this was nausea, vomiting, that could go on, the literature says, for five days. People were breaking ribs, people were refusing medications. It was really nasty untreated, but necessary if you wanted a chance of life. So we understood that and I was able to say to Wes, 'I know how this works.' So by a combination of getting an example molecule of a, not a collaborator, but someone I knew then working at Marion Merrill Dow in France, John Fozard, was able to get his selective 5-HT_3 receptor antagonist, went back to Wes and said, 'Please test it.' And lo and behold, it blocked and from that moment on we knew how we could control this really severe form of nausea and vomiting. There's a lot to that story, there's a lot of, there's a lot of stories surrounding the fact that we were changing that objective, that level of science, that way of approaching how metoclopramide works and how you can treat patients, and change is never easy, particularly in a commercial/industrial scenario where the juggernaut is already rolling towards what was considered to be the objective, and then you come along and say, 'No, that's wrong, do this.' So a lot of difficulties.

I probably wasn't the most diplomatic, but on the other hand, others were quite resistant to change. Not easy, but we got there in the end. One of the things that changed the scenario a lot was a video of these animals that - we were using ferrets at the time, because of a peculiarity in evolution, the normal lab animals, the rodent, cannot vomit. It's a peculiarity they have. So you have to use a different animal to mimic the human situation. Wes made a video of an animal that was vomiting and he was able, through an in-dwelling intravenous catheter, inject in mid-vomit and say, 'I am injecting now,' and the animal just emptied its mouth, shook its head and went back to foraging. Stopped within seconds. That had never, ever been achieved before. To put it into context, in the clinical scenario at the time, people were giving cancer patients five different drugs to try and achieve this unsuccessfully. Here, we were stopping it dead in seconds. He made a video. And after a lot of difficulties trying to persuade my then senior management to accept this, this was good, there was a lot of resistance to progressing this idea, because it was thought cancer patients didn't need this, the job was done, there were plenty of anti-emetics, you were wasting your time, we want to do something else.

[8]. ANTI-EMETIC COMPOUNDS: ACCEPTANCE OF 5-HT_3 RECEPTOR ANTAGONISTS

So Wes made this video and, eventually, we showed it to a new clinician who was Director of something clinical, who had just started, and I went over and talked to him. And we were talking about this, and I said how it worked, and I said, 'Look, here's the video of it working.' And I guess, this was Garth Rappaport, because he was a clinician and he'd seen patients go through this, was blown away, and said, 'This is fantastic. We have to have this.' He then showed it to Keith Mansford, who was the Chairman of R&D [Research & Development] at Beechams at that time, who was equally persuaded by it, and then any resistance to the

change that was being created was stopped. Keith Mansford said, 'We need this, we want one of these, get me one.' So then we had resources and the teamwork. We had chemistry who came on board to get that molecule. So it was, after that point we developed it. But we did it in a way that was unconsciously, and this was a retrospective decision, retrospective description of what we did, we took the kind of moral high ground and didn't mean to do that. We took the moral high ground, because we went out and published; we went out and talked to people, engaged with people. I remember consulting with people. We consulted with then Dr Paul Andrews, because he knew about vomiting, and we didn't. We needed to have some experts.

So he came in through the door and I introduced myself; didn't know him. And I said we were going to work in this area, we were going to talk about drugs that block, and he said, 'Yes, it's funny. I've got Glaxo on the phone as well. They want to talk about a mysterious compound they'd like me to test as well and have a look at.' And I said, 'Oh, I know what that is. We've tested it. We made it. Come into the lab and I'll show you the results on it,' because by then we'd done all the studies, we'd patented the Glaxo compound, we'd patented everybody else's. We were unquestionably the first to do this. So we showed Paul this data and he was knocked out, and I just think we took the scientific approach by being as open as we were allowed to be in a commercial organisation. We never revealed structures of course, but by communicating and engaging with the scientific community - as opposed to other approaches - and I've mentioned one, you just said, 'Here's a lot of money. Test this compound next. We won't tell you what it is and we'll take all the credit.' We adopted a different approach, and I think that was good; I think that is what industry should do. What it means is that you are then working in industry and you are a recognised scientist, not a drug rep. So when you go outside to key opinion leaders, as I used to do, your CV is as good as theirs. And when they talk about papers you say, 'Yes, I published that,' with so and so, and suddenly you know your science has been peer-reviewed and is good. So we took that approach, and I don't know if it was unique but a little unusual at the time, and gave us that good reputation. I think we lost the war in drug development. I don't think Beechams, SmithKline Beecham's was very good at the time in developing molecules, whereas Glaxo had a machine and just rolled through with ondansetron. They unquestionably were second, they picked it up through clinical trials, they noticed anti-emetic effects, but I really think they got it from our papers. We published the data. I even remember walking through the rain in Melbourne, there was a Serotonin Club meeting, where - who was it? - Brian Richardson then running the 5-HT_3 work at Sandoz at that time, then Novartis, apologised to me and said, 'Look, we saw your early data, we just had to move fast. We put money into an organisation, into Brenda Costall and Bob Naylor, we paid them to do the study and get that publication out ASAP [as soon as possible], because we're a business. I apologise for that.' And we were in the pouring rain, and we just laughed it off, and went for a beer.

[9]. MAKING THINGS IN THE LAB, AND A BESPOKE ROBOT

You can have a lot of difficulties, you can have a lot of fun, and certainly, particularly when I was much more in the lab, I would enjoy going off to the engineering Departments. In particular there was a - I can't remember the term - Mechanical Engineering [Department], I think, where they would make things out of materials for you. There was an Electrical Department and a Glass-Blowing Department. As a lab worker a standard piece of kit for me was a tube of araldite, which I always had, for gluing electrodes back on at the right time and so on. But I would enjoy going to these Departments and saying, as I did, to the electronics guys, can you make me a biphasic pulse generator, so that I wouldn't create electrolysis and gas bubbles in my solutions. 'Wow, what's this?' And we sat down and they designed it for me. It was lovely. Got to the glass-blowing bloke, 'Can you make me a flat tissue bath for this shape and diameter?' 'Yes, of course.' They were such nice people, lovely. At one time I had this vision that I could do experiments more quickly if I had a robot working for me, so what we did, so I went to these guys and said, 'Can you build me a robot?' which they sort of laughed and said 'Yes.' So what we did was design an arm that could be controlled by computer, that would be placed on a linear motor platform in front of a set of tissue baths that required injections at set intervals through - in this case, it was going to be the night. I was going to set this up, go home, come in, lots of results and then set up another one in the day, and do that one myself. So we had this robot arm on a linear motor so it moved, and it was programmed to pick up preloaded syringes, approach the bath and inject. It would be having feedback from the computer so we'd have our records and

it would know when to adjust the injection. And it sort of worked. And I had a full team of senior Beecham management at the time come into the lab in the middle of their meeting to watch this robot pick things up. This was regarded as serious stuff, but it didn't work. But it could have done if we spent more time investing and we hadn't got 5-HT_3 that got in the way. It might have worked. And I don't see why it shouldn't. So a lot of stuff, you could do that kind of thing then.

[10]. EMOTIONAL ATTACHMENT TO DRUG PROJECTS

So you asked me what kind of, do I have any emotional attachment, if you like, to the drugs I've worked with. Do I regard them as children? I've only been involved with the successful development of one drug - that was granisetron - and the patenting of other people's drugs - in this case, particularly, ondansetron. Yes, there is, yes you do have a sense of ownership, you invest a lot in them. I can still object when other people claim credit for that whole area. For example, in chemistry, for example when people review the whole areas and the credit always goes to the clinicians who may have done the first trials. Well, no, there were about 100 people and five or so years of work behind there, and maybe lots of redundancies. So we can object to that. There came a time, being in industry where I guess I was seen as a better innovator, and told to go back and do it again, and therefore I had to give this up to people who were better at the developmental side and the positioning of the molecule within the market as it approached registration. So I had to give granisetron up. Was it difficult? Yes, a little bit, but I think we reached some kind of understanding as we moved along.

So was it difficult? Well, yes. Yes, it's always difficult to give up and see other people repeat the same work, but I think it all evened out in the end. Everybody had a job to do and, ultimately, that was what was done. That's the only molecule I've been associated with that's gone all the way. There are many others and are they your little children, emotional investment? I suppose they are at the time, but because they are not successful and it's the nature of the business. At the discovery end of drug discovery most ideas fail. It's part of the business, and you learn to enjoy that and the way I always approached it - and I have collaborators within industry now and I do the same, try to do the same - is that you wrap it up and publish it and get something out of it and then move on, and you're proud of that paper. So ownership, yes, a little difficult, but I think, I think when you command an area, which I and others did, and move away from it, and you see others pick it up, sometimes better, sometimes less well, then you can feel a little aggrieved. In the area of nausea and vomiting for example, I still see reviews coming out which I think we could do a lot better. So myself and collaborators at the time - now friends, now experts - we will try and find the time and reclaim that ownership, if only for a year or two.

[11]. THE HUMAN GENOME AND USING NATIVE HUMAN TISSUE

I guess a career that I've had following those successes kept me in drug discovery, where I've always belonged, have always been. At different levels, at different levels of seniority, during and after different company mergers where business units were destroyed, people made redundant, new ones created, and somehow hung on in there. I'm not sure why, but perhaps I was seen as slightly innovative; I could see things, but certainly creativity is something that fails more times than it succeeds. I think it's meant to, and I think you mustn't be afraid of failure. So that creativity is good. So that's probably why I hung on in areas which I didn't know very much about. Eventually, the industrial career came to an end and I went back to university, and it was clear that industry needed, industry was still - as the whole biological scientific community was - sort of grappling with the unravelling of the human genome. This immense database of numbers that people had no idea what to do with them. In the past if you wanted to select a drug target you probably had 20 odd years of academic research teaching you where it was, what it did, what the side effects might have been. Now you picked up a genetic database and you had no idea, you didn't have that 20 years or so of knowledge behind it, you had to create that and take flyers. So the great predictions that the human genome was going to transform science within a small number of years was wrong. It will and it already is, but in the speed it was predicted, no.

A major problem as people get to understand this more and more, is translation of the science that comes from molecular biology - if you like, a transfected receptor into the host cell, you don't know if it's going to pick up the same characteristics as the native tissue. You don't know if the native tissue, which is usually going to be a rat or lab animal, is the same as human. There are so many translational steps to get it right, and after all making medicine is for humans. So within the industry it was very clear that translation was important - still is - and it's necessary to translate from molecular/animal to human. That is not easy, depending on the area. You can get bloods, if your target it there, that's fairly simple, relatively simple. But if it's brain or something different, that's much tougher. And it's an area, human tissue biology is an area that is not well done. Even today - and I've done this for various talks - you'll go to academic societies and count the number of presentations that involve native tissues. Native human tissues. And they are in the single digit per cent. If you take out the blood abstracts, presentations and talks, and let's face it that's a bit easier to get, they are in the one to two per cent of total. It's just not done. So we, back at the University, we set up this lab to gather as much human tissues as we could. We did it in a way that - this is not me on my own - but we did it in a way that took work away from the clinicians, because they have a busy time. So we taught ourselves how to consent patients, how to talk to pathologists, how to collect and how to catalogue and understand the whole process. We took it away from the clinicians, but worked with them. So to develop human tissue, it's not the only way in which science is going, but an access and a greater understanding of the human clearly important.

[12]. SETTING UP A HUMAN TISSUE LAB

So the reason for, if you like, setting up a new laboratory that focussed mostly on human tissue is, as I've described, a fairly obvious translational step. The reason I did it was because I go right back to my PhD and in particular, my post-doc days, in particular my post-doc with Alan Bennett, who he, and then myself, worked within the Surgery Department of King's College Hospital Medical School. And there he was able to obtain human tissue in those days without consent, but we always took our tissues through Pathology who then gave us what they felt they could give us, therefore not compromising diagnostics. So I think we were actually ahead of our time then. So we always did that, but we were taught how to use human tissues and to do things that no one else could do. When I joined industry I tried to bring the same thing with me, and we did. I collected from the local hospital and we did some good experiments, or I did. Eventually, that dropped as different technologies came on board; no one wanted native human tissue, the molecular took over. You could do it all, couldn't you, by cloning a human receptor, popping it into a HEK-293 or HeLa cell, and job done. Of course no one knew that that receptor might not couple to the same effector mechanisms, it might have a density and therefore the pharmacology is quite different to the native tissue. It might talk to different proteins and diamerise and produce pharmacology quite different to the native tissue.

So the, so of course, let's face it, very old technology was stopped. Human genome science came in, the molecular biology and human receptors and other proteins were being cloned, and, "job done"! You didn't need to worry about tissue pharmacology anymore. You could simply clone a receptor, pop it into a host cell, and job done and then you just moved straight to animals. What no one really understood at the time - and it sounds obvious now and I'm sure there were people who did understand it - was, of course, you transfect a receptor into a host cell, it's not always going to talk to the right mechanisms in the cell to evoke the right response. The density of receptor coupling or receptor expression is not always going to be the same as the native tissue, so you can make an agonist, sorry, an antagonist appear like an agonist, just by raising the density of receptors for example. It might diamerise with another protein or receptor within the native tissues, the pharmacology is different. Lots of reasons to question some of the data arising from that time.

[13]. OLD TECHNOLOGIES: THE TISSUE BATH; NEW PROBLEMS: REPRODUCIBILITY

So, eventually, there became a need to go back and think of old technologies. For the gut, tissue bath was obvious. We've got the, indeed I saw a slide on this just yesterday or the day before, somebody else was showing it. We have the largest source of living neuronal tissue in the gut. Neuronal human tissue. So we

set all this back up again and used it in industry and back at university I thought, 'This is a way of producing a useful lab.' So we set this up, and now the lab is funded a lot from industry who want this kind of technology.

Yes, we have this technology and a big question when using human tissue is, of course, you can pick up a specimen from - don't forget all this work is anonymised: we actually do know the name, but we blank all of that detail out. We certainly don't know the personal life of that person so we could have a nun, and I think we actually did have one once. Or we could have a drug addict who'd lived a hard life. We don't know that. We do know if they are male and they're female, we do know their age, we do know their disease, but a lot of, we don't know if they're vegetarian, we don't know if they drank heavily, all these things for example could affect the response. So some criticism levelled at us a lot, is that we can't do proper science with human tissue, because our variability is so great. I would counter that in two ways: one is okay let's take the criticism on the chin. Let's collect every phenotype about that patient that we can, so that we can spot the outliers and we can make sense. And that's what we do. I think the last paper we published we had about ten pages of supplementary data just to show, look, we do know these patients, it's not random. I would counter it in the second way and that is the common laboratory species, the mouse, is so inbred, so restricted. There was a lovely paper out about eight years ago in *Nature* where people at the Sanger Institute had genotyped common laboratory mice and there were only about five - if I remember correctly - about five variants, and those five variants had given rise to all of the mice used in molecular knock-outs. And if you go through and analyse that, you find there are so many SNPs [single nucleotide polymorphisms] and variations, that it makes human tissue work look easy.

But, in common, people will be using single strains. I know of many examples where people will get a result with one strain from one supplier, but fail to get the same result from the same strain from a different supplier. I work in an area where a receptor I studied does not exist in a functional state within mice. And yet, in other countries, they get responses to activation of that receptor; why is that? Possibly different countries' breeding stations, in-breeding, in-breeding, in-breeding, creating different animals. So I counter the criticisms of human studies in those ways.

But I have to, but I have to admit there are ways of moving forward and that's human tissue engineering, where we start isolating these cells and understanding them, and putting them back together to create organs on chips and organoid models where we put two human cells together to ask particular questions. We can do that because we have a ready supply of native tissue so we can extract and culture them for short periods of time so they don't change their phenotype too much, and put together to ask questions. That's probably the way forward. So even where I am now I suspect is going to be not quite redundant as a technique, but used purely as a validator check for what's to come, and that will be human tissue engineering.

[14]. FUTURE PHARMACOLOGICAL DIRECTIONS AND TECHNOLOGICAL CHANGE

So a question as to what is going to happen in the next 30-40 years, which is impossible. Human tissue engineering, yes. I don't know if it's going to happen in 30-40 years, but certainly a different way of treating disorders and diseases. We already see the rise of antibodies compared to the traditional white pills. We already begin to see the use of medical devices; I am no expert there. I suspect it doesn't take an awful lot, but you see it now coming. That must increase as people who understand that and who have innovative minds create ways of doing things. So engineering, replacement, has to come. I don't know enough to be able to predict that very well, but it will be a dramatic change. I have a story, in my own lifetime, I remember the first fridge my parents had. Wow, I mean. I remember getting the first computer. I went fishing when the man landed on the moon, but nevertheless I sort of remember it. They are transformational changes. The first fridge, which my children would laugh at. 'The first computer. You had to learn?' 'Yes.' So the equivalent transformation is going to happen. I would try and predict it in terms of bioengineering and electronics, and that's as far as I can go. I don't know enough.

[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) (2013) *Palliative Medicine in the UK c.1970-2010*. Wellcome Witnesses to Twentieth Century Medicine, vol. 45. London: Queen Mary, University of London.
3. 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.
4. Reynolds L A, Tansey E M (eds) (2008) *Clinical Pharmacology in the UK c.1950-2000: Industry and regulation*. Wellcome Witnesses to Twentieth Century Medicine, vol. 34. London: Wellcome Trust Centre for the History of Medicine at UCL.
5. Tansey E M (intvr); Tansey E M, Wilkinson A (eds) (2016) *Miner, Wesley: transcript of an audio interview (15-Jul-2016)*. History of Modern Biomedicine Interviews (Digital Collection), item e2016094. London: Queen Mary University of London.
6. Tansey E M (intvr); Tansey E M, Wilkinson A (eds) (2016) *Miner, Wesley: transcript of a video interview (15-Jul-2016)*. History of Modern Biomedicine Interviews (Digital Collection), item e2016095. London: Queen Mary University of London.
7. Tansey E M (intvr); Tansey E M, Zarros A (eds) (2016) *Green, Richard: transcript of an audio interview (17-Dec-2015)*. History of Modern Biomedicine Interviews (Digital Collection), item e2016034. London: Queen Mary University of London.
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