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

Sanger, Gareth: transcript of an audio interview (08-Dec-2016)

Interviewer: Tilli Tansey

Transcriber: Debra Gee

Editors: Tilli Tansey, Apostolos Zarros

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Sanger, Gareth: transcript of an audio 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.

TT: Tilli Tansey

GS: Gareth Sanger

TT: To begin with, Gareth, how did you become a scientist? Were you particularly influenced, from your family or school? What did you enjoy doing as a little boy?

GS: I've no idea why I became a scientist. As a boy I spent most of my free time on the beach with great friends swimming, fishing, throwing people off boats (rubber dinghies, not boats), and enjoying all of that. I guess at school I always thought my best subjects were biology, history and art. For some reason I was drawn more to biology as a direction. I loved being on the coast, I did biology A level projects on the mussel beds and the sewerage output and how things grew, and my father helped me, getting the local tidal charts and the current flows from the local Council, where he worked. It seemed natural to try and drift into a career in marine zoology.

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* 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.

TT: You grew up on the coast - could you just say a little bit about where that was?

GS: That was in a little village called Heacham in Norfolk, which has one claim to fame. Pocahontas lived there for about three months, but now the village sign has it emblazoned everywhere and she's the heroine, with a little plaque in the church. I think she only lived there for a heartbeat almost. But nevertheless she married John Rolfe who came from the village. It's a small village. I was borderline, but passed the 11+ and went to the Grammar School in King's Lynn, which was about a 30 or 40 minute bus journey away. It was not a town life, it was a village life, and for reasons that only a psychiatrist would explain, I tended to gravitate towards those who had also passed the 11+, and that meant there were very few of us, just two good friendships, who I still have. So a little isolated. With hindsight, and by the time one was 18, you think, 'This is boring, I've got to get away.' Going to university I suddenly realised that I'd actually had a life that was different. The newly-discovered discos, parties and drinking were activities that all my new friends had had in their later school years, whereas I never had. So I kind of felt grateful I'd had a different life. I've since talked to my friend from Heacham. We had drifted apart; he went into the oil industry and now lives in Scotland. He said exactly the same: how lucky we were to have that slightly isolated country life and then to do all the fun things associated with going to university, rather than have the same experience all of the time.

TT: You mentioned your father helping your projects. Did you have any family background of science?

GS: No, I was the first to go to university. My father was the child of a shoe or boot mender, who believed in education and saved all his pennies to make sure his two sons got an education, because in those days it was private. You went so far and you either paid or you dropped out. One of my grandfather's sisters married the local newspaper editor or publisher, I've forgotten which. They lived in quite a big house with a room full of books, and my father would come home, drop in on the way and discover Shakespeare, literature and the joys of reading good books. He then went on to publish his own short stories, but that wasn't his career.

TT: What was his career?

GS: He originally wanted to be a woodwork teacher. Then the War happened and after serving in Europe and Asia, he realised there was no money in woodwork, so he retrained as a "sanitary" or public health inspector. He spent the formative years going around Tiger Bay in Cardiff looking to see if people with tuberculosis (TB) had been in association with mad people because there was thought to be a connection. Things like that, and smoking out houses to sanitise them. He eventually became a Local Government Manager and looked after the whole of King's Lynn. But that's how he started, so there was some element of science. I used to go with him in the evenings, if I was lucky, to inspect the meat at the local slaughter house, now called an "abattoir". We'd go in and he'd show me where the TB was on the lungs, and I'd watch the pigs being brought in and shot. That was good fun for a kid! I think there's now a housing estate where that was. So it was kind of interesting and just different, to go in there and see all these carcasses hanging up. I don't think that attracted me, but that was part of the environment.

TT: You mentioned you have a brother. Older or younger?

GS: I've got an older brother and two younger sisters. The older brother - a little wilder perhaps than I was - went into medical microbiology as a lab technician, eventually became a farm manager, eventually into agricultural teaching, eventually dropped out of that to run a pub, eventually moved from there into teaching and now retired, but still keeps his hand in.

TT: You said you had three best subjects: biology, history and art. Did you have any particular teacher who inspired you?

GS: No, I was a very average student. By the time A levels came, I knew I had to do some sciencey things so I ended up doing physics. I'm terrible at maths, so I spent a lot of effort on that, and with hindsight perhaps that wasn't the best choice.

TT: You did the traditional three?

GS: Biology, chemistry, physics, yes. The bits I would remember are those bits where you have the opportunity to get a little closer to the person. I remember my physics teacher moved in about four doors away from me when I was a child, and my mother embarrassed me by making me take him a bag of apples. Another Mr Eels - was my biology teacher - and I naturally got a little closer to him because you'd go in there and do projects and sort of hang about and dissect a worm or something. He would talk a little bit about his life at Cardiff University and his project (a gastro-colic reflex in frogs!). So maybe there was a little connection there, yes. I think I had a very naïve, unstructured mind at that time. I just enjoyed life and did things without really thinking. University happened because I don't know why, it just did. Even though I was the first to go and not everybody did, it was the kind of thing my friends did.

TT: You were encouraged at school, presumably, to apply for university?

GS: I think so, yes. So I went to Newcastle to do zoology. I chose Newcastle because I had a friend that went there ahead of me and because they had a good marine zoology station, Cullercoats. And somehow leaving school and going to university was liberating. I didn't have to do physics anymore. Well, I did actually in the first year, I did have to do physical sciences. But it was liberating. I could do what I enjoyed, I could do it at my pace, which was either faster or slower. I could dig into things that were fun, I could stay in one area and dig around. It was liberating, yes.

TT: The choice of zoology, marine zoology, was very connected with your life as a child on the beach and looking at marine animals?

GS: I knew nothing of the word "physiology", which was the degree I finally took. I'd never heard of "pharmacology", I'd never heard of "biomedicine" or any of the terms now. You had to do three subjects in your first year. You had to do physical sciences, which was for biologists. Thankfully, this was examined by means of short answer question, which meant you could take a lucky guess and get most of them, you know. I had to do zoology and I chose physiology which I'd never heard of before, as my third option. Zoology I loved. It was around the time that coelacanths were rediscovered, a resurrected fossilised fish. We spent the entire year examining and classifying the entire animal kingdom from insects up, you know. So I loved it, it was great. We dissected things, and the practical classes were rows of animals which were laid out for us to observe, measure and dissect. It was great fun. But at the end of it, I kind of felt that physiology was offering me a slightly harder science and a slightly more purposeful direction. I don't know why. So I went to see my zoology tutor, Dr Panchen and asked for advice and he said, 'Whatever you choose will be right, because you'll never know what you missed,' which was some of the best advice I've ever had. So I went and did physiology.

TT: You moved into second year physiology; again was there anything in particular as you're going through your second and third year, any particular course or system that especially interested you?

GS: There were bits that were tough, bits that were difficult and bits that were great fun. There were good lecturers. David Horrobin I remember very well, he became famous.

TT: Of "Evening Primrose Oil" fame?

GS: Yes, he was our lecturer and we used to go round to his house. I'd never had a lecturer give us a lecture whilst sitting on the floor with us, which he did. And we had to buy his textbook and it was good fun - stimulating, yes - he went on to do Evening Primrose Oil and so on. So he was our lecturer. At the time I was there Professor Harper was the Head of the Department of Physiology, so we were forced to call "cholecystokinin", "cholecystokinin-pancreozymin", with a hyphen, because he had originally called it "pancreozymin". He wouldn't let anybody transfer over to physiology if your first year option was psychology, because he regarded that as a weak option; so that prevented some people from transferring

over. He then retired and Eric Blair took over, who was from a local family who did well in the shipyard building industry, I'm not quite sure what, but I remember that we went around to his house once, which was very, very impressive. So I think he came from a good industrial background. Anyway, we did that and perhaps because Eric Blair and Alex Harper were gastric, GI people, there were a lot of the other GI Department scientists: David Reed, David Sanders, Maynard Case, come to mind. Maynard Case became my tutor, then moved to Manchester later and he is now retired. There was a lot of GI there and that somehow must have seeped in and made me interested in the whole area. It was the GI focus that helped to give birth to the GI focus in Sheffield, as Tim Scratcherd moved over. It was the whole crucible - Tim Scratcherd wasn't there when I was there.

TT: I think he would have been in Leicester then probably or moving up to Sheffield. Although Sheffield, of course, already had a GI focus with intestinal absorption.

GS: Of course. The connection from Alex Harper spread out.

TT: Harper was a lovely chap, at least he was to me at Phys Soc [The Physiological Society] meetings. By this stage, you're getting very interested in GI.

GS: Yes, because of where I was, it was a default thing.

TT: And then you moved to Manchester to do a PhD? So was that associated with Maynard?

GS: No, I didn't know what to do, my mind was still open and drifting. And I found this PhD position in Manchester and I thought, "Well, I'll have that, thank you" and got it. I didn't know what to do and it seemed, well let's do that, you know. I didn't know where you went. I turned up and I often say that the only thing I learned from my supervisor was where the good pubs were in Manchester. And that's it.

TT: Who was your supervisor?

GS: Andrew Watt, who was Hans Kosterlitz's PhD-student. An Aberdonian who came down and a really nice chap, but taught me almost nothing. Many years later, when I took my own daughter to Manchester for an interview at the Music College there, I popped in to see Maynard Case, who was then Dean of something there. He remembered me, which was really nice. His office was kind of like yours, lined with books, which was good, and he looked at me at little embarrassed, 'We had to get rid of him in the end, Andrew Watt.' I said, 'I'm not surprised! I really don't blame you, don't feel embarrassed. I learnt very little.' At the end of my PhD, I knew I needed training, which is why I picked up on the enjoyment I had from papers written by a certain Alan Bennett, who seemed to write in a way that didn't just record the results, but pushed the boundaries a bit and speculated on where that might lead to. It was all in prostaglandin work.

TT: For the record, what was your PhD?

GS: It was the effects of prostaglandins on intestinal sympathetic activity. I did a lot of tissue bath work, I did a lot of radio-labelled transmitters, all of which I picked up from different people and developed the techniques.

TT: And you were particularly influenced by Bennett?

GS: Alan Bennett, who was then Professor of Pharmacology at King's College London Medical School in London. I liked his papers, they spoke to me in a way that was pushing it a bit; I enjoyed it. My PhD I think was unproductive, I didn't know how to write papers, I wrote one that was rejected immediately, which I've always regretted because I think it was a good piece of work, and we were the first, I was the first to do it and subsequently it was published by people at the Karolinska.

TT: Can you say a little bit more about what that was and who rejected it?

GS: Oh, it was just radio-labelled choline release (acetylcholine release) from cholinergic nerves in guinea pig ileum. I used carbon 14 choline to incubate the tissues during electrical stimulation, so it would be taken up in the right receptor pools and then measured the radio-label in fractions as it came off, having subsequently washed and stimulated. No one had done that before - in gut at least - so that was the paper, and I was quite proud of it, but then it got bounced.

TT: Where did you submit it?

GS: I think probably in the *British Journal of Pharmacology*. I regret that my supervisor did nothing. Didn't teach me, didn't help me, and say, 'Never mind, let's go for some European or some other journal.' And it lay fallow and nothing happened and a few years later the people at the Karolinska published the method. So we published a few things, and Alan Bennett helped me to get them into shape. They were the sort of paper that died a death, and that's fine. So then Alan said, 'Yes, I will take you on…' because I went and visited him in London, '…but only if you pass your PhD.' So I then made him my external examiner, and passed, and went down to work with him. My PhD was 1977.

TT: Who was funding your post-doc?

GS: I think it was a mixture of money that Alan had put together from various drug industries, it was money he had, so it wasn't a regular, in those days SRC [Science Research Council] or MRC [Medical Research Council]. Not Wellcome Trust at all. John Vane used to pop in and out of the Department. It was pretty good, but a bit overawed; I was only a student, well only a post-doc, still learning how to open my mouth in public, which I didn't really know at that time. So John Vane used to pop in and out, along with Harry Collier and Salvador Moncada. I didn't see much of Rod Flower, but various other people whose names I don't remember at the moment would pop in and out, yes.

TT: You were at King's?

GS: This was Kings Hospital so it was down on Denmark Hill. Opposite the Maudsley. We were part of King's, but based in the Surgery Department at the Hospital.

TT: I was just thinking of your connection with people like Vane and Flower. Because they were probably then with the Wellcome Foundation at Beckenham?

GS: I think they might have just moved that way. Yes, because I published a paper on prostacyclin while I was there but I called it "PGI2". Which was then its true name. John Vane wrote to Alan and said, 'Do you mind calling it "prostacyclin"?' I suspect that was a Wellcome thing.

TT: I'm sure that's right, yes.

GS: Because we had to change it to "prostacyclin".

TT: From your PhD in prostaglandins and then going to Alan Bennett's lab, you're really now moving into becoming a pharmacologist?

GS: Yes, my PhD was in a Physiology Department. I knew no pharmacology, although Andrew Watt encouraged me to do my two presentations to the BPS, the British Pharmacological Society. Like I said, I knew I needed training. I didn't know what but I knew I needed something. I felt lost for three lovely years, great fun, but I just didn't get much out of it, apart from learning how to stand on my own two feet. So Alan knew that and kind of took me under his wing. I went through periods of time when I would come into work and you used to have to sneak past his office and he would jump out at me and say, 'Define a pA_2!' And the first time I mumbled, but hadn't got a clue what it was. Eventually I learnt it and I could say, 'pA_2 is the negative log…' and so on. 'Fine, fine.' So I could now sneak past his office without being attacked by having to give

the definition of a pA_2. Then I had to define pD_2, and that's how he started to teach me pharmacology. He would train me in the presentations, so if I had a ten minutes' presentation to make at a Pharm Soc [British Pharmacological Society] then to begin with we would spend a large part of the day rehearsing. So I would start, and he'd say, 'No, no, no, no, you've got to learn your first line. Do that, that adjusts you to the environment, so learn your line.' I'd learn my line, then the second sentence, 'No! You cannot do that, start again.' And we'd get through about the third line, 'No, no, no! Not right. Start again.' 'No, you're waving your hands about too much, keep them to your side, start again.' And it would be like this, 'No, I didn't hear that, start again.' And this would go on most of the day and you'd come home exhausted, well I'd go to the pub with my colleagues, but that was how I was trained. 'Start again, keep your hands to yourself, switch the pointer,' was it a pointer? Whatever the laser thing was. 'No, just point when you want to. Keep it down, you're distracting people. Don't do that. Keep it down, you're distracting people. No, that slide's not right. Go and redesign it, we'll start again.' And that would be most of the day until I'd got it right, as far as he was concerned.

TT: That was excellent training.

GS: That's what I mean by training. For the manuscripts, I wrote the first draft, he would then tear it apart, usually in red ink. And because there were no word processors it was then given to typists to retype. When I went to Alan's memorial I caught the tube over to King's College, and I was editing a manuscript that we were writing together in the lab and I'd got somebody to do the first draft. And I was inking it, with suggested corrections. So I went in and said 'Hello' to Alan's wife and his daughters. I was telling that story and I said, 'Look, I'm doing the same. Here is a manuscript and I've got red ink all over it, just like your dad did to me.' And they laughed and his daughters said, 'Oh yes, he used to do that to our homework as well.' [Laughter]. So he did that to all of us. He certainly had an untimely death.

TT: I know very little about him; it's not a name I'm familiar with. He died comparatively young?

GS: Prostate cancer, yes. He retired at the right time, he'd built up a business importing and selling saxophones - he was a great badminton player, always beat me - and liked the hobby of music and family life. Great saxophonist, played in the clubs and so on. So was David Alpers, another guy I work with. Still comes over from America, must be in his 80s, he's here every other month and as far as I know, at least until recently, he belongs to a little jazz club and they do the pubs together. But, anyway, being in the Surgery Department, Alan Bennett used human tissue. That's where I was introduced to it.

TT: Obviously human tissue is something I want to ask you about - this is something from right at the beginning of your career?

GS: Yes, he was in the Surgery Department. The then Head of Surgery was Mr Murrey. He was the one who helped to pioneer vagotomy surgery for treatment of ulcer. I've still got some of his papers. Unfortunately, became a little too fond of the drink and a great colleague of mine, Ian Stamford, the Chief Technician at the time, used to help him "recover". Also popping in and out was a guy who worked with Hans Kosterlitz.

TT: John Hughes?

GS: John Hughes, he was a post-doc there before my time. John Hughes used to extract tissue to get encephalin out in the same rooms which became the gents toilets. Anyway, we worked in the Surgery Department and got human tissue without consent or anything in those days.

TT: It was different in those days.

GS: Yes. We used human gut, human uterus and other tissues. It was standard practice for all of us to come into work, swing by the theatre list on the way in, and see if there was anything to collect that day.

TT: When you say 'for all of us', were you a member of a big team?

GS: I was a member of a team, I was the only post-doc; the rest were graduates and technicians. There was a post-doc before me, Helen Stockley (now Helen Leathard). So I kind of took her place, if you like, as she had left.

TT: What was the main focus of your project?

GS: At the time the different prostanoids were being discovered, prostacyclin, 6-keto-prostaglandin F1-alpha [6-keto-$PGF_{1\alpha}$], leukotrienes, they were all new. So I spent a lot of time just dropping them on human gut to see what they did, because no one knew. Defining that and for some reason, I think, it was a drug test we had to do, we started doing the same in human myometrium as well, so then we linked up with a guy who could do mass spectrometry and analyse what was in it. We published a couple of good papers on that. Then there would be a bit of drug testing that we turned into papers, and that was a big focus. We published quite a bit.

TT: It sounds as if almost everything you did turned into a paper at that time.

GS: Absolutely, yes. But it was characterisation of the new prostanoids that were being discovered by the minute at the time; that was mostly what we did.

TT: And that was a three-year post-doc?

GS: Yes.

TT: Towards the end of that, did you deliberately think about going into the drug industry?

GS: Yes. I didn't know what to do and had no idea what an academic life would be, so I met somebody who said, 'It's better in industry, because you haven't got to spend all your time applying for money.' That sounded okay. So Alan talked to John Flack who was then Director of one of the sites of Beecham Pharmaceuticals. He interviewed me and gave me a job. I was put into the GI therapeutic area, not the prostaglandin therapeutic area. It horrified me that I was even being considered for that, because I wanted to stay in GI. Alan Bennett advised me that prostaglandins would come and go, but the GI never would.

TT: Some of your contacts, following John Hughes, were contacts with prostaglandins and industry, people like Vane and Salvador Moncada?

GS: I didn't know them personally. I was the little boy who was honoured to be in their presence.

TT: But you were getting the ambience of the drug industry?

GS: I suppose so. I didn't really think it through. Unlike me, I now look at my eldest son in particular, for whom everything is planned, and it's great.

TT: It's also terrifying.

GS: It's great, but I didn't do any of that. Too busy just going around the world starry eyed, I think.

TT: You started in Beechams, which site were you on? And what was your project there? What were you supposed to be doing?

GS: At the Harlow site. I've lectured on it since. I was almost literally shown a desk in a room that was a small room that was a lab. They cleared out a bit of space for me and found a table and a chair and I was shown that, and I'm sure I can't remember the words exactly, but it was something like, 'Find something to do.' I spent the next period of time feeling a little bit cheesed off with that, a little bit directionless, a little bit lost.

I spent quite a lot of time writing up my old papers, reading the new papers, trying to think of experiments to do. Some of them worked, some of them quite complex, and some of them led to a good direction of research.

TT: But you were in GI, there must have been some indication what sort of things you were looking at?

GS: The area of GI I was in was tasked with finding a better metoclopramide. A better metoclopramide that retained its beneficial activity, but without the extra pyramidal side effects. That was the task. What I ended up doing was trying to understand how metoclopramide worked. I'd obviously not joined the screening teams because I had to find something to do, so I gravitated towards understanding the mechanisms of metoclopramide, and that became my accepted role.

TT: You were very, very fortunate having that freedom. It must have been quite daunting at the time.

GS: At the time. But hindsight, what a gift, yes.

TT: Pat Humphrey tells almost the same story at the Ware site of Allen & Hanburys, walking into a room, with a desk and a technician, and being told to do something on migraine.

GS: I didn't have a technician. No, it was just me. And I reported to a guy called David Turner, who had a BSc in pharmacy. Lovely guy, but wasn't up to the modern job, and I think was retired early. I took his job. He was a really nice guy and I feel cruel when I say that I privately nicknamed him "Brains". He was a man of his times when the industry didn't really do science well, perhaps.

TT: Times were changing and you were the right person there almost at the right time.

GS: Yes, yes.

TT: What kind of experiments were you thinking of doing or did you do?

GS: I gravitated to thinking, 'How does metoclopramide work?' I'd worked out that it stimulates gut movement somehow, I'd read all the papers, and I'd figured that if it was going to stimulate gut movements it would have to do that in a co-ordinated way, and so it would have to involve nerves in some way. I'd picked up a technique from my time in Alan Bennett's on how to stimulate nerves through a complicated method of linking different stimulators together so you had biphasic square wave pulses that didn't oxidise and produce gas bubbles in the Krebs solution. At that time we were fortunate in having lab engineering Departments; we had an Electrical Engineering Department, we had a Glass Blowers Department, and a Mechanical Engineering Department that would produce things for us. I loved that, so I'd go in and say, 'Have you got something better than Araldite?' 'Yes, we can do this.' 'Can you make this? Wow!' So I really used to spend hours in there sort of trying to design things, or not design. They designed, when I'd spend time with them saying what I wanted, and they would do their job very well and make it for me.

TT: But you had to have the idea of what you wanted?

GS: What I wanted was this stimulator that gave me biphasic square wave pulses, so they built one for me. Great! So I stimulated the nerves in rat stomach. Rat stomach, because metoclopramide was meant to be a stimulant of stomach emptying, so let's do stomach. I stimulated that and with hindsight I have lived with that technique almost all my life, and I think I actually changed how GI biology *in vitro* has been done. It's very simple for people to take a bit of gut out, put it in the tissue bath and throw something at it and stand back and look. It's still done by, dare I say it, molecular biologists who really have no idea of the physiology, and will drop it on and say, 'Oh, it does something.'

TT: Oh, they're rediscovering it. It's amazing how 'this new technique…'.

GS: I've got examples that make me cross even now. So that's been with me all the time, and I think it's not novel - far from it - but it's been a very important tool and continues to be, and I think it's taught other people. So I set this up, standard tissue bath work. When I arrived at Beecham it was normal to do some tissue bath work with one tissue bath. I was used to working with Alan who dictated that you would use four at the very minimum, and if you could grab somebody else's kit because you had a valuable human tissue, then you did eight, and that was hard work. But four at least. So I came in and set four up and I remember having people come into the lab thinking, 'You can't do this! Can I see what you're doing? You can't do that, it's not possible.' Now people who work with me, standard, you do eight. And if you've got available tissue, you do 16. So I changed it from one to four, and that was revolutionary! So, anyway, I did that and I found responses to metoclopramide that made sense. I tried to characterise it using known drugs. I'd worked out that the only thing that mimicked it was 5-HT, and there were certain hints in the literature that suggested that was a good direction to go. I couldn't block it, I couldn't modify it, I talked to chemists and said, 'Look, you are making compounds that mimic this action,' and I showed that they did, 'Have you got some that were surprisingly inactive (in those days it was all tested *in vivo*)? Have you got some of that? Were you surprised they were inactive? Can I have them? Can I test them as antagonists?' So we did that and after getting permission, I ended up probably with the world's first 5-HT_4 receptor antagonist, but didn't know it was 5-HT_4.

TT: What date would that have been?

GS: In the 1980s.

TT: That was quite early on.

GS: Yes, so we did that. But, of course, the whole focus of the Department was to get rid of this central nervous system (CNS) dopamine effect of metoclopramide. By default it produced molecules that still stimulated the gut movements, but the dogma at the time said that this was still mediated by dopamine receptors. There was a CNS Department next door that were trying to produce CNS-active dopamine D_2 antagonists as well. So by using those tools, eventually, I was able to show that firstly, dopamine wasn't involved in this action. I published that as a short abstract somewhere. There was a lot going on at the time, but basically by doing this work what I was doing was overcoming the dogma of the time. The dogma that had been established by somebody who I later became good friends with and thoroughly respect, a guy called Peter Blower who is retired. He'd come up the hard way. He'd done his part-time qualifications, got his PhD and became I think Visiting Dean or something of East London University, where he got his PhD. Anyway, he produced this Thesis that said, if I remember rightly - and I don't want to malign him, far from it - that everything was due to dopamine, and it was a question of doses and concentrations and types. And I said, 'No, it's not.' And it caused a lot of difficulty which was quite fractious at the time, quite difficult; who was to blame, I haven't a clue. Perhaps I'm not the most gifted diplomat. Nowadays, I probably would have done the ground work, talked to people, got them on my side, before going to a meeting. Then I knew I'd be attacked so I'd keep it all to myself and talk about something they didn't expect and say, 'Here you are, job done.' And it wasn't popular: basically, saying dopamine was not the mechanism.

TT: How did your bosses at Beechams take all this? Were they quite happy for you to be doing this?

GS: Yes, but I think I was a slightly bad boy. I remember getting a bad pay rise later on because it was deemed I couldn't get on with everybody. In those days inflation was about 20%, you know, or something ridiculous. So just to keep up with inflation you got a ridiculous pay rise. About two years later I became Head of the Department, so it was a very strange environment, topsy-turvy. So yes, I had to turn it around. I thought it was 5-HT, so I was testing drugs like methysergide that would block, but I didn't know why. I found my own molecules, I've forgotten the name of it now, that would block, but I didn't know what to do with them. I started proposing that we had to go for these, because they might be a good therapeutics and we did run a programme in the end and found, many years later, good 5-HT_4 receptor antagonists.

TT: It's intriguing: you've talked about first of all being in prostaglandins research - that was all going on, but so was 5-HT as a neurotransmitter.

GS: It wasn't popular at the time.

TT: There was a group of sort of believers almost.

GS: There was. There was a group within Beechams who at the time we felt a little sorry, because they were working on a drug that had just been in-licensed called "paroxetine". The selective serotonin reuptake inhibitor (SSRI) that became the world-wide success known as Paxil, for treatment of depression! No one quite believed in it then. So there was no real 5-HT interest, there was no real basic research and certainly no drive to work on 5-HT within Beecham at the time.

TT: I don't think that was unusual. I think that's why there was a group of believers; Richard Green will tell almost the same story. And you all suddenly found each other.

GS: Yes, like that. I was aware of the 5-HT_M receptor, subsequently called 5-HT_3. I wrote to John Fozard to say, 'Could I get a sample of your molecule MDL72222 to test?' He couldn't send this, but he sent me a sample of a similar molecule with the same activity (our chemists then made MDL72222 for me). I tried to block metoclopramide with that and I couldn't. And yet I could block other things with it. So eventually by reading the literature, I finally figured out that metoclopramide could stimulate gut movements through this mechanism that I'd uncovered, now known as 5-HT_4. But by reading the literature I could see that it also antagonised 5-HT_3. John Fozard was originally doing that work in the Department below me in Manchester, when I was a PhD-student there.

TT: Where was John Fozard then?

GS: In Pharmacology, in the Department below me, I was in Physiology upstairs.

TT: No, I mean when you wrote to him for his compound?

GS: He was then at Merrill Dow. He'd moved to France. He wanted to find a 5-$HT_{M/3}$ receptor antagonist to treat migraine. So I wrote to him and I asked if could I get a sample, and he sent me one. This didn't block the effect of low concentrations of metoclopramide now known to be mediated via the 5-HT_4 receptor. However, I knew that metoclopramide could also antagonise at the 5-HT_3 receptor at higher concentrations. So suddenly I'm splitting the two. Then Wes (Miner) would be in the corner working with his little ferrets, trying to use dopamine receptor antagonists to block the severe form of vomiting caused by the anti-cancer drug cisplatin - but not successfully. Then I asked him to test the compound now known as renzapride and it blocked. This did not block the dopamine receptor, but did stimulate gastric motility. The reason I had asked Wes to test renzapride was because by then I knew it would also block the actions of 5-HT at the 5-$HT_{M/3}$ receptor. By that time I was working with a great colleague Christine McClelland and we'd set up different assays of 5-HT, and she'd help me set up the 5-HT-induced Bezold-Jarisch reflex, which I was doing myself. We tested renzapride and it blocked the reflex.

TT: Could we put a date on this?

GS: That would have been in the early 1980s. All of a sudden the penny drops. At that time people were thinking, 'Well, it must be due to blocking a different action of dopamine on the gut that was inhibiting the movements, normalising stomach motility and therefore opposing the vomiting stimulus.' And I was saying, 'No, it's nothing to do with dopamine.' However, I couldn't rule out the possibility that stimulation of stomach motility could inhibit vomiting, even though I doubted that. I then went back to Wes and said, 'I know how this works, will you test this?' I gave him a sample of the selective 5-HT_3 receptor antagonist MDL72222. It worked, and suddenly we had the whole thing.

TT: I think suddenly 'having the whole thing' - that's a bit glib, isn't it? You'd spent a lot of time thinking this through.

GS: I did.

TT: Wes says that you, because you understood it all, you felt it physically almost.

GS: I knew the literature. Those of us who have got one or two grey hairs now, including Paul (Andrews) who I met yesterday, and others, sometimes do the old war horse stuff, 'Why don't the younger people know the literature? Why don't they write papers?' We've speculated that in those days you had your little card index file - I see you've got one behind your chair - and I had those. You knew everything and you had little notes on everything. You had to. Whereas now, it's not so necessary, you just go into PubMed, get out what you want, or Wikipedia and then cross-reference. As I do. I try and catalogue, but you don't have to be so dogmatic as you did. I wonder if that has had some impact on not really knowing the literature? But, anyway, I knew every paper at the time. Metoclopramide had been linked to 5-HT, and I had that reference. I had every reference in which it had been tested using isolated gut. I knew all the good and the bad, and I knew it all. I was moving to 5-HT because it appeared to mimic certain actions of 5-HT in the gut, and because of John Fozard's work with the higher concentrations of metoclopramide at the 5-HT_3 receptor. My pharmacology wasn't good enough to do the receptor blocking experiments David Clarke subsequently did in order to prove that the ability of metoclopramide and renzapride to stimulate intestinal motility was because it could activate the newly-characterised 5-HT_4 receptor. However, before this definition I'm doing an experiment in the lab, and I then get a phone call into the lab with a very thick French accent, which I could hardly understand. It was Joel Bockaert who said - I'm not going to do the accent, but he basically says - 'We found your receptor. We've done mouse collicular neurons, we've found it. We've reproduced exactly what you've found, but we've done it in the CNS.' I went, 'Wow! Really?' And that became 5-HT_4. They replicated what I did, phoned me up from somewhere in France and told me about it. It was really exciting.

TT: You'd obviously been publishing your ideas - were there any constraints on publishing?

GS: I was allowed to publish, most of it anyway. Because I was overturning the dogma within the Department, I would sometimes come out of a meeting feeling thoroughly pissed off, so I invented a behaviour which I've subsequently had to use on occasions in my career. Sometimes the only way to get people to believe you is to publish: 'My boss won't believe me so I'm going to go outside and get my peers to believe me. And then maybe you will.' So that's what I started to do. I started to publish. Not in good journals - I didn't know about that then. But yes, it caught the attention of Joel Bockaert who had read my papers and replicated and extended the data in his model. That's when he phoned me up and said, 'We've just found your receptor, but in the brain.'

TT: How did you know him?

GS: I didn't. I'd never heard of him before.

TT: So he just phoned you up? Wow!

GS: He got my phone number, it came through into the lab and said, 'We've just found your receptor, it's in the brain.'

TT: That's even more astonishing.

GS: I was in the middle of an experiment at the time and I just said, 'Stunning, thank you! Can you send me the paper?'

TT: The question I was going to ask was did you know him through the Serotonin Club, Pharm Soc, whatever, but you didn't.

GS: 5-HT hadn't really broken through yet, so I don't think there was a Serotonin Club then. So no I didn't know Joel at all, and he phoned me up - which was lovely of him - to say that he'd just replicated my data, but in the brain. And then he named it 5-HT_4.

TT: So now you had a receptor and you had a name for it. What did your bosses at Beechams think about that? Were you now relieved?

GS: Not really, no, because at that time I was also doing 5-HT_3 at the same time, which was even more contentious. Contentious because I really was now unashamedly overturning the dopamine dogma. Yes. Very definitely, and not being believed. I even teach it now! I would be so fed up I would just go in to meetings and just say, 'Well, here's the molecules you wanted me to test. That's the data. Right, now I want to talk about this.' And we'd go off on some tangent and it would upset everybody, because I was never keeping to the agenda. I understand that, but I guess in my non-politically trained youth, that was what I did.

TT: But you were clearly tolerated. They didn't sack you.

GS: Well, they downgraded my pay rise once. But I would go in and they still wouldn't believe this stuff. And I was then onto 5-HT_3, and I remember working out a marketing size by figuring out how many cancer patients there were, how many got treated, how many would therefore receive an anti-emetic, make an assumption they wouldn't all get it, so let's call it X%, whack a price onto that, let's call it whatever the latest one was, and I presented this to try and turn it around and say, 'Look, this is worth doing. Forget the science, surely this has to be worth some money.' Anyway, Brian Morgan, the then Director of Research told me at the meeting in words something like, 'How dare you present this to me when we've got salesmen out there in the North of England trying to sell bloody Lucozade to people who can't afford it, just to pay your salary so you can deliver this crap to me.' I think that's when Wes said to Christine, who worked with me then, said, 'I'm amazed this guy kept his job.' It was that kind of environment.

TT: Yes, that is in the Witness Seminar and Wes' interview.

GS: Because it wasn't wanted. We had our programmes, we knew what we wanted, but the company didn't want that, thank you very much.

TT: It's quite astonishing now to think that you were allowed to continue. Did you have an advocate at a higher level or were you just so far out, it was a case of 'Okay, let's just see what he comes up with.'?

GS: Yes, I guess so. It wasn't the days when they just hired and fired. And they weren't lean and mean in terms of your staff. So, yes, I suppose so.

TT: What about Wes? Was he in your Department?

GS: Wes was busy doing his ferrets. It was sort of clear that I was a bit unusual, in the sense that I was trying to change things. There was a guy who joined us as a technician, did a part-time degree, and eventually left to do his PhD at Oxford with Alison Brading. Now he's Professor at Edinburgh and runs his own Department and he's good. I bumped into him at the Pharm Soc a couple of years ago. I was doing some work near the posters, and he sat next to me and said, 'Hello.' And I said, 'I'm sorry, I don't remember you,' and then I did! Anyway, his story was he remembered me as somebody who as a little bit revolutionary, changing the Department, doing good stuff in an otherwise fossilised group. And so it was, for people like him and others, it was fun, it was a breath of fresh air.

TT: And then what happened?

GS: Well, the story developed further. Then we had a new Clinical Director: Garth Rapaport came in, and I started talking with him, and said, 'This is what we've got.' Wes had made this famous video of the ferret and I showed it to Garth and, of course, he's a clinician and he must have treated these patients and wow! He then - perhaps being more confident and on a different career path - went to Keith Mansford who was then Chairman of R&D [Research & Development] at Beechams and said, 'Sit down, look at this.' And then it just turned around, it just turned. Keith Mansford then said, 'We want this,' and it all changed. Then I was flavour of the month, yes.

TT: That was when you became Head of Department? Did they create a new Department for you?

GS: No, David Turner was then retired and I took his job. Which was interesting and lasted quite some time.

TT: Is that Director of GI Motility?

GS: Yes, yes. We weren't in Departments, we were in Therapeutic Groups. Yes, Therapeutic Groups; we weren't in matrix organisations, we were self-contained Therapeutic Groups with chemistry, biochemistry, pharmacology and *in vivo* biology. We were all in one Group.

TT: You were Head of all of that? What flexibility did you have to change things, and determine the course of research?

GS: Quite a lot. Yes, it was about 30-40 people, but mostly chemists, and I knew no chemistry so, of course, I relied on the Head of Chemistry there. So we prosecuted the 5-HT_3 receptor, we went back to 5-HT_4 and developed antagonists, then we decided we didn't want an agonist. And I'd picked up on other work that was ongoing at the time and said, 'Well, let's do this differently.' It didn't pan out, and certain other programmes of work were started, which in the normal way of things, didn't work.

TT: That must be part of just a normal cycle: evolution, continuity, change.

GS: Yes, absolutely. Most ideas in industry don't work. Then we merged with Smith, Kline & French and I ran the team that was trying to put the GI interest together, so I was backwards and forwards on an aeroplane trying to put that together. Great experience, but I probably wasn't ready for it.

TT: You were still based out in Harlow?

GS: Yes.

TT: Can you say a little bit more about this merger with Smith, Kline & French and how that changed, so you're becoming much more of a manager rather than a hands on person? How did you feel about that?

GS: Very strange. Almost emotional handing my rig over to Kay Wardle, who now has a very successful head hunting position. When I realised she was better than I was, I handed everything over to her. Yes, it took a little while to learn how to enjoy the science through other people. I got to the stage where I was getting bored with it and wanted something bigger.

TT: Bigger in terms of management or science or both?

GS: Yes, I wanted something more stimulating; something bigger and better, and I was getting interested in the next level. That was never going to happen, because we then merged with Smith, Kline & French. My opposite number was Mike Parsons, so he and I then became equal partners, if you like. I was charged with putting everything together in the GI section, including Mike's group, into the new SmithKline Beecham.

TT: You were doing motility, and Mike secretion?

GS: Yes, I was in charge of the motility. Mike became in charge of the secretion side of it. Well, there had to be some strategic plan to say what we were going to do in the whole GI area for this new company SmithKline Beecham. In the first period of several months, loads of us were flying backwards and forwards presenting plans, getting it all ready to get these companies together. We had to be one company you know. So although I wasn't running secretion, I was running the merger team that put all of GI together for the new company.

TT: And what kind of constraints or kind of brief did you have for that? The whole SWOT [strengths, weaknesses, opportunities, and threats] analysis?

GS: Yes, all that stuff, yes. There would be opportunities, threats, it was finding what have we got, what's in the two companies. What are they aiming for, is it worth continuing it or killing it, what opportunities have we got tucked away? There were some opportunities in portal hypertension from Alberto Kaumann, so that came under GI. We gathered all the opportunities, and put them together, and presented what they were, what the likelihood for success was, what the marketing opportunities were, could we do it, or couldn't we? What should die, what should live? And it was all merger activities ultimately in the presence of McKinseys, the management consultants, who were in my view absolute rubbish. I went through many of those meetings where, effectively, we ended up telling them what we'd do, so what was the point?

TT: This is very different from your life as a research scientist?

GS: Yes, I probably wasn't ready for it but it was good experience. I did all that and then settled down with Mike and myself running GI until the next therapeutic area review when GI was killed, Mike was paid off with a lot of money to go and work at the University of Hertfordshire, and I ended up in neuroscience.

TT: On your CV there's this very interesting expression, '…following a business-related withdrawal from GI research.' Is that a standard expression?

GS: Yes, it is. I went for a job interview at the time, wanting to get out, and with hindsight it was obvious, but the first thing they said, 'You've got this gap in your CV, explain it. Why have you suddenly switched?' So I thought, 'Yes, you're right,' and I had to come up with that. So GI was killed, a lot of people were made redundant and it was my first experience of redundancy. I now know what it's like to experience "survivor's guilt", but at the time I was really cross; most of my team were made redundant. There were tears and it was a terrible day. I stayed behind in the lab unable to confront them, even though it wasn't my choice. And then I just stormed into the general meeting absolutely furious, and I sat down and listened to this crap that I was now being given. Anyway, I survived, but clearly wasn't running things anymore, because I didn't know any neuroscience. I ended up in a group which had a name that I've forgotten. I ended up going outside, getting external money from Europe, a Framework [Programme] 4 [FP4] collaboration, to stitch together a consortium of people studying the role of long-term potentiation in cognition, working with Tim Bliss and others. We got a lot of money and didn't produce a damn thing in terms of drugs, but that's what you had to do at the time.

TT: So this was the mid- to late-1990s. Survivors guilt is a horrible situation, were you tempted to leave at all?

GS: Yes, it was mid-1990s. And, yes, I did go for different interviews. I went to Astra Zeneca, and I actually turned that opportunity, or potential opportunity, down for two reasons: one, I thought what they were doing was excruciatingly boring and behind the times, and two, I had a young family then the rule in Sweden was you have to be educated in Swedish, and I wasn't prepared to do that to them. So I turned it down and stuck it out. I went for other interviews, but I was swimming against the world tide; GI wasn't popular. I slogged it out. I set up other collaborations in neuropathic pain, got money for that, got external money for long-term depression and potentiation, but I was drowning definitely, definitely.

TT: How usual was getting external money in your company?

GS: It was unusual, but it was the way the company wanted to go. The human genome had been discovered, nobody knew anything about it, and you just had to start collaborating and getting external money to try and exploit the new knowledge. When I got the FP4 grant it was touted as a big success, because I'd just effectively added something like ten full-time employees to the company's payroll, which I hadn't, but that's how it was sold. And XX million, or whatever it was, into the company research.

TT: That was for the long-term potentiation (LTP) work?

GS: Yes. When we were doing differential display on hippocampus from animal models that had been made to experience/create LTP, followed by taking the hippocampus out. We got some genes, nothing came of them. We did the same with neuropathic pain, I got extra money for that and worked with people at Bristol, and yes, we were the first, but nothing came of that. We were the first to find the alpha-2 delta subunit for calcium channel regulated neuropathic pain, which is a much-cited paper now. I can't claim a lot of benefit, but I was the leader of that effort.

TT: You were in the situation where you had a gun to your head. Can you reflect a little on the challenges of being forced out of GI into CNS?

GS: I was drowning, and it was hard.

TT: Are there advantages coming from a different field - do you see things differently? You've already talked about overturning the dopamine dogma, you've ought against the tide a lot already.

GS: Yes. I talked to Pat Humphrey a little while after that, when he'd left Glaxo for Cambridge.

TT: When Richard Sykes effectively set him up in a research lab?

GS: Yes. And I was surprised to hear him voice my experience, which was fear that you were going to screw things up, because you'd been shifted from an area in which you were effectively a world leader, into another area you didn't know. It was really having the rug pulled out from under your feet. It was real fear that you couldn't do it anymore. I was surprised to hear him say that, because I thought he'd kind of gone into the same thing, but it was real fear that you couldn't hack it.

TT: And that was the same for you, was it?

GS: Yes, absolutely like that. And for Pat to say exactly the same words, surprised me. So real fear. I didn't know how I could hack this having come from effectively being a world expert in one area to being a child among world experts in a different area. How do I survive and conduct myself?

TT: How did you get the ideas, the confidence, to pick up the LTP stuff?

GS: Well, I was told to go in those areas. I went and talked to Tim Bliss at Mill Hill. We spotted the opportunity to get European money. Tim mostly, got all his friends together and then I brought the industrial bit in, to do the differential display *etc.* And we came up with a consortium and got the money.

TT: Did that make you feel better? Did that make you feel more confident within the company?

GS: Yes, I suppose so, but I was still in an area that I knew nothing or very little about. So you feel kind of disembodied from it all really, you're a manager.

TT: Not only did you not know about it, you don't sound as if you were as excited by it.

GS: No, because it wasn't my science; I was doing the coordinating managing job then. Yes, I would try and get involved but you can't compete with people who have done their PhDs and post-docs in the same area. What can you bring? Not a lot. So you have to just try and find ways of coordinating it, take the money and go home.

TT: And not get too frustrated?

GS: Yes.

TT: You did that for seven, eight years?

GS: Yes, and then we merged again and became GSK, and Tachii Yamada took over as Head of R&D, and he was a big GI man. So GI came back again.

TT: And lo and behold, they had a world expert on GI.

GS: I got back into GI. Not to run it, it was deemed they wanted fresh blood. Somebody was recruited who was utterly, utterly abysmal, just awful, awful. And when I talked to people at meetings, yes, there are so many horror stories around that appointment. I remember one day being sent an e-mail from this person which said, 'I've been here for quite a while now (not that long!) and made a big contribution (that wasn't true!). So from now on I want to be an author on all the publications that come out of this Unit.' I just read that and growled. No! I started to construct an e-mail reply and revised it I don't know how many times. I had to clear my head, so I went out and walked around the site several times to sort of calm down, clear my head. Then I bumped into another colleague who was working with us, only to find out she was also walking around the site trying to calm down, but we'd missed each other! This was in the morning and by now we were in the early afternoon, sitting in the foyer, 'What do we do about this? This is absolutely unacceptable,' because we had no respect at all, and we didn't want our name aligned to somebody like that. So we talked it all out most of the afternoon. How do we deal with this? We drafted all sorts of plans and whatever, and in the end by about mid to late afternoon, I was nominated to be the one to go and talk to the boss. So I went in and said, 'About your e-mail…, we don't think this is right and we don't want to do this,' or something like that. And the answer was, 'Oh okay then, fine.' 'Ah, okay, fine.' After all that! I left and I went back and I said, 'We've just wasted the whole day over this e-mail!' There are many stories like that.

So in the end, I wrote my personal appraisal and said, 'I think I've had a good year,' as you would do. 'I think I've achieved it against difficult odds, in the face of opposition, without any support and indeed hindrance from my line management.' You don't normally write that type of thing if you value your job. I included examples where I was about to start a programme, which subsequently went all the way to Phase 2B. I was about to go on and propose this whole programme of work. Five minutes before, my manager comes into my office and says, 'You've got to cancel. We're not ready. You can't do this. I don't think you should go forward.' Five minutes before the meeting. I basically said, 'I'm sorry, I'm going to do this.' And went in and it was accepted. We ended up with the longest surviving molecule from that group. After writing my performance review saying, 'We've achieved this against hindrance from my line management,' I went into a group meeting with Chas Bountra who had taken over biology by then, waiting for the axe to fall, only to be told that the awful manager had just resigned. So, an awful time.

And then we had, Gareth Hicks. Great guy, but at that time he seemed better at talking than doing the science (he has since built a fantastic and very successful career elsewhere!). He left and they brought in Kevin Lee - who was good. Anyhow by that time I thought, 'Look, I'm just going to go back to science, publish and enjoy,' which is what I've done ever since. About two years before I left, GI was killed again and I went into immuno-inflammation. By which time I'd given up.

TT: This would be about 2000?

GS: Something like that. I just thought, 'Right, fine. I've got children to support *etc*. I'm just going to put my head down and do a job, and I'm going to publish and enjoy myself as a scientist and do whatever they want, but I'm going to enjoy the science bit.' So I've done that ever since. It was a way of doing the job in a fun way, in a good way. You still ask the questions, 'What if?' If I'd been better at politics, if I'd been better at perhaps the vision thing, if the right people had been in charge, not the wrong people *etc*. You have to ask those questions, but like Dr Panchen said, when I was 19, 'You'll never know, because you'll never have gone that way. You went in this direction.' So that's true. So I just enjoyed the science, and that was my strategy after that.

TT: When GI was closed?

GS: I survived again.

TT: You were still valued?

GS: Yes, yes. There's value there. By then I knew the business. I think we were misled by Patrick Vallance who said we'd keep GI in a different guise when we moved to Stevenage. It was very clear then GI was not going to be kept in any form whatsoever. I moaned to my old boss, Kevin Lee. And he said, 'Yes, we were misled, but just get on with it.' So my job became being a sort of wise owl, which was picking up all of these programmes that were then going on at Glaxo Stevenage, and setting criteria. 'If you don't pass that, you die.' They'd never had that before, or at least that's how it looked. Setting criteria for project progression or death, and that's what I did a lot of.

TT: And this was immuno-inflammation?

GS: Immuno-inflammation, yes. Then that came to an end. I had an interview with HR [Human Resources]. The only thing I remember about that interview was that the HR woman who was interviewing me had the most amazing low-cut blouse on, leaning forward, and all I could see was breasts in front of me! It was just insane. How could they do that - this was HR!

TT: That must have been deliberate.

GS: Well, I often wondered, was that a distraction thing? I would have thought HR would have gone on courses for this. I don't know, I don't know. But I joked about it then and I still do. That's all I remember. Absolutely insane.

TT: And this is when you finally left? The MRC Skills Gap Award.

GS: Yes, I left. Jackie Hunter then told me about a grant opportunity which was joint MRC and BBSRC [Biotechnology and Biological Sciences Research Council], which I applied for and I got two years' salary.

TT: This was for you to fulfil a gap in an existing programme?

GS: Yes, a gap in university skills, which from industry I had certain skills and I could move those over to university and plug - not just plug a gap, but grow and develop things. Hopefully that's what we've done.

TT: And why did you choose QMUL [Queen Mary University of London]?

GS: Because there were no other GI Units within commuting distance, so I didn't have to move home as well. And there was a clear place to go, although I knew there was a lot to be desired. We'd been there not long before as a GSK team, and looked at the place, did some "show and tell" things, and I came back to my then boss, Kevin Lee, I had made a strong recommendation: 'We should not go there, it's bad, they're stuck behind the times.'

TT: This was just the London or Barts and the London?

GS: It was Barts and the London. The GI section only, I'm talking about. But it was GI, it was commutable, it was an obvious place to have a go at even though I had had that view. But I was now not talking about GSK investing there, I was talking about going there; it was a different job.

TT: Yes, and the possibility of correcting the problems? What was so bad?

GS: David Wingate was great and he was actually our Group Consultant when I was at Beecham, and he was great fun, a raconteur, well known for it, and he would come into a consultancy and just tell us all about what everyone else was doing. I was trying to do things that I realised was competitive, so there came a point where the usual consultancy appeared and I refused to participate, because I didn't trust his level of confidentiality.

TT: Because what he was telling you he was learning from others, and then learning from you and telling other people?

GS: Precisely. I love hearing him speak, but I refused to participate in the consultancies - I think that was only one occasion. So by the time we went down on a visit he was great, I loved his after dinner talks, but there was nothing there anymore. We were shown tissue bath work, which I knew very well, and it was just appalling; just archaic. Backward, there was no good science in my view, at that time.

TT: So when you're now wearing another hat, moving to QMUL, you obviously had a clear mission almost to rectify that situation?

GS: I had no authority so I had a clear mission to set my own lab up. I had no authority for anybody else. So once again I was given a room that was not fit for purpose. My first task was to clear all the junk out, including ancient vials of blood and needles. I didn't know what to do with it, so I dumped it in another unused room. I wasn't liked, but it was fine. I'd got money then from GSK and hired a great post-doc. We needed to get the kit up and ready. I was told I couldn't do things, do that, and so on, and so on. I needed a shelf. There was a plank of wood in the corridor that had been there for about a month. I brought my drills and screws from home, we put the plank up. 'You can't do that.' 'Sorry, we've just done it. Did you want the plank for something else?' 'You can't do that.' 'Done.' So we did all that, and moved everything out, and created a functional lab.

TT: What was the project you were supposed to be working on, on this MRC Skills Gap? What were you going to do?

GS: Yes, it was to set up a lab to use human tissue. I went back to my primary skills from a long time ago, which was functional translation. Only now I was using different words to describe the same job.

TT: So this goes back all the way to your King's College days?

GS: I picked up what I used to do, yes. I'd done human in my post-doc. When I went to Beechams I started doing human and I contacted a surgeon, Mike Morgan, at the local hospital who used to give me tissue. On one great occasion he turned up at my house, I've forgotten the time, but I remember it was dark, and said, 'I've got colon in the boot of the car. Where do you want it?' 'Okay, thanks, Mike.' I think it was cold; I can't remember if I went into work and got some Krebs or not, or did I keep it in the garage, because it was cold? Anyhow, when I took it in I wasn't ready to use it, so I left it in the cold room at work. The container leaked and all sorts of complaints came out of that, because of blood in the cold room. So that wasn't universally popular, but I started doing human tissue work at Beecham. Obviously that didn't continue, but it did set a slight precedent, and other people started using human tissues. And then, of course, in my industrial career, it was important to establish confidence that your drug would translate to humans, so I would contract work out. Eventually, I hired good people like Selim Cellek, who could work with human

tissues. He is now a Professor at Norwich, University of East Anglia. So I always did human tissue work a little bit.

TT: It seems to be what, to the general public at least, that's what drug companies should be working with.

GS: Yes. You have to translate to human. I've got a history of this, and that was the skills gap that I tried to fill. It didn't really matter what you did within that, but that was the gap.

TT: Yes, which you've continued since then. And that then led into collaborations with the surgeons.

GS: Yes, Charlie Knowles in particular, who said, 'Yes, you can have this, that and that.' And it was difficult at first, because he didn't really understand our needs. I'd go and moan at him and he'd say, 'I've given him one already, how much more do you need?' I said, 'No, we want it fresh. Ideally I want one every day.' So, eventually, the penny dropped after we'd provided progress charts of how many we got and with a great post-doc, John Broad, we and others have now established what is almost an industrialised collection of tissue, which other people share in and have contributed to making it good. And, I think that's now one of the big strengths of the Unit. We work on human, and we can get it.

TT: Once you've got humans you need a variety. Again, just looking at the grants you've had since leaving industry, there's an interesting range, because you've got the applications for the polyposis stuff and cancer, Age UK, and there is an increasing interest in aging. But you've also been involved with the NC3Rs, and there's public engagement about animal work and human work.

GS: The NC3Rs frustrate me. They are basically interested in toxicology or safety testing, so I have backed off. Tomorrow I'm at a Hadwen Trust conference.

TT: I'm very aware, first of all the time is going on, so it's five to one. Do you think I've sold you short? There's so much you've done, Gareth.

GS: 5-HT_4 agonists, antagonists, 5-HT_3 antagonists. Then I got involved in NK_3 [neurokinin 3] for a while because I had to, then ghrelin, then motilin, and a whole ton of discovery programmes that you never see, apart from the odd paper that pops up, because for one reason or another they don't make it as drug targets.

TT: Do you want to say more about that?

GS: It's part of the business where you've got to take a gene and run with it, particularly in the early days of the human genome discovery. I was actually at a meeting on incontinence last Friday morning. I met the guy who coordinates charity funding. He was once my chemist on a discovery team at GSK. He and I ran it. I'd pulled out a gene from the database - that was what you were told to do. 'You've got this great opportunity, now mine it.' So we pulled out a *P2X4* splice variant that was novel, and we did a high throughput screen and got nothing. The programme was dead because you can't move forward. And he asked me, 'What ever happened to that $P2X_4$ programme?' I said, 'Look, it was a splice variant. We didn't know much about it then, but I would never do that again. I've learnt now what splice variants are, and what their limitations can be.'

TT: Well, I don't know. It sounds like it's some sort of hybrid or something?

GS: Yes, it's the way the gene is transcribed. I said, 'I didn't know what I was doing. I wouldn't do that again. I would have chosen a better target, but that was what we were told to do at the time: 'Mine this database. Pull out anything that's novel and recognisable and run with it.' We thought this was going to be drugs galore in five years time or something, and how wrong that was.'

TT: You list some very impressive honours. Which of these do you value the most, or what has given you most satisfaction?

GS: At the time 5-HT_3 came out and was being worked on, there was an economic depression, and I didn't really see the patients. What I saw was the numbers of jobs I'd created. So what I, at that time, was most proud of, was the fact that I'd created quite a lot of skilled jobs, and I was really proud of that in the middle of a depression. So that was a feeling I strongly had: I felt proud I'd created jobs.

TT: I'm going to ask you a question I've asked other people, and particularly Pat. Looking at your CV, there's some things one might have expected to see there that are not. Perhaps you have not been as honoured as you should have been?

GS: Wes always keeps nominating me [laughs]. Yes, there was the competition with Glaxo, and because they had a much better clinical development and marketing machine than Beecham did, or SmithKline Beecham, so they ran away with ondansetron. They shouldn't have done. Granisetron is a better molecule, a cleaner molecule, but SmithKline Beecham didn't know how to do it as well. Glaxo had a machine and they were ruthlessly operating it. So we lost out. They ruthlessly operated the honours systems, and were rightly honoured, I think, perhaps *etc.*, but it meant they cleaned up a little bit.

The one I would have loved to have had if I think that way is some recognition from the cancer community, because I think we changed the whole landscape. I would love to, well when I think about it, and I don't often think about, I would love to be recognised by those guys. And I've had personal experience, when my late partner was dying with cancer, I was able to get the right anti-emetic medication for her. I was able to get her the right medication, but it was an emotional experience for different reasons, sitting in the outpatient treatment ward, watching the chemo going online, but it was a family ward. And one of the nurses came up and offered her a sandwich. Now no way would that have happened. And it was family. There were children coming in and there were several people there, and you just laid back under treatment and took your medicine and ate a sandwich. Our work helped make that possible.

TT: And probably no one there had any understanding of the change that had been.

GS: No, I was emotional for the obvious reasons, but also emotional when I realised how that had changed from what the scenario used to be.

But I was just thinking of one other story that's popped into my head based on 5-HT_3 and anti-emetics. When I was eventually asked by a guy called Robert Twycross of Oxford Palliative Medicine, to give a talk at one of his hospice care meetings. It was a round table workshop and I went in, there's a talk going on and I sat at the back. As it progressed I realised these guys had no idea of what to do. And I then became quite noisy and said, 'No, no, no, you can't do that! Why not use this drug?' Robert was great with me, explaining the realities patiently. 'These people cannot take oral medications, Gareth. We have to give it by i.v. [intravenously].' So, suddenly, I realised that I was in a different clinical world - palliative medicine - but I was still appalled at the level of ignorance. So I made a big fuss and I kept getting invited back after that, and I became invited to all sorts of places and would prep medical students giving talks in the end. There was one in particular down in Bristol, where the medic came in and there was a cancer patient who had serious vomiting problems. I can't remember the details, but as he progressed with the story, I almost wanted to shout out, 'You bastard. You did that to your patient? Why don't you know the science?' I got really quite annoyed and I don't normally do that. For many years I would give lectures at the hospice down at south London. Eventually, that became outdated and I don't do any of that now, because they have caught up. I thoroughly enjoyed it, the people there were lovely people. Very caring, very gentle. All of them, all of the clinicians, and that was an eye opener.

TT: I know Robert because we did a Witness Seminar on palliative care and one on pain control - he contributed to both.

GS: We wrote a paper together with Robert - well, an article, an opinion piece - because he said, 'I've got these patients with pruritus.' And I said, 'Well, there's one or two papers out now, we can block that.' 'So how does that work?' 'Well, it's probably synergy with something else.' 'That's really interesting.' So he was so curious he just pushed me and in the end, we wrote this little opinion piece on how it worked. He was Editor of the journal, so it walked in. It has never been cited, I'm sure, but it was a really good time.

TT: That's an interesting side light on pharmacological and drug research.

GS: But the clinical oncology community at that time lagged behind. That's not true anymore, which is why I don't lecture there anymore.

TT: One final area: as a drug discover and developer, given the kind of career you've had, do you feel possessive about the molecules? Are they your children in some way? You talk about the emotion of handing over your kit, your lab rig. What about the drugs?

GS: Yes, I had to hand over granisetron. It was deemed I was a good drug discoverer and it would be a waste to keep me linked to the molecule for its development. So it was handed over to Peter Blower who did a good job and that became his niche. He was very good at it, and he worked a lot with Paul (Andrews) on that. We patched up our initial disagreements about the dopamine hypothesis. I've had drinks with him since, and we both talked fairly openly and honestly, and we both said, 'That's past, let's shake on it,' sort of thing. Anyway, at the time, I was told to go back to research and so I had to let it go, and a little difficult, yes, but I did what I was supposed to do, and I did let it go. Occasionally I'd say, 'That's crap,' but more or less I'd let it go. But a little difficult.

TT: I can imagine. Because it's your baby in many ways, you created it, from your imagination, and your knowledge. I think it's in one of the Witness Seminars, actually Jackie Hunter talks about you having a little drug-inventing genie on your shoulder or something.

GS: I think she wrote that afterwards. I remember at the time I said that the biggest of killer of innovation was process, and Jackie loves process.

TT: No, she said it in the meeting. I remember it very well; it was a great analogy. And talking of meetings, I wanted to talk to you about the role of scientific societies. You've mentioned Pharm Soc quite a bit. How important have they been in your career?

GS: Pharm Soc in particular, going back to Alan Bennett, who taught me how to present and that discipline of getting it all in within ten minutes. The Pharm Soc when I joined was - and I saw it then as a junior - a place of really good science. You were questioned on your science. The abstracts you submitted had to be changed according to the questions. At the end of the session, the chair of the session asked all the members to vote on whether they wanted to accept it or not, and some weren't. And it was tough. It was hard, it was scary, but serious training. I then was lucky enough to get into the 5-HT area and I think that is peculiar, because the basic discovery of science came largely from industry and largely from Europe, and I include the UK there. And a lot of that activity took place at the Pharm Soc. It was a serious hotbed to be at, and you had to be there. I have mostly worked in GI research and I never attended the GI meetings, like the British Gastroenterology Society and Digestive Diseases Week and others. I never attended them because I didn't see the kind of science there that I wanted to do; the new ideas, the discoveries. So I always attended the BPS for the buzz of discovery, the hotbed of discussion that you could learn from, ability to rub shoulders with the great and the good, and do things. As years have gone by, I think the BPS has dropped off. I think the molecular and therapeutic areas have ascended. That's been good in many ways, and molecular certainly had to ascend, but I think there's also been a loss of that core understanding of the basic discipline.

TT: You are probably the sixth or seventh person who has sat in that chair and said almost exactly the same thing.

GS: So it's difficult now and I've said that I used to avoid the GI meetings, because I'd never go to them. Obviously in the industry there are times when, for your job, you have to go, and I used to go there and do that. Now I'm back in academia, I've been to some of them and realise I don't get anything out of them. I go to the pharmacology meetings; I always go to the annual one, which this year is next week. And it's good. It's lovely to see old colleagues, it's good to be there, talk my science *etc.* But it's not as demanding as it used to be. It's not as creative as I knew it. And that leaves me with a dilemma. I don't know where my scientific home is anymore. Yes to pharmacology always, but where do I go to get maximum benefit now. I don't know. It's not to the therapeutic areas, you only go there if you've got a drug and you want to sell something to a clinician. Go to the Pharm Soc, yes, it's good fun, but where do I go now? I'm not sure.

TT: Yes I know lots of homeless pharmacologists, physiologists, biochemists, all wandering around in the same boat actually. Even some of the historians. We're even more out on a limb.

GS: Yes, it's a problem. I'm going to the Hadwen meeting tomorrow, which is bioengineering and we whacked in an abstract, because I wanted to get in, and it's an abstract with no data. I said to a couple of post-docs I've got, 'Let's write an abstract.' They're trying to pull different cells out and they haven't done it yet, but they've done a great job; we're on the way. So I entitled it something like "Strategies for identifying…", whatever it was.

TT: It's an art being able to write an abstract without data.

GS: I sent it to my colleagues and they said, 'That's got no data in it. You always tell me off if I write like that.' But now they have risen to it, and it's not bad actually now, we've got some data. It's preliminary data, but it's there. Not bad. So we'll see, and I've told them, there's three of us going, my two post-docs plus myself, and I've told them all, 'I don't want you to come back without at least three collaborators.' That's the purpose of going to this meeting.

TT: Yes, it's networking. Do you have any stories of any particular Pharm Soc meeting or Pharm Soc presentation? Were you at the famous one at Birmingham when Philip Bradley organised a 5-HT meeting?

GS: Can't remember.

TT: I think you would have remembered if you were there.

GS: Probably. I was doing a lot of work on 5-HT, but I, to begin with, wasn't part of the club. I became part of it, but I wasn't initially.

TT: Was that because you were more in GI?

GS: Yes, and I was probably the new boy on the block as well. So when I published our paper on 5-HT_M receptors, I think it was John Fozard who said, 'I wish you'd used "5-HT_3". Why didn't you do that?' By then, the proposed nomenclature was out and I felt, 'Well, if you've not inviting me, I'm not going to play ball with you.' Which is a bit childish.

TT: Were you at the Heron Island meeting?

GS: No, the first one I went to was Melbourne. I wasn't part of the club to begin with. And, of course, I've since moved on, so I haven't stayed in touch either.

TT: Yes. What about any other societies? Did you go to Phys Soc?

GS: We did do a presentation at the Phys Soc. My then post-doc gave the presentation and there was some crusty old Professor at the back - I think it might have been Cambridge actually. She'd used the word pH

and protons interchangeably and he said, 'I don't know what they teach you in the commercial world, but in academia…' or something like that, '… we would have hoped you would have known the difference between that.' [Laughter]. Yeah, all right. I haven't been back since.

TT: An important part of academic life, is work on editing and advisory committees; you did an awful lot of these whilst you were still in industry. Was that quite well accepted? Was it something that just you did or did other industrial pharmacologists have these sorts of academic activities?

GS: I don't know, I just did it. I don't think the powers that be in industry were aware I did it, or cared, as long as I did my job. So whereas now you'd probably have to have it as a metric somewhere, then no-one really cared as long as you did your job. I was asked to do them. The first time I was asked, I was absolutely flattered. So it was, for me, an achievement to edit the *British Journal of Pharmacology*; I did that for seven years. And then, eventually, I was asked to do it again, by which time I was getting a bit jaded with it. Also with the career changes in industry, I just couldn't keep it up. At times I had to dedicate myself to just surviving, so I dropped some of those things.

TT: But you're pretty busy now, you're still doing peer reviews?

GS: Yes, but I don't edit anymore. I know there was discussion about inviting me back for the third time, and I winced when I heard it. It obviously hasn't happened, so it's fine. So no, I'm not editing at all. I kind of think that I did my bit. I was asked to start *Frontiers in Pharmacology (Gastrointestinal and Hepatic Pharmacology)* off, and I did. Then my then partner died and I just, emotionally, couldn't do it anymore, so I gave up.

TT: Understandably.

GS: And I've never been back since.

TT: One final question. Pasteur said that fortune is favouring the prepared mind. Is your creativity like thinking outside the box, or thinking a little bit further ahead than the box almost? And something you said very early on in our interview was, you were good at art at school. I just wondered, when you're thinking about molecules and receptors, do you have a visualisation of them? Do you have a picture?

GS: Um… I'm not a medicinal chemist. I don't look at molecules. I think I probably collect bits of information and then synthesize that into a story. I've got those bits of information in my head. They've got to connect somehow. What's the story there, you know? I probably do that. A bit of a collector, I think.

TT: Did you have a favourite toy as a child? You didn't have Lego or Meccano?

GS: A bit of Meccano, yes, but not much. The bits I had I've still got actually, because I inherited off my cousin who died with brain cancer at the age of about 11. So I was given them. I played with that, and didn't have the heart to throw it away. But a favourite toy as a child? [Laughs]. I was into jigsaws, which I loved.

TT: Tell me about jigsaws. Once a year I still do a big jigsaw as a treat. I've now got an adopted grandchild who is getting big enough to be able to pass on my old jigsaws. When did you start doing jigsaws?

GS: I don't know, when I was little. I enjoyed them. I don't know why. My father made me a little jigsaw board, and off I went. I always loved jigsaws - I still do, but it's not something I do. But when I'm ancient and bedridden, perhaps.

TT: Do you continue to do them?

GS: No, I've done them off and on, but no - life's not appropriate to have a jigsaw out for a couple of weeks or whatever it is.

TT: Geoff Burnstock does.

GS: Does he? [Laughs].

TT: Yes, or used to.

GS: For some reason I like that. How would I start doing a jigsaw? It would be sorting all the pieces out, collecting, organising and synthesizing.

TT: Were there any particular kinds of jigsaws you did?

GS: Not really, no. Difficult ones. They would be of their time so they'd be houses and countryside, lots of green in them and things. Then my mother gave me a jigsaw, which I didn't do for a long time, of an apple, a red apple, so it was about 80% red. And the rest was just something else. There's another jigsaw even worse than that, that she gave me too. That you can't do by vision. Well, you can't do it by colour vision, you do it by shape vision.

TT: Seeing patterns. That's almost what you do with drugs and receptors.

GS: It is that, yes.

TT: At that happy juncture, I think we have to stop. Thank you so much for your time Gareth.

[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.
8. Tansey E M (intvr); Tansey E M, Zarros A (eds) (2016) *Green, Richard: transcript of a video interview (17-Dec-2015)*. History of Modern Biomedicine Interviews (Digital Collection), item e2016035. London: Queen Mary University of London.
9. Tansey E M (intvr); Tansey E M, Zarros A (eds) (2017) *Sanger, Gareth: transcript of a video interview (08-Dec-2016)*. History of Modern Biomedicine Interviews (Digital Collection), item e2017138. London: Queen Mary University of London.