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AUDIO INTERVIEW TRANSCRIPT

Miner, Wesley: transcript of an audio interview (15-Jul-2016)

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Miner, Wesley: transcript of an audio interview (15-Jul-2016)*

Biography: Mr Wesley Miner BSc (b. 1948) is a graduate in physiology from the University of Edinburgh. From 1982 to 1986 he worked at Beecham Pharmaceuticals (GlaxoSmithKline since 2000) with Gareth Sanger. During this time, Miner and Sanger discovered, and were the first to publish that serotonin receptor type 3 ($5\text{-}HT_3$) antagonists were extremely efficacious pharmacological agents for preventing and treating anti-cancer therapy (chemo and radiation) induced nausea and vomiting (Miner and Sanger, 1986). This seminal experimental work translated very well to the clinic when granisetron (Kytril) was shown to be highly efficacious in patients. Importantly, this discovery became one of a very select few where research into 5-HT mechanisms actually culminated in a marketable drug that markedly improved the quality of life for patients. Following this ground-breaking research at Beecham, he relocated to another major international pharmaceutical company and became a key member of the biology team that discovered darifenacin (M_3 selective antimuscarinic), which is now indicated and marketed for over active bladder and urinary incontinence.

TT: Tilli Tansey

WM: Wesley Miner

TT: The first thing I really want to ask you Wes is about your childhood, schooling, and influences, and how did you become a scientist?

WM: Right. Okay. I kinda suspected this might come up so I have been sort of reviewing it all and thinking back about it all. So actually, was brought up around the Chicago area and lived there for a number of years. And of course you say 'How did I get interested in science,' so, how did I get interested in science? And I tell you, I put it all back to one of my aunts who actually for a birthday present bought me a book club subscription. And this book club subscription got a book every month, and in fact you got novels but it also had a series of books and these books were called *All About* books. And they may still be going today. But the first book I ever read, I got this from the book club, was *All About Dinosaurs*. Now I didn't have a particular interest in dinosaurs at that time but I found the book kinda fascinating. I was about eight-years-old and it struck me that, oh my gosh, you can get all this information, in a book like this. And there were a couple of other books in the series, I was about seven or eight years old. The next one I think I read was *All About the Solar System*. And then an *All About the Atom*. And by then I was starting to get really kinda hooked on science. And I went through school, enjoyed science and also enjoyed mathematics, had one teacher in particular as I'm sure we all kinda do look back to, and she got us into mathematics quite early. We were only about nine, I suppose, ten-years-old, and she started us off in algebra. And all of a sudden I saw equations and how to solve x and all that. And again I just found it absolutely fascinating.

But I have to say actually I was quite a lazy child and never really kinda excelled, certainly in my younger years, along that line. So is that kinda what you're…?

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* Interview conducted by Professor Tilli Tansey, for the History of Modern Biomedicine Research Group, 15 July 2016, in the School of History, Queen Mary University of London. Transcribed by Mrs Debra Gee, and edited by Professor Tilli Tansey and Mr Adam Wilkinson.

TT: Yes, that's the kind of thing, people all develop their interests in different ways, and that's a fascinating story. Did you have siblings?

WM: Yes, I had my sister who was superb at everything [laughs] and about three years older than me and so she of course went through school and did exceptionally well and straight A's and all that, and then along came me. And I was really kinda a dozy kid which I'm not sure I actually put it down to possibly my hearing loss. I think I had it ever since I was quite young.

TT: Were you aware of it as a child?

WM: I wasn't, I wasn't, and I think I just lived in a little land of my own. But I do remember, although if a subject caught my interest then I would do very well at it. And we did all these IQ tests back then and for some reason I just happened to be good at doing IQ tests. So I guess I had the feeling that yes, I could do things but I really had to be interested in doing them otherwise a bit of a slacker. And then kinda went through grade school and then when I was 11-years-old I had a pretty sharp change in direction in life. And what happened was I was in an airplane crash or an aeroplane crash, as they say over here. And in the crash actually my mother, father and favourite cousin Ritchie were killed, and only my sister and I survived the crash. But what it meant was then I ended up living with my uncle, my father's brother, and he brought my sister and I up, and in fact he was very educational oriented, interested in education. And from there he made sure that my sister and I just really got pretty much top-notch educations. We ended up going into a school system in the State of Michigan that was probably the top school system in the State. And probably one of the top school systems in the country. But as I said, I was still a bit of a slacker. If the stuff caught my interest I'd do okay but I was certainly, I don't know if you have it over here, but you have kinda grade point averages, A, B, C, D, Es and all that so by the time I finished high school I got about half Bs and half Cs. Nothing really outstanding by any means.

And at that point I was thinking about, well, what am I going to do? But one of the things that actually influenced me and being a bit of a lazy person anyway was of because I had a trust fund and an estate set up by my parents. So I finished high school at the age of 18 and thought about university, going on to university, again I was interested in science, but didn't really know quite where I wanted to get to with it, and had this trust fund which became all mine when I was 21. And the trust fund, it was sizeable, by today's standards it would probably come out about $800,000(US), so it was a good size trust fund. And this was a sort of a bad combination, somebody who is really lazy, knowing that the money is going to be there. And so I got out of high school at 18, went to a couple of junior colleges, kinda not doing too much but just kinda keeping going, not gaining any sort of qualification, and then hit 21. Well, 21, all of a sudden money is there and accessible for me. I had this $800,000 and from the time I was 21 till I was 24, 'I spent 95% of my inheritance on fast cars, fast women and booze and wild parties.

TT: Did you enjoy it?

WM: Oh, enormously. Enormously. And in a funny sort of way it did kinda get my interest going more along kinda neurology, because what can I say, we did dabble, I shouldn't put this in print [laughs] and I got interested in the effects that drugs could have, psychoactive drugs at that time. Anyway, so there I was 24, I'd spent all my money and it suddenly dawned on me I was going to have to go to work to actually support myself and feed myself, and that was pretty appalling, that was quite a frightening thought. And what I did, I ended up I had $10,000 left and I thought, 'Well, if I stay in the United States I'm just going to fritter the rest of that away in 6 months or so. So what I'll do is I'll go to Europe and if I got to Europe I can probably kinda string the $10,000 out for maybe a couple of years before I have to go to work and actually support myself.' So that's what I did. I bought a one-way ticket to Munich, Germany, bought a really good sleeping bag and a backpack and got on the plane and went to Munich.

TT: That in itself is quite enlightening, you had some self-awareness and you were brave doing that surely after having this rather hedonistic lifestyle.

WM: Or ignorant.

TT: Can I just go back to one thing, Wes? What did your parents do? Were they scientists? Did they have a science interest? Obviously they were quite well off setting up this trust fund for you.

WM: No, well my dad was pretty much a self-made man. I come from real working class roots. I think my uncle who I lived with was the first one who actually went on to university of the whole family on both sides of the family, mother and father's side. Mother and father very much working class. They were first generation Americans because grandparents came over from Germany around 1900 on my mother's side. And then on my father's side, grandfather's side of the family were French Canadians, bird-trappers as far as I know, fraternized with the American Indians; I am actually part American Indian, and then my grandmother's parents were also German and we're not sure if she was born in Germany or the United States, she never kinda let on. But very working class. My father was a very ambitious man and he went on to start his own business actually selling foundry equipment to companies like Mars, Campbell's Soup, Coca Cola. Then he built up his business and this is actually why we ended up in an airplane, because he had the airplane for flying, for business purposes and all that. So, but, he always made this claim he was going to be a millionaire by the time he was 40. He wasn't quite there, but he was moving in that direction with his business.

TT: So we'll come back to you. You're 24, you arrive in Munich. As you had German heritage did you speak German?

WM: Not at all, not at all.

TT: So that was even braver. You went to Munich rather than London for something else?

WM: This is where the ignorance comes in. This is where the outright ignorance comes in and Hollywood. And I tell you this was a huge shock to me. I flew into Munich, right, and I expected everybody to speak perfect English like they do in the movies [laughter]. It was just total ignorance on my part. And I got into Munich and all of a sudden all the security people they talked to me in German, 'What? What?' And of course almost all of them can speak English anyway, but they don't want to. But no, it was just pure ignorance on my part. It wasn't real bravery or anything. But got into Munich and stayed there for a little while. I will say spent a lot of time in the Hofbräuhaus.

TT: You have to, it's only polite!

WM: It was during one of the festivals. And then I came out quite nice. And then I decided, well what I'll do, actually I had enough money so I bought myself a Volkswagen car and I figured I could get one pretty cheap over here, which I did. So I got this Volkswagen, it was a nice little car, after Munich, stayed there for a little while and then went south through Austria, then Italy, Genoa for just a little while, and I did have a friend who I must say was actually a little bit of an inspiration to me. He was from back in high school. His parents actually were quite wealthy and he actually was studying music in Aix en Provence just above Marseille, and he'd been over there for about a year. So I figured, well what I'll do is come around through Austria and Italy. I actually drove through Nice and Monaco and I don't think I could afford to stop [laughs]. And found him and ended up staying with him in Aix en Provence for a few months there and got to know the area a little bit, never really picked up any French or anything. And then from there I decided what I'll do is I'll go north and so I got my car and headed North, made it through France, made it through Paris and came onto the coast and came over on the ferry. Now this would have been 1972/73 somewhere in that region and got into England. So there I was in England. And I got in about 10 or 11 o'clock at night and I tell you, this is how stupid I was, this is how ignorant I was. And I figured, well I'm going to drive a little bit further North. So I'm driving further north out of London and I'm thinking, 'I've got to find a hotel.' I've got to sleep here sometime, right? I can't remember where I was exactly but it was more a little seaside area somewhere north and I kept looking at these hotels and they all had signs out front and it said, 'Residents Only' and I thought, 'Gee, I'm not really a resident of the country' [laughter]. So I'm driving for miles past all these hotels with 'residents only'. I didn't know. And finally found a motel that didn't have 'Residents

Only.'

TT: So you're heading up the M1 or whatever.

WM: I think I went up the east coast, the A1 and everything.

TT: And so when did you stop? What were you going to do in Britain?

WM: Well, I sort of kept heading North, I don't know why, but I figured I'd head north, and ultimately made it up to Scotland. And to cut a long story short, I met my future wife up there. She was working at a hotel. And we then kinda went out a little bit for a few weeks and all that, a few months, and then I convinced her, and this is way back in the free days and all that, I convinced her that actually, 'Why don't you come on down and we'll go stay in Brighton?' Why Brighton I don't know, it just seemed a good place to go. So she came with me and we went down and we lived in Brighton for three months. And at that point my visa, I think, ran out. And I think my money was running out too. So I said, 'Okay, I'll go back to the United States and I'll sort something out and you come on over. And then once you're over there we'll live together over there.' She was from Perth, my first wife was from Perth. And so that's kinda what we did. I went back to the States and then my first wife came over, and we were in the United States and she really didn't settle in well.

TT: Where in the States? Did you go back to Chicago?

WM: Detroit. Family was kinda located around Detroit/Chicago area but it was more around Detroit. That's where my sister was living. And I had to live with her actually, because I'd run out of money. She was smart, she held onto all her money. I used to try to talk her into giving me some of her money, but she never would [laughter]. So we went and we lived around the Detroit area for about a year and then my wife really didn't like it so she decided she really wanted to come back to Scotland and I figured, 'Well, okay.' Notice I say Scotland, I'm trying to say 'Scott-land' not 'Scart-land' [laughter]. So we did. We came back to Perth. Now I will say the one thing, you said where did my interest in science come, it was after I actually first got over here, came over on the ferry, and I had actually stopped at this hotel that I finally found that wasn't just for residents [laughs] and I was kinda lying there, I think I had a pint of beer or something, probably a pint of Guinness and I spent a long time trying to look through it and see the other side [laughs]. That's actually beer? And right about then - it was almost like a revelation - I decided, look, I really want to get into some form of medical science. I don't know why. I just had a, this is what I want to do, I want to go into some form of medical science. I want to go into neurology or pharmacology, physiology but that's what I want to do. So I want to get into university, get my degree and then go further if I could and then that's, I would see from there. So that's really where that started.

So when my wife came over with me to the United States I started off going back to what they call the junior colleges over there and I started taking a few courses in physiology and getting the science back up. Because again my grades from high school were pretty average.

TT: And had you done much biology in high school? You talked about maths.

WM: I did a year of biology, it was called the college curriculum or college prep curriculum, so you had the sciences and all that. So we did have science, we did have some. So I got back into that and then we decided 'okay, we'll go back to Scotland.' Well, my wife wanted to go back to Scotland, I'll go with her.

TT: Can I just ask you, you had got married by this time?

WM: We had to get married in the United States because my wife's visa ran out in the States, and so in order to keep her in the States, I can tell you that's a whole funny and strange story on its own really, but it has nothing to do with the later things.

TT: I'm happy for you to tell it if you want to.

WM: No, no. So we went back to Scotland and we were living in Perth where her family was located. And by that time my son was born, my first son, and I decided well, yes, I still want to go to university, I still want to get into some form of medical science, physiology, pharmacology. And I actually through whatever means I actually got an appointment with the, I think it was the Department of Science Head at the University of Glasgow. He probably saw I was American and thought I had money, which I did not at that time. And so I went down for the interview and I talked to him and I said, 'This is really what I want to do. I want to get in this area.' And he said, 'What are your qualifications?' And I told him high school, effectively science in high school. And at that time, and I'm sure it's probably still the case, actually getting into a Scottish university and an English university, they were about two years in advance of any American university. So what was required was you had to have full two-year university in the United States before they would admit you to the universities over here. Very good school system over here, much in advance, much more focussed, at an earlier time.

So anyway it dawned on me, he said, 'What you're going to have to do, is you're going to have to go back and get your O grades and your Higher grades in science before you are going to be able to get to university.' Okay, well, if that's the way...

TT: This is a bit daunting because you're in your…

WM: At this time, I'm 25 and I thought, 'Well, if that's what I've got to do, that's what I've got to do.' And so what I did, again living in Perth, they had Perth College of Further Education where I could do my O grades and my Higher grades. And so what I did was I got a job working nights. So used to go into work at night at 10 o'clock and it used to be in a textile manufacturer, made carpet backing. So I used to go into work at 10 o'clock at night, work until six o'clock in the morning, come home, get about two hours sleep and then I'd go to all my classes at the college to get my O grades. And I did that for about three years, but managed to come out with, with my Higher grade in physics, chemistry, mathematics and biology. And I really put in a bit of effort so I got straight As all the way through; even got a prize [laughs]. But it just tied in with exactly what I wanted to do at that point and then of course went through the system and applied to the universities and Edinburgh was my first choice.

TT: Why Edinburgh? You'd been to Glasgow; you'd been to see this guy at Glasgow.

WM: Edinburgh just, by then I started looking into seeing the reputations of the universities and I looked at biological sciences at Edinburgh and they had exactly what I was looking for because I could see that I could sort of get into chemistry, pharmacology and physiology. So applied to Edinburgh, and got my, what do they call it? Conditional offer, had to get my two As and two Cs or something. But I managed to get all my As, got all my As in my Highers, so got accepted at Edinburgh. And of course the great thing about all this was I thought I was going to have to work the whole time to put myself through but by the time I actually applied and got into the University, and I'm sure it was still the same down here [in England], I'd been a resident for three years and the government paid for it all.

TT: At that time, yes.

WM: Phenomenal system. I was just astounded, absolutely astounded. They paid all my tuition and we got an allowance and stuff like that. We didn't live well but we lived.

TT: So your wife and you had one child by this time?

WM: We had two by this time.

TT: And then moved to Edinburgh?

WM: Well yes, eventually. We started out, we were in Perth and then I would travel back every weekend from Edinburgh up to Perth until we actually found accommodation, were given some sort of I think a little bit of priority status or something with the university and then we, yes, we all moved to Edinburgh and then my third, my daughter was born, my third child was born when I was at the university. But at university I just found the whole thing fascinating, I was exactly where I wanted.

TT: So you did physiology from the start?

WM: No, at Edinburgh what you had to do is you started out in biological sciences. If you're familiar with the way the system works up there, what you do is you do three years and actually at the end of it you come out with, in the third year you come out with a BSc, what they call your BSc. Then your fourth year you're allowed to specialise if you've done well enough during your three years. And in biological sciences I think you could have gone into ecology, pharmacology, chemistry, biochemistry, physiology, genetics, molecular biology, bacteriology. So those were all under the scope of the university biological sciences. And then you got into your fourth year, you had to go for interviews, to the Head of the Department and say, 'This is what I want to do.' And this was Bill Watson, was Professor at Edinburgh at the time; John Russell was Assistant Head of the Department. Great guy.

TT: Had they taught you during your three years' biological sciences? Were you at KB, the Kings Buildings?

WM: Oh, yes, good old King's buildings, as an undergraduate, yes.

TT: Had you been at Teviot Place [the Medical School] as well doing physiology?

WM: Yes. We did most of our second year all out at Kings Buildings. I remember walking down to Kings Buildings; first year was pretty much all up by George Square, the Appleton Building, we did all our biology and chemistry and everything up in Appleton Tower. And then we also, actually by the time we got into third year, actually that was all back up by George Square because that was Teviot Place that we were, doing physiology. But physiology just really struck me as, 'Boy, that's really what I want to do' and pharmacology too. At that time the Pharmacology Department was the number one prostaglandin centre of the universe, it was Eric Horton who was Professor at the time with Norman Poyser, Bob Jones and all those guys, they were all my tutors up there. And so I got in and decided I wanted to do physiology and talked them into letting me into the honours year and went from there.

TT: Was there anything in particular in doing physiology that really got you? Or any Lecturer? Or was it just the whole thing?

WM: Well, we had some certainly very colourful lectures. We had Andrew Packard, do you Andrew?

TT: I knew him very well. I did my first PhD on octopus brain.

WM: Oh, well gosh, you will have known Andrew.

TT: I'd forgotten that.

WM: He was quite a character. He was really a character but the work he did was absolutely astounding on the cuttlefish with how they change the colours and all, and the octopi and how they change all the colours. And I actually, I found Andrew quite inspiring because he actually started making me think about how things actually work in physiology and the body. And how related they are to chemistry and chemical equilibriums, and effectively if all the chemicals are in the right places and the enzymes are in the right places, the reactions go. And that's all we're made up of. And so it got me thinking along those lines, about how that actually worked, but there were quite a number of just outstanding lecturers. Paul Andrews was very entertaining.

TT: Well, you would have known Paul in the final year, in 1979/80?

WM: Yes, I graduated in 1980. I certainly remember Paul and it was actually knowing Paul from Edinburgh that got us back together ultimately when I was at Beecham later.

TT: In your final year in physiology did you do a dissertation or research project?

WM: Yes, yes, did a dissertation actually not an area that I was particularly focused on at the time but it just kinda struck me as fairly interesting. It was about muscle tone. And so Martin Lakie and Geoffrey Walsh were the ones that were actually involved in that area. Unfortunately Geoffrey Walsh, I think, was a bit ill at that time and so I interacted with Martin Lakie on that. Also up there another very sad story actually, I don't know if you remember Martin Prestige; I think he may have stopped before you arrived.

TT: He was sort of leaving or on the way out.

WM: Well he died, and what it was Martin, he was a Lecturer, Senior Lecturer there, and as a child I think he had polio. And he actually had this problem, I think his carbon dioxide (CO_2) levels go up because he couldn't breathe so well. We'd be sitting there in sort of doing an experimental set up or something like that and you'd look at Martin Prestige and it looked like he was sound asleep. And what happened was that Bill Watson actually convinced him that he needed to get something done about it because he wasn't getting enough oxygen. And he went down and they actually did something where he ended up ventilating a lot. Of course he blew all the CO_2, somebody wasn't monitoring him, and he just stopped breathing and that was it. Horrendous, absolutely horrendous. Very nice guy. Elizabeth Hobson, she was there.

TT: She was a very motherly figure.

WM: Oh, very much so. She was my, I think she was my tutor in my final year, I'm pretty sure Elizabeth was and I cannot remember the guy's name, kidney man. A young guy.

TT: Yes, went to Australia. Peter Harris.

WM: Good kidney man. But the whole Department was very good. John Russell, very droll sense of humour, very nice guy. Watson I think became Head of the Physiology Department at the time. Pharmacology at the time was also very good and even biochemistry. By the time I finished my third year I had enough chemistry on board that I could have actually gone into chemistry on its own. But very high quality obviously, I mean you can't dispute that. Got my interest really going in physiology, kinda fed my interest in the neurosciences which I thought was very interesting. Additionally, so was working with Paul [Andrews] though I can't remember a lot about what Paul taught us actually [laughs]. I just don't remember doing the gastrointestinal system (GI) with him and I say that for a reason because ultimately it was the GI that really caught my interest once I got into industry.

TT: So you've come to the end of your degree and you're having a fascinating time, really enjoying it, so you're thinking of carrying on?

WM: I suppose I did but then again I started thinking, 'Well, I got three kids, and really at this point might not be a bad idea to get a job.' And of course coming into the final year, right from the beginning of the final year, you start applying for jobs. And I applied for anything and everything. I was applying to British Rail, I was applying to be an accountant, you name it! I applied to all the pharmaceutical companies and ultimately I was really very, very fortunate in that I got a job with a small contract research organisation, I say small actually it was the second largest in all of the United Kingdom, Inveresk Research International (IRI) out there, which I do not think exists anymore. I think they were bought over. But it was only second to Huntington for research.

TT: Contract research?

WM: Contract research, yes. Of course the wonderful thing about Edinburgh and the whole course, honours degree physiology course, was just we did *in vivo* work. We were all actually licensed by the Home Office. I just don't think anywhere does that anymore. We were all licensed in our final year and we were doing experiments, we cannulated everything. We worked on rats, we did work on ferrets. Because of the association with the farm we were able to work on sheep doing open heart surgery and stuff. It was quite amazing that course, and I came out of the university with a pretty good *in vivo* experience which a lot of people just wouldn't have these days. But it did mean that when this job offer came up from the contract research it kinda really played to my strengths and they were doing a lot of *in vivo* work at the time. So I was able to slot right in, just changed my licence, they didn't even have to apply for a licence for me, and got into IRI.

TT: Inveresk wasn't very far away, was it?

WM: It was really quite nice. It was in Musselburgh. Well, that's where the original company started in Musselburgh and it was an old estate owned by a family of admirals, it was a beautiful old place. You kinda went up the hill and you had the estate and then, but they had also purchased a facility out in Elphinstone and that was the more of the actual Pharmacology Department and Toxicology Department, out at Elphinstone. In fact, I talked with one of the ladies, because you had Lord and Lady Elphinstone and one of the ladies who used to work with IRI when she was a child she told me how she used to go into the Elphinstone estate and see Margaret and Elizabeth (the young princess daughters of King George VI, the elder, Elizabeth, becoming Queen Elizabeth II) playing. They would sit hiding behind the fence and see them playing because apparently they visited with Lord and Lady Elphinstone quite a bit. Now that was up in Musselburgh and so we didn't have much money as we were still living right in downtown, the centre of Edinburgh. So I got myself a bicycle and I used to cycle out to work every day and I got very fit, got very fit, heart rate went down to about 45 beats a minute [laughs]. But worked there and picked up on experience particularly recovery, surgical experience - because a person I worked for, my supervisor, had actually gone to Edinburgh University too and they were very much involved in studies investigating drug dependency. And so what they were looking for actually was to develop models actually in primates, non-human primates. There weren't many places using non-human primates and I wouldn't want to do it anymore along that line, but at that time it was quite a selling point because you could actually develop models in the non-human primates of drug dependency, and then looking to see, there's all this substitution, what you can substitute for cocaine and all of that. And at the time actually it was a lot of the big tobacco companies were looking for what happens with nicotine and what substitutes for it. But I learnt a lot of recovery surgery from that.

TT: What kind of animals were you doing recovery surgery on?

WM: Recovery surgery was actually being done on baboons *Papio papio* and macaques. And this was allowing them to self-administer drugs then you could see what they would actually substitute, if you started them out on cocaine, you could see what drugs would substitute by the various tobacco companies.

TT: What sort of monitoring were you doing? Physiological monitoring, behavioural monitoring?

WM: It was pretty much behavioural. You could monitor how much they self-administered the other drugs and keep a record of that, and behavioural monitoring. It was very much behavioural. It wasn't physiological.

TT: So the behavioural monitoring means what? Aggression, grooming, feeding?

WM: You had a whole list and you would sit back and you would watch them and you could tick this off on that. So that certainly got me into those type of skills too.

TT: Did you have any say in the kind of projects you were involved with?

WM: Well, at that point we were actually quite a small department, we didn't have a lot of us. There were five or six of us I think, something like that. And have you ever worked in contract research? No? Well, don't. The problem with contract research is you have a client comes in and they go, 'Oh, well, we'd like this study done and here's what we're interested in.' And of course you're sitting there, I can remember sitting around the table with my supervisor and the rest of us and the client telling us, 'This is what we need done' and kinda looking over at my supervisor and, 'Can you do that?' 'Yes, of course we can do that' [laughs]. 'No problem, no problem.' And we all had a coffee break, we'd come out and say, 'Can we do that? How are we going to do that?' We had no idea how to do it but you couldn't turn down the business and so you had to do it. This is one of the things that actually drove me out of contract research because it became what I started calling the instant expert syndrome. In weeks, maybe months if you were lucky, you had to become an expert in what you were doing for a particular area. In one study we were looking at neuropathy in animals, guinea pigs dosed with lead.

TT: With lead?

WM: Lead, yes, which produces a very nice neuropathy, but we had to just develop the expertise very quickly and I just really didn't like that side of it.

TT: Who were your customers mainly? You mentioned the tobacco industry. Government?

WM: No, it was actually mainly the pharmaceutical companies. There were quite a number from the Continent, France, and the other problem was you had to get out and you had to sell. So it wasn't just the science side of it, you had to meet the clients, you had to sell, which was okay but it wasn't something that I really wanted to do. My father was a salesman, he loved it. It was a game to him. If he could convince somebody to buy something, it was his game. I'm not a salesman and so I didn't enjoy that part of the work.

TT: And so you were there for two years? You developed new skills, enhanced your repertoire of practical skills and had your eyes open for something else? Did you deliberately think, 'Okay, I now can start looking for another job.'

WM: Yes, two years, I was there for two years. It was exactly that, I figured I could see during the two years I had been there, I'd pretty much picked up what I was going to pick up sort of skill- wise, and I really decided, "Well, look, if I'm there any longer I'm going to have a hard time" because you've got to remember I'm 10 years behind in age than everybody else. I didn't even start till I was 25 into thinking about this, didn't graduate from university until I was 32, so I'm 10 years behind. So I figured I'd better get out and see what I can find in Big Pharma at that point, and that struck me as where it was going to be most likely that I was going to find a position. Because back then, I don't know if you remember, you used to look at *New Scientist*, you'd turn to the back, the classified section, and they were packed with job adverts. Have you looked recently? Absolutely nothing. But back then, just packed out with jobs because you had a lot of pharmaceutical companies growing, even had several up in Scotland. But I was inspired and, 'Yes, I'm going to do it' so I got the old CV together and applied for positions. And I got two offers, well I can't say I got two offers, I got two interviews. And the first one was with Wyeth in Maidenhead, somewhere down in that region. I think it was David Green who was the Head of the Research down there and Nick Shepperson was working with him. Nick is fairly well known in the cardiovascular area. And so it was a cardiovascular job, I went down for the interview, pretty interesting stuff. Cardiovascular, glamour area, as in neuroscience too. And then right almost exactly at the same time that's when I got also called down for an interview at Beecham and went down for a Beecham interview and realised it was going to be in GI motility, the GM project. And I have to be honest it really was my second choice. I'm thinking, 'Yes! Cardiovascular, wonderful glamour area.' But luckily, quite fortunately, I didn't get the offer from Wyeth, they didn't make me an offer and Beecham did make me the offer and so that was it, I figured, 'Yes, okay, Beecham, well known company, big company and all that, I'll certainly go for them, I'll see what GI is like. If I'm in the company if I maybe don't like it I can always sort of shift myself around a little bit.' So that's what I did and that would have been 1982, because I'd been there for two years and 1982 moved down to Beecham.

TT: And this was Harlow?

WM: This was Harlow. Terrific actually, very nice research site. We also had Merck, or sorry Merck Sharpe and Dohme, over in Harlow. But the Beecham Harlow research site, it wasn't a big site, it was, I can't imagine it being more than 300 of us on the whole site. It had I think Gastric Motility and it had Gastric Ulcer, Cardiovascular Department and then there was the Arthritis Department and then there were two CNS Departments. So it wasn't particularly big, there couldn't have been more than about 15 biologists at most per each project area, and then of course you have the chemistry. So each project area maybe only had about 20-25 people in it. So a smallish site, you got to know everybody which was really nice. It was a modern site, very just recently built and set in a very nice little pleasant area. So that fit it quite nicely and additionally the buildings themselves, because they were new, they had phenomenal facilities, they were amazing. In fact, the research building, when it was first designed, they put in a surgical suite with it and just off this surgical suite was an x-ray suite and this X-ray suite had a full fluoroscopy unit, everything, you name it. Somehow, the way I heard the story was, they were building the new research building, somebody had just thought, 'Well, this might be a good idea,' threw it in for an extra couple hundred thousand pounds, and it got put in [laughs].

TT: Amazing.

WM: Well, this fluoroscopy suite, with the surgical suite, you had two full surgical areas where you could do clean surgery, and this fluoroscopy suite right off it. And I had actually been to some medium sized hospitals and they did not have this nice a facility. It was quite astounding what they had. But the fluoroscopy area nobody used it, it was just sitting there, absolutely sitting there, just not used at all. And so I started in on the GI work and the head of our section was a guy called David Turner, and the whole structure at Beecham at the time was amazingly horizontal. So you had your project area, for example, we were in gastric motility and I think there were about, of course there was Gareth Sanger, Christine McClelland, Mike Kelly, Brian McRitchie, myself, Steve Cooper and a couple of technicians, Mark Evans is now a Professor somewhere, and Jane Burridge and we all reported directly to David Turner. There was all this very horizontal structure. And so I started up in that and reporting to David and David actually started me in on investigating lower oesophageal sphincter pressure, which I knew nothing about [laughs]. I didn't even know, I don't even think I knew a lower oesophageal sphincter existed! But I thought, 'Okay, here we go' and once I started in, what we were going to do is we were going to measure the lower oesophageal sphincter pressure in dogs. Now I won't go into all the details but the model was fairly straightforward to set up with this but there were a lot of problems with it as it had been set up. So what I did is I went right back to square one on the literature. Now a lot of Australians were doing stuff on lower oesophageal sphincter pull. What you do is you take a little tube and pull it through the sphincter but you have little ports on this tube which are connected to pressure transducers. But you have to have everything sorted out just right and you have to have the right compliance tubing and you have to have a flow through the tube to measure it all.

So I went right back to square one on this and all I can imagine is our poor librarian. She must have got more requests for me on articles on this, her workload must have gone up tenfold when I actually came there just because I wanted to know everything I could about this lower oesophageal sphincter and the measurement. So I got stuck in on that and that was quite fascinating.

TT: May I ask you, Wes, why the dog?

WM: It was probably because they had the colony. They had a conscious dog colony there which was quite a nice facility so it was all beagles and additionally what they did was looking at gastric motility. They were looking at gastric motility a lot and so a lot of these animals had Heidenhain pouches and also gastric fistula put in. So what we would do, poor little beasts I think on this now, we'd take the dogs and we'd put them under with an anaesthetic, we'd get the tube in through the stomach and then we could get it to exit through the gastric fistula. So we would tie a little weight on it then so when we pulled it through, once the ports had come through the lower oesophageal sphincter then we can take it and pull back on it and get it to come back down.

TT: So it was a standard technical reason?

WM: Yes. So it made use of what we had there already surgically with the dogs but the dogs were, the ones that we also ultimately ended up using, and after the lower oesophageal sphincter pressure, we got into gastric motility studies, and of course the dogs were the ones we could do the gastric motility on. And this is where the x-ray suite came in because what we were looking to do was actually trying to work out a non-invasive method to actually measure gastric emptying. Gastric emptying is extraordinarily difficult to figure out how you are actually going to measure it. At the time people were feeding technetium meals and measuring the radioactivity. And so what we were doing was we were actually taking the dogs and we were giving them a radio-opaque meal and using the fluoroscopy to look at them about every half hour. We could do this by keeping the dose levels of the X-rays down and this beautiful unit, this X-ray fluoroscopy unit, these poor dogs they had to get up on the X-ray table and we had them in a sling. They were comfortable, they could sleep and all that. And then we would look at the stomach and see what was still in the stomach. Of course that's fine but how do you quantify it? Well, we came up with this idea that we want to do gastric emptying, motility we can measure from pressure changes, we want to know what gastric emptying is and we want to quantify it. So we figured, 'Aha! What we'll do is we'll take the dogs and we'll feed them a radio opaque meal, dog food, and what we'll do is we'll put in 50 little radio opaque glass pellets, little lead glass pellets, they're only three millimetres in diameter. And then we'll feed the dogs this, which the dogs loved.' I used to come in and make this stuff up in the morning and I'd take about a half a tin of regular dog food, put in the little pellets and then mix in this radio opaque medium, which had a vanilla flavour. It sounds terrible and the dogs absolutely loved it.

And they eat up all this stuff and then as soon as they eat it up, they have the meal in them with all these 50 little radio opaque pellets in the meal. We figure what we'll do is we'll get them onto the table and then we'll just watch and we'll count how fast the little glass spheres empty and that will give us a wonderful quantification method for seeing how they go out. And then if you give a drug that increases the gastric motility and gastric emptying, well the pellets are going to go out faster, aren't they? Great in theory [laughs]. It doesn't work that way at all. First time we did this we get the dogs and we feed them all this stuff and we get them up on the table and this is about eight o'clock in the morning. They're all okay, so we X-ray the first one. We can see the radio opaque medium, the meal, was starting to empty. You can start to see it outlining the intestines. However, the stomach not a single one out. After two hours not a single one, right? So we go on, four hours. The meal's almost completely emptied out of the stomach, not a single pellet out of the stomach, they're all just sitting in the stomach. To cut a long story short, 10 hours later all of a sudden they all go out at once. And what it is, and we had started investigating this, there's a phenomena of the gut that's called a migrating myoelectric complex. The GI tract is marvellous and this is one of the things that started really getting me interested in GI. I would think how on earth does the stomach know, to keep these things in and then to get rid of them like that? How does it do that?

And what it is is, if you think of dogs and even people 10,000, 15-20,000 years ago, we ate a lot of garbage. Probably a lot of bone and bits of gravel and everything in there. And so that would all obviously go into our digestive system. But at some point of course the stomach needs to clear all this stuff out and keep it going and that's what this migrating myoelectric complex does. The only problem is the migrating myoelectric complex won't even come in, it starts at the oesophagus and it's this little wave of muscular and electrical activity that works its way down through the whole intestine and it will only start once the meal, sort of nutrient meal, is almost all the way down to the colon. So everything has got to get all the way through the system and then finally this complex comes in, says 'stomach is empty for the most part, let's get rid of any garbage that's in there' and knocks them out, and that's what happens, and that's what we saw. But it was quite phenomenal. And the phenomenal part of it is that the stomach and pylorus and the pyloric valve and the duodenum are able to discriminate the size of what it will let out during the normal meal and it won't let out anything probably bigger than about two millimetres. And not only that we were looking at it, and I can't remember how we did the pressure recordings, but the stomach actually chugs away and pushes things right up to the pylorus. You'll see it mixing, you'll see these little spheres and all of a sudden they bang against the pyloric valve and they bounce back into the rest of the stomach, and okay,

that's fair enough. But then when the complex comes through it opens the pylorus, the stomach is going, but that isn't the whole thing. It's only when the duodenum, the first part of the intestines, is ready to accept it, then the stuff will go through. If the duodenum isn't ready to accept it, it won't go through. And this, this was another kinda wow! What's going on here? What's the coordination, the neurology that's going on to actually do something like that?

And then it was at that point I really started talking with Gareth saying, 'Man, there's a whole lot more to the GI tract than I just ever previously thought with the whole enteric nervous system and what was going on and the layers of the nervous system.' And that's when I really started, 'yes, this is very interesting stuff.' And by then we'd started talking with our clinicians and it dawned on me that these are the things that drive people to the doctor, the problems with their GI tract, the problems with the urinary tract. The unglamorous little things. This is what gets people going into the doctors and from there I was pretty well hooked, and boy this is really one interesting area. It does tie in with my physiology and my interest in neurophysiology because the whole thing is going down that line.

TT: How much independence then did you have to develop a project?

WM: I was pretty independent in my own way. What happened was I became actually pretty good friends with a guy who actually knew how to operate all the X-ray equipment, Geoff Heald. And he was sort of a guy who wasn't working in any project area, he worked more as a service area and Geoff I think, he'd been called in to get his hands on the fluoroscopy but nobody used it. Jeff and I got talking and he and I really got on well and this is where we got together and 'yes, okay, let's use this and this and start looking at this' and it was Jeff and I working together that started out, well how are we going to quantify what's going on with motility? I kept David Turner updated on this, he knew what I was doing all the time and said, 'Yes, okay, this is what we're going to do, this is what we're going to try.' And Geoff Heald and I worked out a system where we weren't going to have to use these little spheres because they were kinda useless anyway in quantifying just how fast things happen. Where we could actually look at a dog's stomach and then by almost produce a contour map of the radio opaque meal that was in it to get an idea of how much that was going down. And that again I found absolutely fascinating. I got to a point where I just didn't even want to go home at night, we were working away on it and over the one year we were working on it, much to my wife's dismay, I don't think I took more than two days' holiday. I just wanted to keep going on the thing the whole time it was that exciting and nobody else had done anything like that.

So we were reasonably autonomous. We were producing results and certainly we were taking the compounds at the time BRL 24924 and I have to say, I don't know if you've worked with pharmacologists a lot but I still remember all the numbers. I've got this horrible feeling that when we're all going senile and grey and living in the homes together we'll go, 'Do you remember old BRL 24924, boy that was a heck of a compound, heck of a compound' [laughs]!

TT: I've had similar conversations in this precise situation.

WM: You get all these numbers. People are going to look at us and go, 'What are you talking about?' So yes, we were looking, at that time were looking for a gastric motility stimulant which did not have dopamine antagonist activity, as this is what was causing the problems with metoclopramide. And this is the work that actually Gareth Sanger was pulled in to do. He was effectively given metoclopramide; we knew it was a gastric motility stimulant. So, 'How does it work, Gareth?' - that's where he came in on it. And from there we were working on it and we were saying, 'Okay, we can put in the BRL 24924' which had no dopamine antagonist activity, it was a benzamide, no dopamine antagonist activity. It showed up in the rat models we had too, and we looked what it actually does in the dog, and were able to show quite marked effects in the dog with the compound too.

TT: Were you able to publish this?

WM: It was a little tricky. I think we probably could have if we'd really pushed it, but at that time there always

was this, it's going to have to be quite far down the line. We were able to put out abstracts and we started putting out abstracts on BRL 24924 and at the Gordon Research Conference we were able to present on that. So the motility side of it we were able to get going on it. You could put out a certain amount.

TT: That's the constant conflict of people in the industry, isn't it?

WM: It is.

TT: Particularly when you're exploring, when you're getting in to looking at the basic mechanisms. Where do you draw the line?

WM: Well, this is it. I mean you want to publish, it's the icing on the cake and all that, and this is where I have to give Gareth Sanger such a phenomenal amount of credit because you look back on his publishing career and Gareth was putting out, as an industrial scientist, Gareth was publishing three to four papers a year as an industrial scientist. That was almost unheard of to be able to do that. But he's kinda the only one who knew the area so well from the serotonin (5-HT).

TT: Clearly Beecham were tolerating you doing all of this and allowing you quite a lot of leeway.

WM: It was, it was, because I think I have to say that's kinda down to David Turner and probably the head of the site at the time, Bob Poyser, Norman Poyser's brother from Edinburgh. Bob was head of site at the time. I think Bob saw Gareth's potential very early on and the amazing ability that Gareth had. And so Bob I think was encouraged by our work. He saw it, he got it. And then once Bob was kinda bumped upstairs, Tony Ainsworth came on over as head of the site and Tony was a real nice guy. He encouraged our work too but like you say, I don't know if I would be given that sort of leeway anymore. I think we were actually producing enough things and it was novel enough that Bob had enough insight to say, 'Okay, yes, this is novel stuff.' I do remember Bob, and I made a comment about him in your 5HT meeting (Witness Seminar). And what happened was Gareth had found this metoclopramide antagonist and nobody knew what to do with it. It was a 5-HT_4 antagonist although nobody said 5-HT_4 back then. And then Bob Poyser, I remember the meeting, he got up and he said, 'look, things like this just don't come along. I don't know what we're going to do with it but we're not going to forget it.' So on the site itself, because it was a smallish research site and all that, I suppose we did have a lot of leeway.

TT: Did you have any interactions with people from other companies?

WM: We certainly got out to meetings, the British Pharmacological Society meetings, which were very good and I think at the time the whole attitude which I think we sort of brought up with the 5-HT work. There was a different attitude then and okay, nobody was giving away any big secrets, they're not going to do that, but we talked to each other. We'd say, yes, okay, this is what we're doing. And the other big thing was, and it just got so difficult later on, people were pretty free with their compounds.

TT: That comes across remarkably in the 5-HT volume (Witness Seminar), how you all exchanged compounds and gave compounds to academe.

WM: Yes, and without the clause written in that 'anything discovered has got to go…' and the involvement of big management and the lawyers, and yes, people gave out the compounds. I mean that was certainly the key to Gareth and I on the anti-emetic work because it was John Fozard who gave us the MDL 72222 and he gave it to us quite freely. Gareth wrote him 'can we have some' otherwise we would have been in a position where our chemists would have had to sit down and really make the compound, we would have had to gone through all the literature and find out all the credentials on it. Whereas with that we wanted it published quickly and get it out there and have the compound.

TT: And can I ask, at what point did you get back in touch with Paul Andrews? Was it during that motility work or was it later?

WM: Well, I had been working in the motility side, I had been working with the dogs, we had been doing all the X-ray work and then David Turner, our head of project, came to me one day and he said, 'Well, what would you think about doing this work with emesis because we know metoclopramide is an anti-emetic, we're not sure what the dopamine side of it is doing, but, let's have a look at developing emetic models.' And I think David saw that once I got my teeth into something and if I found it interesting then I would really go for it. And so he selected me to take on the anti-emetic work. And at first it was just David Turner and myself and we actually got a hold of the ferrets, I can't remember who supplied them, it was another pharmaceutical company up in Loughborough and they're not around anymore and I just can't remember the name. And so we got a hold of them, and we got our ferrets and we got them down and we got them all housed and everything, and that's kinda how all that work started out. And David Turner and I got in there and we took the poor little ferrets and we dosed them with apomorphine. I think initially we dosed them too high with apomorphine and it didn't hurt them as such but they just went around in circles for about four hours and wore a little track in their pens, poor little things. But then David sort of stood back and he said, 'Well, you're going to take it on', and I was, 'Yes, okay, I'll take it on.' And by then I had started working, again I was really good friends with the guy who was working in the animal house, who was supervisor of the animal house, Bob Collie and he and I got down to it, we got our vet, and we went in and we started working how we were going to do all the surgery on the ferrets. Because if you wanted to dose a ferret intravenously [laughs] you just ain't going to put it in their little legs, I can tell you. So it was pretty much my remit to sit down and figure out how we're going to do the surgery and it had to be clean, we had to have clean surgery, we had to have all clean procedures.

And we got the vets out to show us how to do clean surgery, I had a bit of an idea anyway from my past experience. And then we got our own little dedicated operating theatre and that's where it all started out. We started, David and I had sort of set the preliminary side of it, knowing the apomorphine and then additionally we had certainly gone by the literature from the Bristol-Myers group of John Schurig and Jonah Gylys. And they had started looking at metoclopramide against this platinum-induced emesis and they are the ones that actually developed the whole idea using the ferret in emesis, as far as I can see. But in conjunction with that of course Paul Andrews was using the ferret for a lot of his GI work.

TT: And motility, not secretion, because so many people worked on secretion.

WM: Yes, exactly. Well that was the big thing of course because you had Tagamet at the time and everybody wanted to do Tagamet. Well, Glaxo did it, didn't they? But yes, everybody was going down the secretion route and motility had sort of taken a back seat to the secretory side. So we got the ferrets and we set up the surgical procedures, setting them up and, well the whole surgery was actually implanting intravenous cannulae. What we would have to do is obviously cannulate the jugular vein but with the ferret you had to exteriorise it at the back of the neck so you could actually do something with it or they bite you. Because they're nice little beasts, they're not bad, but that's how we started out. We got all the clean surgery sorted out. And at the time we started, we had metoclopramide and we started looking at metoclopramide in the ferret model. So of course first of all we had to get the dose right of the cisplatin. That looked key, but we had an idea of how to do that because of John Schurig's work. We set that up and we started out with the cisplatin after we'd done the apomorphine. And we got a very nice consistent response, and in fact it's probably why the whole 5-HT_3 area worked as well as it did because we actually had a model, and I say a model, not an assay. We had an assay that mimicked the clinical situation fairly closely. And that's a problem today, you get so many people today that say, 'We've got a model' and so many of the models are not models, they're assays. But to actually mimic the clinical situation with the model, it's very difficult. And that's where we had a terrific advantage because we could model it.

So we then started looking at the cisplatin and we worked away at it and we got a pretty decent response to the cisplatin. In fact, I say decent, if you gave the animal cisplatin, they vomited. No question about it, 100%, which was another big thing. And the way we used to do the thing is we used to have eight animals on the go, so what we used to do is we used to spend a day and a half or two days of surgery where we would be in this little surgical theatre and I had, Bob Collie and I, he was helping me. He would be clean, I would be

clean, we'd have one clean nurse and one dirty nurse, the whole works. It was quite well set out. And we'd start out about eight or nine o'clock in the morning cannulating these ferrets and we'd get through about four a day because it had to be a clean procedure. But we used to get out of there by the second day, we were pretty tired, just straight surgery for two days solid. And we'd give them a three-day recovery period. This was all set out by the Home Office, and we'd give them a three-day recovery period and that's when we would do the cisplatin on the third day so they'd recovered.

I'll tell you a slightly funny story. We had this little theatre, this little surgical theatre, maybe double the size of this room, which is about 5 meters by 8 meters, no it wasn't even double this, it was one and a half of these rooms. And we'd work away in there, it was completely enclosed, and of course we were using halothane. We were using halothane anaesthesia and we had the big anaesthetic trolley and all that, and we'd be working away in there, and after about eight hours I started feeling, 'Jeez, I'm feeling a little funny' and of course what's happened is we're working away with the anaesthetic, the halothane, and for some reason nobody noticed it but the scavenger wasn't working [laughs]. So we're working in this stinky little room and I used to go pretty high getting home just from this halothane, after doing this all day. But we persevered and we never lost a ferret surgically and that was pretty reasonable. We had to watch with a bit of infection but we never lost a single ferret. They were all pretty comfortable, they were all given analgesics, to tide them over the period of the surgery and the other thing with the ferret, is the back of the neck, the skin on the back of the neck is roughly one centimetre, one and a half centimeters of solid, thick, durable tissue and when ferrets fight, especially the males go for each other and all that, they latch onto the back of the necks. And you look at the backs of the neck of some of these things when they've been housed together and compared to the surgery we did, it was nothing compared to what they did to each other. They just used to tear their necks apart when they were together so we used to have to keep them all separated. But we had a good survival rate and the first thing we started looking at with the model, once it had started and we had it up and running, we were confident about the cisplatin, the control responses, and again the cisplatin was great because that was it, you gave cisplatin, they vomited.

And we started looking at dopamine antagonists because the competitor compound, domperidone was up there, it was a Janssen compound. And Janssen was making a big deal at the time. The whole issue with the cisplatin-induced vomiting, I'm sure you're familiar with it, it's just horrendous, absolutely horrendous for the patients. Back then if you got cisplatin, same with the ferrets, you were going to vomit and you're not only going to vomit, you're going to vomit for at least two or three days, probably seven days. And people were actually refusing cancer treatments that potentially were curative because they didn't want to go through this vomiting. After if they did it once they wouldn't repeat. So there was a huge problem there. We looked at the cisplatin and then of course everybody was looking at dopamine with domperidone to help the sickness. And there were a number of claims that the domperidone actually worked pretty well, at least had some efficacy against the cisplatin induced vomiting. Of course metoclopramide is a dopamine antagonist and it did work. It did very well in the States, it was put in patients at higher doses. And metoclopramide worked well, okay. So we actually started looking at dopamine antagonists.

And I looked in the ferret with domperidone against the cisplatin induced emesis and everything I could see, the dopamine antagonist actually made it worse. And in one of our papers it actually shows we dosed with domperidone and it actually makes the response look worse. So we knew that it wasn't dopamine and Beecham had some of the most potent dopamine antagonists known to man because they had been working in that area for a while at one time. And you could dose, you could take dogs and dose them with apomorphine and they have an emetic response. And you could take them, these dopamine antagonists and give them subcut, subcutaneous, and you can't get these dogs to vomit to the apomorphine three weeks later, these compounds were so potent. But against the cisplatin, it didn't do anything, made it worse probably. And then we had this compound, which was BRL 24924. This was developed specifically as a gastric motility stimulant void of dopamine antagonists, and Brian McRitchie was one of my peers working at Beecham at the time and he was working quite extensively with that. I'm pretty sure Gareth was too, yes. Gareth was working with the BRL 24924 because this was going to be a big compound for the company. And ultimately become Renzapride, a kinda a competitor to Cisapride although it never made it to market. And so I can remember somebody gave me the compound, Renzapride, it was probably David Turner, and

said, 'Okay, test this in the cisplatin model and let's see what it does. It doesn't have any dopamine antagonism, it's a benzamide, might be some way to metoclopramide.' So I put it in the ferret and lo and behold it worked. And that was it. I should say, earlier we'd looked at the metoclopramide and went to high dose metoclopramide in the ferret and it did work too, so we repeated the work that John Schurig had done and we could see that yes, it could be stopped with metoclopramide. And metoclopramide actually worked pretty good. It didn't inhibit it completely, the cisplatin induced vomiting, but quite a bit. And then we put in the Renzapride, which actually was more of a motility stimulant, gastric motility stimulant, than metoclopramide was. So it was very good as a GM stimulant, better than metoclopramide. But put it in the ferret and it didn't work quite as well but it worked. It worked. And that was the thing.

So now we had, we knew, that it wasn't dopamine antagonism that was stopping the cisplatin induced emesis. We knew metoclopramide had whatever was there and we knew BRL 24924 Renzapride had it. And this is where Gareth came in and Gareth had been working *in vitro* with all the compounds and he just really understood the pharmacology of what was going on. He had a real good idea. And he looked at the compounds and he looked at the 24924, I don't know if he'd actually done some basic work by that point with 24924, he may have, this was in the rat, and at that time I'm sort of sitting there thinking, 'Well, it's not dopamine antagonism, what do we know? We know these compounds are GM stimulants so maybe this is what's driving things here, increasing gastric motility stimulation.' So Gareth's looking at it, and I have to admit I'd never even heard of 5-HT receptors at this point [laughter], never in my life, I didn't know anything about 5-HT other than it existed. And Gareth is looking at this thing and he just makes this absolute quantum jump and he goes, 'It's 5-HT M-receptor antagonism.' Couldn't believe it. And that's where, went to John Fozard because Gareth had known John was working on this 5-HT. This is the old classic Gaddum, 5-HT M-receptor. Even in our first paper we call it "5-HTM".

TT: I noticed that, yes, I did notice that.

WM: It's called M. Gareth just cringes when he sees this. But that's all, it was just classified as D and M back then and then you had subtypes one and two from the binding. So Gareth looks at it and says, 'It's 5-HTM, that's what it is,' goes to John and gets the compound, the MDL 72222 and just kinda gives it to me, says, 'Okay, come on, let's test it.' And I think, 'Okay, that sounds a good idea' and we had the ferrets prepared. I think we had them all prepared at the time and we got the compound and I put it in the ferrets and it just stopped it cold, stopped the cisplatin induced vomiting cold. Absolutely cold. It was just absolutely astounding because I hadn't even seen that from the metoclopramide or the 24924. And the animals just looked perfect, it's like they never even had the cisplatin. One animal did have a little bit of behaviour and did vomit I think right after. We tested four and the one animal did vomit very near the end of this observation period that we had. But it was day and night type of thing it was so clear. And this is what made it so powerful because (a) the cisplatin always caused the animals to vomit; and (b) this stopped it completely. And it was right about that time I think that I got a hold of Paul Andrews because we started having a difficult time getting our ferrets, the supply of ferrets. And I got a hold of Paul on the phone, 'Paul, where do you get your ferrets from?' He goes, oh, he told me, as I recall and 'we're looking for a supply of ferrets.' And he goes, 'Why are you looking for a supply of ferrets?' 'Well, because we're looking at cisplatin induced emesis.' 'Well, I think we might have a common interest here.' Because he was obviously getting into it quite a bit at that point too. So that's how we got together.

TT: So this is when you're still at Beecham?

WM: Oh yes.

TT: This is an amazing four years that you've had at Beecham.

WM: It was packed, it was really packed, and again I just got so into the work, I just didn't even want to go home. I just wanted to keep doing it. Well this was again because the problem was so significant in cancer patients. And I have to be completely honest, I was again so naïve and so ignorant that I think when David Turner first came to me and he said, 'Okay, well here's the problem, cisplatin induced emesis' and I looked into it

and said, 'Yes, it is a heck of a problem. Okay, we'll solve it' [laughs]. It never dawned on me that we wouldn't. It was Gareth that supplied the answer but I just said, 'Yes, okay, let's just solve it.' [Laughter]; I was that naïve back then.

TT: I'll come back to naïveté and ignorance later because those may be very positive attributes, people forget about that. We'll come back to that later at the end of your career. So you've had this amazing eureka moment seeing this cisplatin induced emesis stop just like that and you start talking to Paul Andrews and you're developing it in the company. At what point do you go public about this?

WM: When did we go public about it? It was 1986 and it would have been the first abstract that was even out on the subject, the cisplatin, it was in the ferret and was presented at the BPS, the British Pharmacological Society. It was 1986. At the time we put out the abstract we knew exactly what was happening. We actually knew all the way back around 1984, it would have been 1984, it would have been two years prior to actually doing it. In fact, it was probably late 1983 where we, when I got the MDL 72222 and we did those first experiments and really knew what was happening. So we knew it all the way back then and of course we couldn't publish. And we did know that the Bradford group…

TT: Bob Naylor and Brenda Costall.

WM: They were working certainly on the 5-HT M-receptor area. I don't know if we knew they were actually involved in anti-emetic work at that time but they were. And this is, I think, just a bit after that that Mike Tyers got in touch with Bob Naylor to start testing it, which Bob never told me [laughs]. We ended up publishing, if you actually look at that abstract, that went out in 1986 and I remember Bob Naylor's group actually came down and had a look at the abstract. Now I think they were already onto things by then themselves but I know they had a real close look at that abstract, and in the abstract we actually say that what's happened is either down to 5-HT M-receptor antagonism or GM. Now we knew it wasn't GM changes but Gareth is so conservative, he couldn't state it because we hadn't ruled it out formally but we knew it wasn't because we had the MDL 72222 which had no effect on gastric motility at all but we couldn't say it. So we put that in, Gareth put that extra little line in, and of course the Bradford group came along and they were having a real good look at this, and then they had a number of studies down themselves. But I've talked with Bob any number of times and gone over what happened, and we published our first paper in *British Journal of Pharmacology* and if you look at the title of our first paper *British Journal of Pharmacology* came out roughly I think about four weeks before Bob Naylor's group published their paper. If you look at the title in the papers, it's about a 10 or 12-word title and there's about two words difference. It's one of these things, a parallel discovery. It's absolutely astounding. But what Bob didn't tell me until I just actually read it in *Drugs Affecting 5-HT Systems* was he didn't believe it was going to work [laughter].

TT: But you just mentioned another name there, Mike Tyers. Where was he at that point?

WM: He was Glaxo. Mike's from Glaxo. So the way the whole thing worked was, certainly Glaxo was looking at the 5-HT_3 or M-receptor antagonist, but they were going down the line of migraine more.

TT: Well, that was with Pat Humphrey as well and all of that research.

WM: Yes, so they probably certainly had an idea but as far as I can figure, I've tried to look back and trace it, who came up with that at what point and all of that, and as far as I can figure, Gareth was really the first one by several months to actually put this together and say, 'Yes, this is actually what's going on.' And from there on we had a heck of a time with Beechams, they didn't want to know it as an anti-emetic. The problem was they had been in the area before and they'd been looking at cannabinoids and these things effectively probably stopped forms of nausea and vomiting but they did it in dogs. And the poor dogs, they couldn't even stand up, they were knocked right off their feet, so they probably couldn't vomit even if they wanted to, and had such high side effects. And so senior management at Beechams at the time said, 'Well, we're just not going to do it.' And I did say something about that at the meeting, I remember the meeting so vividly. And I'll tell you the name of the guy was Brian, second in command of research at Beecham. But

he was a really nice guy, he was a really nice guy. He was just saying the company line on it.

TT: Well, it's easy in retrospect to see these things, isn't it? But, and as you say, there's always a company line.

WM: He was, 'No way! No way are we going into anti-emetics at all; we're just not going to do it!' And Gareth and I was just got up there and we said, 'Yes, but…!' And I remember I even pointed at Brian. I said, 'Brian, if your child was vomiting, would you refuse them this anti-emetic?' We came out of the meeting and Christine McClelland, our colleague, looked at me and said, 'Jeez, I thought you were going to get fired right there.' But we had all that data and I could see that it was going to do something. Again I was probably just so naïve that I assumed it was going to do something for people too, and no one would actually turn down something like that.

TT: So how did you react? That must have been such a massive bucket of cold water over you.

WM: I just wouldn't allow it. I said, 'We're going to do it.' I think Gareth was really into it at that point too. And so what happened was Brian said no but, pretty close to that point, we'd not only developed the cisplatin but I'd gone ahead and I'd developed a model of a cytotoxic drug using doxorubicin and cyclophosphamide. And this caused a vomiting response even worse than the cisplatin when you put them in together in the ferret. And as for the drug, the 5-HT_3 receptor antagonist worked even better against it. And then finally the guy that I was working with, with the radiation fluoroscopy we got together and said, 'Let's do a radiation model of emesis.' And so we said, 'Okay, fair enough.' And Geoff Heald was so good he worked out how to do this right down the line. We had this old X-ray machine that was an industrial X-ray machine supplement to the fluoroscopy and it was a dirty old thing and it just threw out horrible amounts of radiation. But he worked it out and we had the ferrets and we used to put them in a little Perspex cage, and ferrets love little enclosed spaces, they'd curl up in this little cage and we'd put them under this X-ray machine and we'd irradiate them.

Now this is the first time we'd done anything like this and I don't know how Geoff Heald worked out the dose to give them but he had it pretty well worked out. And we had 5 animals and they had had a cannula implanted and stuff, and put them in these things. The first one, we put it in, we didn't know what to expect, we got him out of the X-ray room because we had to stand way back in a shielded, leaded room, this X-ray machine was so dirty. So we get this little ferret out of the room and 21 minutes, bang, he goes on, the vomiting response, complete vomiting response. That went on for 30 minutes, a lot shorter than the cisplatin and after that period of time the animal looked right as rain - he'd got the vomiting done. Okay, we got a response, we were real happy with that. We did another ferret, we irradiate him, we know from when we started to what was going to happen and the next one, 20 minutes, bingo, he goes off, he starts vomiting. We did five animals and out of those five animals the first one started at about 21 minutes, the longest was 21 minutes when it started vomiting and the shortest was 19½ minutes. It was that close. And it stayed that way in everything we did. Tightest response I've ever seen.

And they had almost the identical pattern to vomiting. And so then we did the 5-HT_3 antagonist against the radiation and it worked even better against that. And so then we had the cisplatin, the doxorubicin and cyclophosphamide and we had the radiation, pretty big ones in anti-cancer therapy. And that's when we got called in by Keith Mansford. What happened was I actually was dosing animals with, I think it was cisplatin, and I used to have to do this control animal and the control animal wouldn't get the 5-HT_3 antagonist. And so they'd all get their cisplatin and they'd all, if they got it they'd vomit, if they didn't have the 5-HT_3. And I had a little control animal, that didn't get the 5-HT_3. Of course it went right off on time. I was thinking, 'Oh Jeez, I can't just let the little guy just keep vomiting like this' and that's when I sort of worked out, while he was actually vomiting he just wouldn't be looking at me. And I fastened this little connector on really fast and just within five seconds I just wacked this 5-HT_3 antagonist in, I mean that went in fast. And the animal, I remember the first one I did, he'd been vomited, he was retching and vomiting, it was kinda right in the middle of the retches, and he just shook his head and then he looked up and that was it. He was absolutely perfect, and then I couldn't get the thing off him, could I? [Laughter].

TT: Because he was fine by then.

WM: And so that's what I was saying, in the 5-HT volume, I knew they loved milk so I had to get him a little bowl of milk and he ran over and got his milk and that's when I could get the connector off the thing. And we videoed that, again Geoff Heald again did this for me. He was great with all this equipment and everything so he actually, he and I got in there and did the whole thing and we videoed it and that was the video that you got a copy of, the ferret vomiting video.

TT: Well, I gave it to Mark Walport, he wanted it for the Wellcome Trust.

WM: So it was again that fast. And that's when the Head of Research, Keith Mansford, requested that we come to a meeting.

TT: So Beechams was now having a change of mind?

WM: Once Keith saw that I think he was fairly well convinced that in fact yes, there was something there and that's when everything sort of changed and said, 'Yes, okay, let's go for it.'

TT: So Beechams have finally woken up. They've got these great guys who have done this amazing experiment without a great deal of support or help, and sometimes against the company attitude. What did Beechams do with it?

WM: Well, at that point things started changing over and it was at that point actually, this would have been 1986 that I actually moved to Pfizer. It was right at that point. The experimental work had been, I'd certainly done the three models and all that, and in my last time at Beecham I was kinda handing the models over to Liz Boyle, Lady Boyle actually, and Joe Bermudez and they took the work on. I was absolutely terrible when I was handing it over because these were my models and Liz Boyle, she was very good, she was very good. She took it all on and all that and, but I just keep hanging around, just kept watching. 'You can go now, Wes.' 'Okay, I'll go.' [Laughs].

TT: What was the set up? So you were handing it over because you were leaving but even if you'd stayed there it would have moved into clinical trials. And you's have lost touch with it anyway?

WM: Yes. It moved very fast. I mean Glaxo did the same thing with Ondansetron. Once things started up it moved really fast. So probably the fastest two compounds: I think it was only six years for Ondansetron. Granisetron took a little bit longer because they initially decided to try to look for it in IBS [irritable bowel syndrome] so you had to do more extended tox [toxicology] on that. But yes, it was just moved very, very quickly. We had Garth Rapeport who I think oversaw quite a bit of that. He ultimately moved to Pfizer himself but was originally at Beecham and I don't know exactly how it was moved forward once I left. What I will say is that by the time I left I think I'm sure we'd only actually put out a couple of abstracts and the initial paper, the cisplatin induced emesis M receptor one. But then there were three more papers after that. Now Gareth Sanger made sure my name went on all those papers and I was already at Pfizer. Now that's quite exceptional.

TT: Yes, but it's what you expect. But you're quite right, people don't do it.

WM: I know what industry's like and once you leave somewhere, you are left. Even though you put work in on it. But Gareth always made sure, whoever did the work always got credit for it. He was quite exceptional in that way.

TT: And Liz Boyle. Liz Boyle is on some of these papers as well. So some of the 1987 ones, you've already left, she's taken over and Gareth is making sure your name is on them.

WM: Exactly.

TT: So why did you leave?

WM: Well, I was still interested in the GM side and one of my former people, Brian McRitchie had left earlier and he'd moved to Pfizer, and Pfizer was just starting to get into IBS. Because I figured, we pretty well had the emesis down the line as far as it was going to go for a while and the next big steps were really going to be in IBS. I could see this being like a huge area in Pfizer and other pharmaceutical companies. And Beecham was certainly in that area but this opportunity came up at Pfizer to say, 'Okay, well we're just starting out with IBS, we have an idea', which at the time was a gut selective calcium antagonist.

TT: So they head-hunted you or they recruited you?

WM: Yes. So I went down, talked to them.

TT: This would be at Sandwich?

WM: This was Sandwich, yes, with Roger Burgess and Rob Wallis and at the time Ken Blackburn was head of research, Simon Campbell was head of chemistry. So Simon I think he's Sir Simon now [laughs]. Good old Simon. But yeah, it looked like an interesting time to get in at the bottom again and sort of push forward and see what could be done on the IBS side. So that's when I kinda moved on over to Pfizer and certainly got involved in the work there. But it never really took off, it did in a way, we ended up looking at a calcium antagonist, gut selective calcium antagonist. The whole background with Pfizer was, at Sandwich at the time, they were huge in cardiovascular, a lot of cardiovascular work. That was Pfizer's real key area at Sandwich. And of course they had nifedipine looking at it. And then the idea was to replace nifedipine with something a little bit longer lasting and all that, and that's where Amlodipine came from, and then the Amlodipine calcium antagonist programme moved on and somebody made an observation and I can't remember who it was exactly, but in fact it looked like you could get some sort of GI selectivity with the calcium antagonist where you weren't actually affecting the cardiovascular system. And that became the basis of the project - it was to look for a calcium antagonist that would actually slow down GM, lower gut motility, and this would of course help the symptoms. Of course it was a load of rubbish, because nobody really knows where the symptoms are coming from with IBS. This is the real problem in the area.

But from the calcium antagonist area what happened was we then went into gut selective, M_3 selective anticholinergics. So they don't have much effect on the heart, lowered effect on salivation. But by then I was transitioning anyway from GI to the urogenital side and bladder problems and in fact it was reasonably well known that you could use anticholinergics in urinary urge incontinence. So these selective M_3 selective muscarinic antagonists are actually pretty effective in urinary urge incontinence. Now nobody actually knew why. I do [laughs]. It took me years to figure it out but I actually did some experimental work which I actually, I can't even make public because I'm going to see if I can pursue this with the company I'm consulting with. But they actually do have efficacy in urinary urge incontinence. So that's where that programme came in and I was on the team looking at that.

TT: How soon did this come into your career at Pfizer? Because you were at Pfizer for quite a long time.

WM: I was there for about 23 years. So I started out in the GI area and then after I'd been in the GI area for a little while I ended up going over into pulmonary oddly enough, still sort of visceral I suppose in a way.

TT: All autonomic nervous systems.

WM: Yes. But that actually, that was purely, I had very little knowledge of the area when I got into it but what I found was I was actually able to lead a team. I hadn't done it a lot before because Beecham's structure was very horizontal whereas Pfizer very much more pyramid type structure but I found I was able to work with

people. And again it's one of these things where I was working with a man, Dr John Perry who had a pretty good idea, he'd been in the pulmonary area for a while, worked with Val Alabaster. And he had pretty good knowledge, so I kinda got pulled in as project leader and I ended up, I just got on with people. I was able to sort of, 'Oh, let's to do this and let's do that' and if I had any real problems I'd just go and see John and go, 'John, what does this mean?' And John would explain it all to me. And John was a great guy. Somebody higher up in the company once said, 'The problem is when you asked him a question you got everything. He was sort of like an encyclopaedia without an index.' [Laughter]. But he was a great guy, very knowledgeable. So I was the project leader and the team leader and one of the things I always found with that, it was quite fascinating, I found that when you're actually leading a team and you're there, that the whole thing everybody is looking for is just somebody to make a decision. That's what they want. And I realised they'd come to me and I'd realise it didn't make any difference at all if my decision was right or wrong, I just had to make that decision and say, 'That's what we're going to do.' If you get down that one and it's the wrong decision, you can always come back. But you have to have somebody who is making the decision and that's what I could do. So I could make these decisions, yes okay, and we actually got down the line where we had what was a PAF (Platelet Activating Factor) and histamine receptor 1 (H_1) antagonist, which was a tricky compound to actually come up with because it had two activities. And this was back when the Food and Drug Administration (FDA) and everybody else didn't want combination compounds. So we had to put both activities in the same compound and so we had to have a PAF antagonist and a H_1 antagonist in the same compound. And that was tricky, that was tricky because we effectively had two projects running and we had to balance it so that they had the same activity, lasted for roughly the same time. And that was challenging but fun, but it never worked out in the clinic. It was one of these things that sounded a good idea to begin, it was not a bad something for allergies but it wasn't something that was going to cure asthma or something like that.

TT: And so from there you then moved into the urinary side?

WM: Yes, I was into the urogenital side on that, and that was quite fascinating work. That really kinda got my interest again really going because here was an area I could kinda get into and try to understand. And certainly working in that area on 5-HT and that, 5-HT_{2C} which came out very interesting, some very interesting studies with that.

TT: So it's almost coming back to some of the things you'd done previously?

WM: Yes, it was, and again it sort of played to my strengths because it was *in vivo* work and surgical work and very fine surgical work. And I was able to set up a model ultimately in a guinea pig. And I used to have these guinea pigs and I anaesthetized the guinea pigs and I found this absolutely fascinating. And what I'd do is, I'd do surgery and I'd just kinda pull back the abdominal wall over the bladder and then I was able to actually look at the bladder as it was functioning and I could fill the bladder, and I was recording little electrodes from the external urethral sphincter and all that. I was watching the bladder and you think the bladder is just a little bag, don't you, it just kinda sits there and it fills up. Of course the way I'm telling you, it's not.

TT: I've looked at it myself. There's all this activity going on.

WM: Astounding, astounding! I'm looking at this guinea pig bladder and the thing is twitching all over the place, it's going like that the whole time. And this is some of Jim Gillespie's work, not John Gillespie [Glasgow pharmacologist], but Jim Gillespie the physiologist from Newcastle had done this *in vitro*. He isolated the bladder and you see this activity. So when we did it I actually took the whole thing and I did it *in vivo*, and the bladder was just moving like mad the whole time. And you could fill it up and then I used to empty it, I used to empty it until it was absolutely flat as a pancake, a deflated balloon on the bottom of the abdominal wall of the guinea pig and it was still going [laughs]. Well, I started looking into this and thinking this is quite a fascinating physiological phenomenon; there must be a reason for it moving around and all that. And I started tracing the literature back, and I can't think of them all but I mean I got right back into the 1890s where this type of phenomenon was recorded in cats. Sherrington maybe?

TT: Sherrington or Langley.

WM: And then Denny-Brown, I can't think of where he actually did the work, but he did it on himself and he recorded the pressure movements and all this with one of his assistants and all that.

TT: These things get forgotten, don't they?

WM: Well this is what gets me and I suppose this ties in with your interest in the history and recording the history of it all because when I first started doing this stuff in the bladder and looking at it, I'm thinking, 'Oh wow, this is terrific, this is very unique!' and all that. I was tracing the literature back and I'm going, well Klevmarkark did that, oh yeah, such and such did it, Coolsaet did it. My gosh, it was back in 1890 they were doing these things. Now what we had, we were lucky because we were using a technique called "sonomicrometry". Sonomicrometry, you take these little electric crystals, dinky little things, they're only about two millimetres in diameter, and they're connected with a little wire obviously. And what happens if you get two crystals, they talk to each other, and they tell you how far apart they are from each other. So these little dinky crystals, so I used to superglue five of these little crystals onto the bladder. I'd get down to the bladder and glue these little crystals on. And I could get them, the crystals, to talk back and forth that way so I could record about six or seven different types of motion with these little crystals. And you get your little graph.

TT: What's it called?

WM: Sonomicrometry. Well, I think it's a fascinating technique. It has been used actually in the GI tract to look at the stomach moving in I think it's rats. I think it was originally developed actually to look at the heart so as the heart's contracting and all that. These little crystals, they just talk to each other. And they tell you how far apart they are. And of course you get, what you see in the bladder is you'll see very distinct patterns coming this way and that. It's a fascinating, absolutely fascinating technique. I got a number of traces at home, unfortunately I suppose they still are Pfizer property, on that. I could have a look at it.

TT: So this is used experimentally. Is it ever used in patients as a diagnostic tool?

WM: I'm not sure it has. Maybe. It was at a meeting where I picked up on this. I can't remember what the meeting was but they had a stall and the company may be named "sonomicrometry" or something like that, but they had this big banner right in front and it caught my eye and it said, 'If it moves, we can measure it.' And I thought, 'Yes! That's exactly what I want.'

TT: I get the impression because you're very, very animated about those four magic years at Beechams, Pfizer didn't quite match, wasn't quite parallel, or am I misinterpreting?

WM: Pfizer was interesting. What happened, I think, was I came into it and Pfizer at the time was very, very pharmacokinetic oriented and I probably didn't have a particular good grounding in pharmacokinetics. I could understand the basics and all that but the whole idea with Pfizer was the project system saying, 'Yes, okay, let's get all the drug metabolism pharmacokinetics right' and a lot of emphasis was put on that, to get the compounds right. And what I found was that I tended, and it probably relates to the anti-emetic work although I can't say we ever understood exactly what was going on, I always had the kinda feeling, 'Let's understand what we're doing physiologically.' If we can't understand the normal physiology how can we ever hope to understand the pathophysiology? And I used to say it's like taking a car that suddenly has stopped. Now you don't know anything about the car at all, you're not a mechanic, so you change the windscreen wipers and see if the car starts up, and it doesn't. 'Well, let's change the headlights.' [Laughs]. You don't know anything about how the drive chain of the car works. So my feeling always was, 'Look, we really have to understand the physiology of it.' Now that the time at Pfizer, Pfizer was, as most companies were, I can't say this was just Pfizer because it's not, most companies went down this way. They were very much involved in absolute chemistry-led projects. They wanted chemistry-led projects so you've got to have

a lead, ideally a nanomolar lead or something like that, and then the chemist will take that lead and will work it on down into the chemistry-led project.

And in fact the ratio of chemist to biologist at Pfizer at the time I think was about one to one, which is actually pretty high. I mean I always thought you'd have to have about, you should have about three biologists to every chemist. And what this meant was you had to keep the chemistry department going with the chemistry led projects. And it got into a situation where I found it difficult and almost unethical because we just didn't understand the physiology on a lot of things. We didn't understand the physiology of irritable bowel syndrome; I don't think anybody does at the moment. But it needs to be looked at. Pulmonary I didn't understand it anyway, so I was just leading the team. But then urogenital we were starting to make a go at actually understanding the physiology, this is when I got into the guinea pig model and all. But I never felt that in fact we never put quite enough into exploratory biology. And the problem there is it isn't really management, senior management's fault on the discovery side, all this of course is driven by shareholders, and they want to see the goods. So what happens is you have to keep the pipeline filled. And in order to fill the pipeline you have to constantly believing the chemistry led projects producing compounds that are going to move into clinical.

And so there's this constant drive to keep this pipeline filled and hence, 'Oh well, let's try this.' But you end up in a situation where you're taking stuff into the clinic and that's when things get expensive. And the attitude, and again this isn't just Pfizer, the attitude of clinicians actually became within Big Pharma, 'Kill the compound as fast as you can.'

TT: Yes, that came across in the 5-HT meeting.

WM: Yes, it did. So the idea was the clinicians, they got a compound coming in, their whole goal was to kill that compound off as fast as they could so that money wasn't spent on it. And then I suppose if something did make it through, fair enough it would be good. The problem was nothing was making it through and you were ending up in situations where compounds were coming through Phase 1 okay, fair enough, pretty much progressing into Phase 2. By Phase 2 you should be seeing efficacy. That's what the whole idea is with Phase 2. About 60% of the compounds in the pharmaceutical industry were going down in Phase 3. They should have never made it to Phase 3. That's when you're talking hundreds of millions. That's when the compounds were doing down. No company can sustain that. The pharmaceutical industry cannot sustain that.

Yes, well there's been a huge shift now because as far as I know, the big pharmaceutical companies aren't doing a lot of research. This has all been contracted out and in fact I now work as a consultant for a couple of companies and the whole idea is for the smaller companies to come up with the goods, do the work, and then when it gets a certain way down the line, it looks promising, then they will pass that on and virtually sell the company to Big Pharma. And I think that's the way it's got to go. I mean the old system was, well at Pfizer, and I'm sure the other pharmaceutical companies were the same, it was candidate alerting notice system (CANS). So you had quotas, each project had a certain quota. They'd ideally have two CANS a year, and when you had a CANS, you'd pretty much done all the drug mapping, initially biomarker pharmacology on it, and it would be starting to be considered for moving on to higher things, even a Phase 1. But the projects actually had quotas to do.

TT: I've never heard that before.

WM: So yes, okay we've got to have this by, this is our quota, what we're supposed to have. And of course everybody just, 'Oh, we've got to do that,' so the possibility of going back and looking at the physiology, the normal physiology and the exploratory physiology, just became very, very difficult. And this is why you see the pharmaceutical industry pretty much in the situation it is now.

TT: I'm just thinking about your career, Wes, and as I said earlier, you used words like naïve, ignorance.

WM: [Laughs]. Very much.

TT: I think it was Einstein said that the person who makes discoveries is the ignorant person, because the clever person knows it's impossible, and the ignorant person doesn't know it's impossible and so therefore does it.

WM: That sort of ties in really. That rings a bell [laughs].

TT: So the sort of thing you're saying is you've gone into things and you've thought, 'Well, I don't understand that; I'll try to understand it.' You're not going in preloaded with all these ideas of 'can't do that'. Is that a fair assessment?

WM: Yes, it probably is. It's probably, again it probably goes back to what catches my interest or what caught my interest but yes, it was, it was just naïve in the sense of not understanding that I couldn't do it, and thinking, 'of course I can do it' type of thing. Well, why not? Why can't we do it? And that attitude with it. And I think yes, if you start really looking into things and you become a real expert in these things, this is one of the problems I have with a number of pharmacologists. You get some very high powered pharmacologists who have done a lot of really top notch experimental work but if you look for pharmacologists who put the meat on the table and said, 'Here's a discovery that has actually gone forward to make money or help people, improve conditions' then there's a lot of pharmacologists out there that have not been able to do that. One of the things that's an example that I keep thinking of is 5-HT_1 and 5-HT_2. Now people banged away at 5-HT_1 and 5-HT_2 for years and years and yet you look at it and you say, 'Well, nobody even wanted to know about 5-HT M-receptor prior to about 1985/84, it was all 5-HT_1 and 5-HT_2.' And what's come out of 5-HT_1 and 5-HT_2? You can do a lot of pharmacology in a lot of animals and you'll work out what's going on in them but does it put the meat on the table? And I'm not so sure it does.

TT: I wonder about something else in your career because you are very, very unusual to have got to your position and had your career without a PhD. And again I'm just wondering whether a PhD would have knocked the ignorance and naïveté out of you in a way?

WM: It may very well have.

TT: You're almost self-taught as a professional drug discoverer. Okay, you had a wonderful background from your Edinburgh degree. I've just been reading some stuff in *Nature* actually about the PhD thesis and how as a sort of rite of passage it stultifies some people. You escaped that.

WM: Well, yes, perhaps maybe that's something. I suppose you can end up in a situation which again I probably did avoid as you go down the PhD line, you do become very specialised in an area and very focused in a particular area. This is one of the things that I've found disconcerting with the British Pharmacological Society (BPS). I remember when I first started going to them back in the 1980s and all that, and you'd go around to all the different posters and you'd talk to almost everybody, and you'd go, 'Oh, that's really dead interesting.' And now if you go, and I'm sure it's in the other societies too, don't get me wrong, I'm not singling out the BPS, it's so very focused in a particular area.

TT: Yes, 5-HT_3 people talk to 5-HT_3 people.

WM: And that's all they want to hear about, rather than going around and talking to the other people. I actually don't go to the BPSs anymore because I find it is so focussed in on stuff that I've lost touch with anyway. But I do wish they could instil that feeling of 'let's go around and look at all the posters. Yes, that's interesting!' I can understand that. One of the other things I found actually quite frightening was I went to a BPS meeting, I think Gareth was giving a presentation and I wanted to go and see it, and so I went down to it. And there was a whole section actually on pain research, which I'm kinda involved in with the companies I'm consulting with, and I went into this, it was about a three-hour morning meeting. And they got up there, and the people, there were about seven presentations, six or seven presentations, and this was

only last year. I'm sitting there listening, looking at what they're presenting, and about halfway through the second or third presentation I'm thinking, 'Crikey, this is what we were talking about 30 years ago!' You've got to move on; it just doesn't go anyway. Particularly with pain. I mean I've always held that, well the companies make a fortune, if you can find the Holy Grail of Pharmacology, I call it the Holy Grail of Pharmacology, the broad spectrum, truly broad spectrum, non-opioid analgesic, my gosh, you're going to have something huge. So this is what I would say, this is where research should be aimed. But the stuff I heard, it just doesn't seem to have moved on. I could understand what they were saying. Now if I could understand what they were saying from stuff I'd picked up 30 years ago and saw the same stuff coming up, then I think, 'Oh boy, they're not quite approaching it the right way.' You get so many mechanisms. 'Oh yes, here's the mechanism.' Well, we used to run into this problem at clinical meetings, I don't know if you ever went to those meetings? Terrific meetings. I loved the hospitality suites.

TT: Some great people used to go to those, I haven't been for years.

WM: I haven't been to them for ages. But we used to get up there and of course you'd get a lot of the clinicians in and we were looking at irritable bowel syndrome at the time, this is going back about 20 years I suppose. And you'd go, the clinicians would get up there and they go, 'Oh yes, here's a patient population of irritable bowel syndromers and they have raised levels of such and such.' And they go, 'Therefore such and such must be the cause.' And you're thinking, 'No, you've got correlation, you don't have causation!' And you'd see poster after poster, somebody would come up with a correlation of raised level of something.

TT: Compared with somebody like say Gareth, or Pat Humphrey, although even Pat Humphrey has been overlooked, you sort of missed out on awards and honours.

WM: [Laughs].

TT: Would you like to comment on that?

WM: I've got no problem with that one at all. I mean the reward in all that is actually seeing the drug go into the clinic. I often look at that one paper, that first paper that Gareth and I put out, the inhibition of cisplatin-induced emesis and you could come up to me and you could say, 'Look, I would give you a 100 other papers, publications for that one,' and I wouldn't trade anything for that one paper. It means that much to me. And as far as the rewards, there's no reward that can reward me more than actually knowing and hearing the stories of the people, patients, who have actually benefitted from the work. Chris Davis, he wrote the 5-HT book, I think it was from the Oxford meeting, and in that right at the end he finishes a paragraph and he does a quick review of history of nausea and vomiting because the whole 5-HT_3 area had stimulated the thing at that time. And right at the very end of his review and history, he goes on about how the discovery of the 5-HT_3 antagonists were made and he refers to it as 'seminal paper by Miner and Sanger' and his very last sentence is something along the line of 'for this breakthrough, for it can be justifiably called that, has in some instances meant an improvement in the quality of life and I'm sure in some cases life itself.' How can you get a better reward than that? [Laughs]. And I thought that was so nice of him to write it that way.

[END OF TRANSCRIPT]

Further related resources:

1. Christie D A, Tansey E M (eds) (2007) *The discovery, use and impact of platinum salts as chemotherapy agents for cancer*. Wellcome Witnesses to Twentieth Century Medicine, vol. 30. London: The Wellcome Trust Centre for the History of Medicine at UCL.
2. Miner W D, Sanger G J (1986) Inhibition of cisplatin-induced vomiting by selective 5-hydroxytryptamine M-receptor antagonism. *British Journal of Pharmacology* **88:** 497-499.
3. Minet D W (2012) *From Chicago North into Peril.* Wisconsin: Worzalla Publishing.
4. 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.

5. Overy C and 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.
6. Reynolds D J, Andrews P L, Davis C J (eds) (1995) *Serotonin and the Scientific Basis of Anti-Emetic Therapy*. Oxford: Oxford Clinical Communications.
7. 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.
8. Tansey E M (intvr); Tansey E M, Zarros A (eds) (2016) *Humphrey, Patrick: transcript of an audio interview (08-Feb-2016)*. History of Modern Biomedicine Interviews (Digital Collection), item e2016020. London: Queen Mary University of London.