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**Professor Sir William Paton CBE FRS in interview with Dr Max Blythe  
Oxford, 10 December 1991**

**Part One**

MB Sir William, I've just come upon for the first time this marvellous 'good ship Pharmacologica.' Perhaps you could tell me a little about this?

WP Well, that was the ... department when I retired being very kind.

MB This was in Oxford?

WP That was a presentation, yes, when I retired in '84. And what they'd done actually, it's a, it's a kit of some sort, and two men, two men that worked for John Hughes and Peter Flaxman(?), they settled down and slowly built it up, there are thousands of bits to it. And every time I was near, down the workshop, they had to throw a curtain over it. So I, so I knew nothing about it, and then out it came. And there were some nice things, some, they even got (?) Hogg(?), from another ... department, to make them a model of molecules and that's one of the things I sort of worked on, that's the model of tetrahydrocannabinol and so on, and so on and so forth. So it was awfully nice. And there was a little model diagram...

MB So that's the trawl of your molecules, is it?

WP It's a sort of trawl, yes.

MB And this is the diving bit, because there was a diving phase, wasn't there? A diving phase.

WP And that represented the diving, which goes back to the beginning of all my scientific life really, back in '50, in '44...

MB Hampstead, yes.

WP ...back in Hampstead.

MB Yeah. And you had all the...

WP And all the various bodies I've been associated with, you know, the Rhodes House and Balliol and all these, all these different...

MB I see the College of Physicians as well there...

WP College of Physicians, and of course I...

MB ...which started this series we're, we're taking part in...

WP Yes of course.

MB ...today. So it's rather fine. I wish I had something like that. It's a wonderful...

WP Well, it's very nice of them indeed.

MB ...sort of trophy.

WP And hand-made by them.

MB Oh yes. That's a great thing to have, yes.

WP Grand.

MB Yes. Sir William, I was going to start today and talk with you over the, the main phases of your career. Perhaps I can go right back to the beginning and just talk briefly about parents before we come to the pharmacology and the, and the main, and the main years of your professional career. What about parents?

WP Well, can I go even one step further back...

MB Please.

WP ...and mention my mother's father, grandfather, maternal, David McDonald, whom I'm very proud of because he had a battle with the anti-vivisectionists back in 1911. He was a Presbyterian minister in Derby, and he had one of them come down and talking what he thought was ... well he called it 'suppresio veri and suggestio falsi'<sup>1</sup> and was then sued for slander by the man talking and won his case and so on, although he was very poor man, and so on and so forth. Anyhow, that was my mother's father, McDonald. She was a very, very nice and clever woman, very, the most kindest person ever. Started a British restaurant, before they were started, in St Albans. And she was a very kind, modest woman, and lots of my sort of undergraduate or young friends would come, they'd come and unload their woes to her while she ironed. Very characteristic. My father was a medical missionary who was out in Calcutta, they both were. I had a year out there but it didn't agree with me, so I came back.

MB How long were they out in Calcutta? What kind of years were those?

WP Well it, this, well I came back when I was 5, so that's the 1920s.

MB Right, right.

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<sup>1</sup> "The suppression of the truth is the suggestion of falsehood."

WP Actually she wrote, before that she wrote a little book on, *The Child and the Nation*<sup>2</sup> it's called, all about education. She was ... she was...

MB A woman of many interests?

WP She was an able woman, very modest, so she worked for everybody else all the time. She...

MB Did she live long enough to see much of your career? Did she...?

WP Yes, she saw some of it.

MB Good.

WP She out-lived my father. He died back in '43, unfortunately. He came back and was very prominent in trying to get churches together, so-called ecumenical movement, and he was distinguished in his way. And they had a, William Temple presided at a memorial service for him at St Paul's after he'd died, you know. He'd made a lot of friends.

MB Were you close to him, or closest to mum?

WP Oh, I think we were all...

MB A close bunch?

WP ...I think all the family liked each other, you know. Yes, they... He was very busy, so one didn't see as much of him. But there was, no, I think we all liked each other very much.

MB But he was an immense churchman.

WP And he was a prominent churchman. He died too early really. Yes, he died too early.

MB Yeah. But you came back from Calcutta in the twenties to go to school over here, I guess?

WP And then I came, went to school here, and...

MB Where was that? We'll just pin that in as we go.

WP Well to begin with was ... I went to school, I suppose, it's a place called Winchester House School in Brackley. A prep school.

MB Is it still there, do you know?

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<sup>2</sup> Grace M Paton, *The Child and the Nation*, London: 1915.

WP Still there. The boys still have little bright red caps. It was a nice school. A man called Hayman ... was the headmaster. He was called 'Bags' by the boys. He was a sort of shambling... He'd been a member of the AC, MCC [Marylebone Cricket Club], a cricketer and so on, and he was very good with the boys, a very good teacher. And I, even now I can see him. I was started off on classics, you know.... If you want to know what a Latin word means, you take one thumb and you take the other thumb, and then you place that over the parts of the word like that, you see. He'd teach you how to dissect how some Latin words are built up.

MB Terrific.

WP Now, that's a very simple, trivial thing, but ever since then if you're, if I'm not quite sure what a word means, you dissect it.

MB Great impact man, yes.

WP And he was good. He told marvellous ghost stories. We'd all sit in blankets in front of the fire down in his study or something, little boys, be told 'two circles, two circles, a point and a square!'

MB Golden years! Golden years! And obviously well etched, and you can remember him with great clarity.

WP Well, he was a ... I think it's the person, he was, you know, one valued that.

MB And then you moved on, to Repton?

WP Well then I had to, a parson's, minister's son, you had to get a scholarship. I sat the scholarship to Repton just after recovering from a go of pneumonia, of which I'd had several, and, but that got a scholarship. I think probably a rest in the san[atorium] is a very good preparation for writing a scholarship paper actually. And then I went to Repton and they, then they...

MB Was that very different? Was that a ... a tougher regime?

WP I suppose it was. I'd had two brothers go there before me. I was Paton three.

MB So it was known territory. You'd had a lot of feedback?

WP Partly known. And one was a fag, but that was very, it was very ... it's a nice, very good all-round school actually, Repton. And it played games well; CB Fryer(?) was there for instance. It had good academic qualities and both Fisher<sup>3</sup> who was my headmaster and Christie(?) who followed him, they were both good scholars. And the science teacher, well there were two science teachers, one a man called Barton, EA Barton(?), who was, I think was really very well known as a science teacher. He wrote some very good textbooks, and I remember him giving me some special

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<sup>3</sup> Geoffrey Fisher.

coaching when I came to do a scholarship to Oxford, in Eddington<sup>4</sup> and things like that, you know. He was right up to date with things and not afraid to put quite advanced ideas to us boys.

MB While you were at school, and I was just moving in to say, when did the scientific view begin to ... to prove dominant? When did you decide to read sciences rather than...?

WP Well, I'm not quite sure, there... Ever since I can remember, the idea of being a doctor was ... was in my mind. I had an uncle doctor who had a very nice car, very fast car, and the way I remember is being driven at sixty miles an hour...

MB Powerful. Yes.

WP ...on the road from St Albans to Dunstable!

MB And he made an impact, did he?

WP But ... he was a nice man, and I'd like... But I think the medical missionary side would be not far away, because my father was a... And I was always gadgety, I was by far the most gadgety of the, of the house. I wasn't a particularly natural historian. But I had, like other children have, a string round from the light switch to my bed and things like that. And I was gadgety.

MB Good, yes. And so it was all moving that way?

WP And then, at Repton, now Williams(?) and Barton... Williams, I haven't mentioned, he was a very attractive character who taught, also taught the sixth form, sang in Gilbert and Sullivan. He was a very humane man, he was attractive too, and I ended up as godson to one of his children actually. But the two of them I think made science attractive. So I switched over after ... I think it's three years, against the bitter opposition of the headmaster who was Fisher, but I did switch...

MB Right.

WP ...from classics to science.

MB And then Oxford became a logical goal?

WP And then, well my father had been at Oxford. I think, my mother had, well, she had some trouble earlier in her life, so university wasn't on for her. I don't know where she'd have gone. But Oxford was the obvious thing. My father was, like his generation he'd read Mods and Greats as it was called, and he thought a First in Mods and Greats was the acme of ... academic achievement, you know, that generation. So...

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<sup>4</sup> Sir William is probably referring to Sir Arthur Stanley Eddington (1882-1944), astrophysicist and mathematician.

MB Where was he at college? Where was he...?

WP Pembroke.

MB He was at Pembroke.

WP Where Bannister<sup>5</sup> is now.

MB Yes, yes.

WP And happy there, I think. Full of, full of practical jokes and things, but I think he was happy at Pembroke. He didn't do especially well. I can't remember his degrees. But ... but then he went, he went on to theological college...

MB And so you came up to Oxford?

WP So I came up to New College.

MB On some award?

WP I'd got a, I'd got a, I had to get a scholarship and I managed one. I personally think it's because, unlike most people reading medicine, I did the Greek unseen in the entrance paper! This is a small relic of my sort of start as a classicist.

MB Impressive, impressive.

WP So I think, I think that Oxford rather likes giving people a chance if they, if they sort of do something... But otherwise, it was straightforward I think. I had a happy time. I had a very nice tutor, a man called R S Creed, who was in New College. Very quiet, not ... not at all famous, but I think he, but he did an awful lot for physiology in his own quiet way.

MB Right. He was a dedicated tutor?

WP He was an intelligent man, and... Well, I'm not quite sure if this is quite a suitable thing, but I remember he liked you to go to primary sources, and he, one of his first essays he asked me to write was on the, on the facial muscles, muscles expression. That's right, muscles expression. So I wrote a little essay and looked it all up and so on. And he listened to it, 'Yes, that's not bad,' and then he got up off his chair and opened his shirt like this, and said 'Can you make your nipples move?' And then he proceeded to show that if you make a terrific grimace, the facial muscles, they do extend right down to the (?)... Well now, you see that's, if you're talking, you know 'Facial muscles, what can they do?' The answer is the excursion is, goes all the way(?) Of course it connects with Darwin, you know, it's expression of the emotions, it's all in Darwin and so on, and... But, I liked that. I thought yes, this is the way to go about things. Go for primary sources, not what everybody says about everything all the time.

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<sup>5</sup> Sir Roger Bannister, master of Pembroke College 1985-

MB Right. But he was a good man to have a, have a dialogue with, although...?

WP He wasn't, he wasn't a great wit or exciting.

MB But, just a good tutor?

WP Yes, he was absolutely... Yes, there was a great integrity about him too.

MB That's ... that's a great starting point in any relationship with a tutor.

WP And the other, the other tutor, I was very lucky that the other tutor was professor of theology called R H Lightfoot, who was an incredibly radical theologian, but he was a sweetie-pie. And he was very precise, and you'd, if you'd ticked you ... if you had a, he had a, if you had a date at 4 o'clock, he'd say 'It is one minute past four!' and so on. But he was a very nice man, took me on holiday to the Channel Islands, Sark, while he was writing a book. And then he'd consult me over the book, over lunch, we'd have lunch together. He'd say 'Do you think, did I think that 'Locality and Doctrine' was a good name?', you see. And I sort of ... and so on and so forth. But he was a nice man, and a very famous manager. And then the other stroke of luck I had was I went up there, I said to Lightfoot 'I'd rather like to try and learn the piano. I did try it but never got anywhere, I'd like to learn it.' And he sent me to the organist, who, called Sydney Watson, who went on to Winchester and Eton and God knows where afterwards. And he said 'Yes, I'll take you on.' And so for a term I plodded through Beethoven's Minuet in G, and at the end of the term he said, well not in these words, 'That's six guineas.' And I said 'Oh, oh yes. I'm afraid I, I didn't really mean to ask you to teach me, and I can't afford it. But I'll, you know, I'll pay, but I can't go on. I just wanted advice.' So, he took me on for two years for nothing, and gave me, just gave me enough to, I've been able to make my own way on the piano and things ever since.

MB Must have been terrific, yes.

WP But that was nice, because he was, he was ... he was an attractive man. He'd have a, he'd have ... you know, people like Adrian Boult and so on were his friends, and if one of them comes to visit him, perhaps he'd ask me up. And you'd hear the two of them improvising at a piano and things like that. And so one, it gave one a sort of feel for music. And again it was primary, primary stuff. Very lucky, very lucky.

MB So, your Oxford days were rather special?

WP So Oxford was a happy time really.

MB Mmm. How about the ... the movement forward towards this medical career? How did that go?

WP Well I, that just went straight ahead. I, the course was fairly straightforward. I enjoyed it. I enjoyed dissecting the whole body. In fact, I wish everybody could.

MB Yes. At that time did you do three years non-clinical and then move over to a clinical school? Is that how it was done?

WP That's right, yes.

MB And you did your clinical in Oxford?

WP No, I went on to UCH.

MB Right. That was going to be an important link.

WP Which was important... I think one did it because... Well, I, before going up I did a year as a demonstrator. After you've done the school if you've done well, they quite often ... they wanted someone to help teach in the classes and you did a bit of research. And I got one of those and taught histology for a year, of all things, and did a little ... futile research. But it gave me another year.

MB You had a small income as well, yes.

WP And I, and I had a little car and lived in Holywell [Street], it cost £5, you know, and so on. So it was a nice break, and I, I was able to do other things as well.

MB And had the arrangement made to go to UCH and...?

WP And then I got a scholar-, a scholar-, an exhibition to UCH. And ... so that helped. And the county provided...

MB And went to UCH at a remarkable time?

WP And UCH, well it was just, it was just at the outbreak of war, '39, and the, and its peak had passed, I think.

MB Right. Sir Thomas Lewis still there? People of this...?

WP Tommy Lewis was there but they, they were ... London was, if you remember, was, a lot of it was evacuated in the blitz, and my year went down to Cardiff with Max Rosenheim. It was a good year because it had John Gray, who was secretary of the MRC [Medical Research Council]<sup>6</sup>, and David Innes Williams who's president of the RSM [Royal Society of Medicine] at the moment, and ... oh, so there were lots of other people. It was a good year actually, somehow. And Max Rosenheim was a marvellous teacher, and a marvellous sort of ... he looked after his flock very well, so we were lucky as it were...

MB Very committed, he was.

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<sup>6</sup> John Gray was secretary of the MRC 1968-77.

WP ...to be out of London. We were treated rather specially. And the only bomb, and the only bomb dropped in England during that time, in Britain in that time was in Cardiff Docks!

MB So how did you find Cardiff?

WP So then we, so then we came back in time for the blitz.

MB Yes, right. But you went to Cardiff only for a short time? Yes.

WP It was just a year, the first clinical year, 'Introductory Clinical Medicine' I think. But I still remember the cases. I remember clerking ... one did most of one's clerking then because when you were in London the blitz was on. You know, a case of monocytic leukaemia, and an old boy with ... with trichinosis who'd been, worked in a hotel, and a high ... delightful hypertensive congestive heart failure. And there, you know, I still remember these, particularly the boy, aged 12, with monocytic leukaemia. All you could do then was to ... the nurses would clean out his mouth with slightly lemony, something dry, to get rid of all the infection, the agranulocytosis, and you saw him die and so on. So, one remembered that.

MB Mm, powerfully, yes. But then back to London for, in time for the blitz?

WP And back to London, and one, then one had to do one's ... stint, it's very minor really, but in the, there was a casualty clearing station, you had to go and take bits out of, out of people's faces and help, stand in somewhere in operations and help, you know, just miscellaneous things. I lived out at St Albans most of the time, so I wasn't doing much firewatching though. But we had a little ... unit, we, it's called a shelter unit we started. I think there was John Gray and Beric Wright<sup>7</sup>, and me, and ... I can't, Jim Wilson I think. The ... sort of, my UCH contemporaries, going round the tube shelters, just in case, you know, giving clove oil for toothache or... It was very minor stuff indeed, but at least it was something, just seeing if you could help...

MB Your contribution to the...

WP ...and ... just see if anything, to make their life a little less tiresome.

MB A contribution to the kind of needs of the, of the time.

WP Well, the tubes were just packed with the people sort of lying there, and they always had minor ailments, and somebody taking an interest I think was a help.

MB So this was a remarkable time to be having a medical training in London.

WP Well it was, of course this, the medicine I think was pretty good. Himsworth<sup>8</sup> was professor of medicine, Rosenheim his number two.

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<sup>7</sup> Henry Beric Wright.

<sup>8</sup> Sir Harold Himsworth.

MB Did Himsworth have impact?

WP He had his, he had his patients out in, at Leavesden, near, where is it, near Watford. There was a hospital there, they'd moved.... Yes, he was a ... a more remote, a less personal impact at that time. He was professor of medicine, rather scientific, and one remembered him for that reason. But, you know, if I'd never met him again I would have remembered some of his teaching.

MB I was just thinking who contributed... We're talking of the people at Repton who contributed, and people who made the maximum impact at various times before. Who were the people at UCH who made the most impact ... on the way you wanted to go?

WP I suppose Rosen-, well if one, Rosenheim undoubtedly did. He was such a good doctor. He had rather large hands, and when you saw him percuss a chest you'd think he's clumsy, and yet it was sort of firm and totally controlled. And he percussed my chest once and so on, and it was very comforting actually, you know, that sort of... He was a very good doctor. He looked after my mother, and she was devoted to him. And that comes across. I think on the science side, you see the, some of them had gone, were distributed. Lewis you didn't see much of. I think he had other duties of some sort. We saw a little bit of him. And the others, physicians, was Kenneth, there was Kenneth Harris who was great in therapeutics, but I've forgotten who else there was now. It was depleted, you see, a lot of them were in the Army, you see. And Gard-, the surgeon Gardham<sup>9</sup> was, did the surgery, and E K Martin, but they were preoccupied and they ... were going off to the war and so on. I think in a way one's other, one's fellow students were the ... great stimulus really. You got to know a new gang and...

MB So there was an impressive year. Yes.

WP ...new people to see, so they were ... good people, and I ran the UCH magazine for a year. And there was a bit of a kerfuffle about opening a third, a second front now, you know, and med-, UCH medical students doing this and that, and so people were in quite a froth. But they got on with the medicine and it was, I think that was a good time too, really.

MB So, you came through that and by about 1943, '44, you were due to have your...?

WP So '42 I had a, I qualified, and then I did a house job.

MB Right. This was...?

WP Well, in medicine.

MB Where? That was in...?

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<sup>9</sup> Arthur John Gardham.

WP I did it in London. Actually, John Gray and I, we shared a medical unit house job, and he was out in ... in Watford, in Leavesden, and I was in London. And I've, I'm not sure who did the work. I think Kenneth Harris mostly, so it was a fairly ... yes, Kenneth Harris did it, standing in as a, for professor of medicine in London. And the only thing I can remember of that is ... the cases, one or two cases, there was ulcerative colitis was one of them. But the main thing I remember is making, making my medical students, the medical students on my, the firm – I was houseman – take the medicines which were prescribed, I think I, so they would know what it was like to be a patient. And the sisters, this rather pleased the sisters, I think, that...

MB Yes. Was that innovative? That hadn't been done before there?

WP Not that I know of, but I thought, you know, you looked and you saw these patients taking those frightful bottles of stuff you had in those days, and you thought well dash it, I think that we ought to know what this is like too, so we... But then I did... And then, and then just about the end of the house job I got a ... a fifth go of pneumonia...

MB Yes, this, this was not referred to...

WP ...which was, which was...

MB ...but you have had a...

WP Well this, well I ... I think it may have come from India, I don't know why it's come, but repeated goes, yes. The story, I know my fath-, mother used to say, the doctor standing by my bedside said 'Ah well, here it is, he's had seven happy years.' So that dates one of them. But I don't know when the, I can't remember all the others. But this was, you see this was '42 and sulphonamides had appeared, it wasn't M&B 693<sup>10</sup>, but was sulphadimidine as we'd now call it, and of course that made a whole lot of difference. I'd had, but then after that they did (?) and found past pneumonias had left some damage, but of course I recovered pretty quickly from that. But it meant the army didn't have me, and I had to take some time off, for a while, and they, on the whole they decided I couldn't really do the residencies then required, you know, very hard work, residencies, for the time being. So, I tried for a job at The Brompton which I failed to get, but then, and tried this and that. And in the end the physician, one of the physicians who'd been looking after me suggested I went as a pathologist, to a TB sanatorium at Midhurst. And so I was ... and taught me some bacteriology for it, and a man called Gloyne, Roodhouse Gloyne, who was a pioneer in the world of asbestosis. He believed asbestos caused the whole trouble, but nobody else believed it, so he was fighting a battle to make asbestos be taken seriously. Interesting.

MB Prophetic kind of...

WP And ... and, but he was a very nice man, taught me how to cut sections and report pathologically, and off I went to be...

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<sup>10</sup> M&B 693 was sulphapyridine.

MB With these new skills!

WP ...with these month-old skills to be resident pathologist at a TB sanatorium.

MB Was that a nice, was that a nice time? Sounds as, sounds as though it might have been a mixed, a time of mixed blessings.

WP Well, it was, I had my own lab and I cut, I had to, I enjoyed cutting sections. And I enjoyed going round the wards. And I'd have to get a, some sputum and I'd analyse it for TB, tubercle bacilli, look for them, or culture if necessary, and I'd do a sedimentation rate. And you'd get to know all the people in the sanatorium, and how they were; one had been sort of a chaplain to Montgomery in the northern, in the desert and things like that and taught me, told me how to drink two pints at a single gulp. And then there were other, there were sort of, there were, there were some rather nice-looking girls. They'd be sort of, I don't, I don't know, twenty or twenty-five sort of age. But they, this was the old(?) tuberculosis, and it tended, they'd lost a bit of weight and had this very delicate flush on their face. A very characteristic look.

MB A Somerset Maugham type...

WP Probably, yes.

MB ...type facial...

WP So, that was interesting. And then you saw...

MB I think he wrote of some of his heroines in that, in that condition.

WP I think he... Well, he would, he would have, I think. It's a characteristic sort of thing.

MB Yes. And he came across with the idea that they were quite beautiful.

WP Well, they were, yes, in a sort of slightly unearthly way. And then of course you, the other side which one still remembers, is they used to do thoracoplasties in those days, take out all the ribs on one side, so that...

MB Sounds horrendous.

WP And then you'd see these, again nice-looking people but they had a curved spine because all the ribs had gone one side and distorted their shape. But it was interesting and I enjoyed the... What I didn't like very much was the ... the superintendent, who was an Australian of considerable energy and push. I think we could have got on famously if I hadn't been so young, but I, he liked being rude to people and expected them to answer back. I only did that on one occasion which was, which was on my last night there. We used to play billiards together in the evening. There were several residents, and I was the most resident – the others were married and sometimes lived out. And at the end of the, he, I felt at, in all honesty I ought to tell him I thought he was an absolute bastard. So I told him in not quite those words,

and he beamed all over his face and was delighted, and said ‘Ah yes, yes. You know, I think I, I’d like to get research, tuberculosis research going, a unit here, couldn’t you stay on and run it?’ And, which taught me, you know, that you, you know, you mustn’t take things quite at face value, but people are sometimes very rude because they want you to be rude back.

MB Yes. You might have had a good relationship over a longer period?

WP Actually, it wouldn’t have, it wouldn’t have paid me, it’s a different, my gain would have been different. But it was interesting, very instructive.

MB Yes. How did you make the next step? Because you went to...

WP Well, I’d been offered a job ... by Miles<sup>11</sup> who was professor of pathology at UCH. He then went to the National Institute of Medical Research, to go and do pathology there. And I said no, I didn’t want to do pathology.

MB This tuberculosis work had turned you off really from pathology?

WP Well, I don’t know. I just wanted to do clinical medicine at that time, experimental medicine, actually. And then a man called G L Brown, who lived at St Albans, heard about me. I think he’d, he’s, he had UCH connections I think, and Rosenheim had probably mentioned me. He said he’d like somebody to come and help him with his diving programme. And I said ‘No, I don’t want to do a diving programme.’ And then after a year of this superintendent, I thought God this is awful, and the nephew of the then secretary of the Medical Research Council, who was called George Little, it was Mellanby’s<sup>12</sup> nephew, said they were still looking for a job, looking for somebody to help them with the diving thing. And I thought well, I don’t know, I think I’d better, it’d be better than this anyway!

MB And that was at Hampstead?

WP And that was at Hampstead. So, off I went to Hampstead. Folk demur on the third offer, you know, and yet, and yet of course it was just a very, very good place for me to have gone.

MB It must have been a marvellous place, and quite exceptional place at that time for medical research?

WP Well then, well then of course... No, not as of then. Well, you see, it’s a marvellous place anyway, but in a way then it was, the department I went to which was, physiology and pharmacology I think they called it, had gone over to ... to join with the Navy in research into diving problems. And so they were doing things they didn’t know much about, they were having to learn their way. And all the past history of the Institute was almost irrelevant actually, except that it was good science, and they were trained scientists. But it was a marvellous place, and the boss, G L Brown,

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<sup>11</sup> Sir Ashley Miles.

<sup>12</sup> Sir Edward Mellanby.

was a very good boss with enormously high spirits and energy. And he had a large fund of indecent stories.

MB Was he a physiologist?

WP He was a physiologist. And he'd done, made major contributions to the theory of chemical transmission. You won't want me to go on about that, but one or two of his things were actually key, they got rid of a block in the development of the story. And ... and his number two was F C MacIntosh, Hank MacIntosh, who in his own way was equally remarkable, but very quiet, the most modest man I ever met, but a very deep thinker and remarkably considerate. He was really, he was a very nice man. And the two of them, I think, between them created a remarkable atmosphere, because Brown gave energy and ... and so on and Hank gave a sort of solidity and considerateness. And they were both jolly good scientists. And then along with that...

MB So, it was a good move to make?

WP So it was much better than I realised actually. There was Horace Barlow, was the, was the young medical student seconded to them for a while. He'd been awfully good and he was, he's now professor in Cambridge, and a great pioneer with vision. A technician there was a man called Boycott, Professor Brian Boycott, who is also another of these distinguished chaps, but he was just a technician, and in due course he was going to do an external degree at BSc, and then he's gone up and up. And I forget who else there was at that time. It was a fairly small team. And the head technician, a man called Collinson, L, Len, L W, Len Collinson, who'd made Dale's<sup>13</sup> tracings look good ever since the year dot! He was a marvellous man at ... mounting tracings we'll call it, you see, (?) little, little things like that. And he knew, and he knew, he'd known, he'd been Dale's technician for a long, long time and so was still full of stories about him. And I had to, and what they were doing then was studying the, how carbon dioxide was absorbed in a diver or a submarine by the ... CO<sub>2</sub> got rid of by the soda lime. And they were trying, MacIntosh was trying to make a really good thing which would test the canisters which divers or submarines used. Well, they discovered that quite often the soda lime wasn't properly packed, so there'd be a little air channel past it, and so a diver could easily, if he was working very hard, could easily accumulate a lot of CO<sub>2</sub> in his breathing set ... and so on. So there was that, and then...

MB What kind of work were you pitched into? I mean...

WP Well, the first thing I was told to do was the, there was a question of a correction factor and the working of this ... this canister testing device. It had, that had been called, that ... they expressed their results in terms of what's called the 'physiological dead space', you know, there's a dead space, and of course if a canister doesn't clear properly then it adds to the dead space. And they were looking round for a name to call this device. It was mentioned to Haldane<sup>14</sup> – Haldane was also in the,

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<sup>13</sup> Sir Henry Hallett Dale 1875-1968.

<sup>14</sup> JBS Haldane.

in one of the other teams – he was, he looked in, delved into his classical past, and said ‘Ah, *kenon*, to *kenon*,’ the empty space.’ So, they called it a kenometer(?)! It was a nice bit of classics, I think.

MB Yes, excellent.

WP And anyhow, I had, I settled down for a little while just doing some calculations as to what possible corrections were needed for this. And then ... then they were doing tests of the effects of CO<sub>2</sub> on you. The fundamental discovery, which I think is probably an old one but nobody knew, was that if you breathe carbon dioxide in air, you ... or you just take a, you're, it's actually a rebreathing situation, if you're in a submarine and you're sunk you just rebreathe all the air that's there, the oxygen goes down, the CO<sub>2</sub> goes up. If you rebreathe under those conditions, then before you become, before ... long you begin to get a very strong respiratory stimulation. The CO<sub>2</sub> stimulates you, the oxygen lack stimulates you. However, if you're breathing oxygen and you, CO<sub>2</sub> accumulates, the hypoxic stimulus is removed. CO<sub>2</sub> is just left, and there's not enough really to do much except make you breathe a bit deeper, but you can be unconscious before you suffer from respiratory distress. And of course that's what had been happening with some of these, there was a thing called 'shallow water blackout' where there, they were working extremely hard, the canisters weren't working, they got enough CO<sub>2</sub> to make themselves unconscious, like an anaesthetic, which it is. And so there was a lot of work being done, just showing how if you, if you rebreathe from this way and this, this way, how the different effects of the mixture of oxygen and CO<sub>2</sub> decline and the respiration went up and so on. And then of course I...

MB (?) fair share of CO<sub>2</sub> I think at that time.

WP So then I ... I think Barlow went off fairly soon to qualify in medicine, and I was left doing, trying to determine what, at what level did CO<sub>2</sub> begin to anaesthetise you. So you plodded through all the different amounts in various tests and, and so on. And I think I've been anaesthetised by CO<sub>2</sub> more than anybody else! It's like, it's like being sort of drunk. You get fed up with it after a while. But ... but anyhow, 10% CO<sub>2</sub> will make practically everybody become virtually unconscious, they lose... Some were resis-, are a bit resistant. MacIntosh was rather resistant. Brown would go off in whoops of girlish laughter very soon, you know, on 10%. And the, the tests we used with handwriting, and again a thing which, I was amused ... (?) how you wrote on the pad in front, I was very amused that the sign of intoxication [that] proved very effective was when your handwriting becomes indecipherable. And I was very amused to find that the last thing that became indecipherable in my own signature – you know, the WMP – was the BM for Bachelor of Medicine! My last clutching onto reality was my medical degree. And so on. But anyhow, that... And then, well that went on, then one went on to decompression sickness, 'the bends', and Brown was a general adviser on ... on these matters springing from diving and high pressures. And he had links, he was advising the civil engineers on bends and he recruited me into that and that, and he asked me to referee a paper on decompression sickness for the *Journal of Physiology*. And that interested me, so I got a bit interested in the theory of how bubbles(?) separate and so on and so forth.

MB Right. And this was in the period '44-'46 that we're looking at?

WP So this was coming up to '44-'46. Yes, that's right actually...

MB Just keeping the time...

WP That's right, that's right.

MB ...the timescale alongside it. But you've gone to Mill Hill, no you didn't, you went to Hampstead, you went to Hampstead as a physiologist essentially?

WP Well, I went as a phys-, and I still had hopes of getting back to medicine. I even... I can't remember how it showed, I remember it did ... well I, one thing, I, when the director asked me to be the Institute's doctor, I very willingly agreed, so I'd sort of dish out, you know, the pills and things they'd need, and send them to hospital as necessary. But I still now hoped to get back to experimental medicine, for some reason, I don't know why. And ... but I think essentially it, [if] it hadn't been for one thing I would have gone on to be a respiratory physiologist. I got, I was quite interested in it.

MB Right. Because you were...

WP And I was doing experiments on...

MB ...into it by then.

WP ...how, on their, lung compliance and things like that. When, when you breathe in and out of bags a lot of the time you notice, and breathing underwater was... You see one of the things we did was study respiration under water, when of course the gravitational pull is removed and your viscera move up, and your lungs are slightly collapsed and so on and so forth. It was really, we really found that the ... the operation under water is roughly the same as ... as at the surface, with some differences. And the pressure, another thing was to find the most comfortable pressure to breathe at under water. You have to compromise, you see. The water is a continuous gradient outside your chest and your bag is a single pressure, and if the bag, the bag collapses about that level so it makes a working pressure, that's about the...

MB Was it well equipped at Hampstead? You had tanks to do this in? You had...

WP We had a tank.

MB ...had good facilities?

WP Well, there were, there was a tank Brown got from somewhere, and he looted the, there was a compression chamber which old Haldane, JS Haldane, had had at the Lister Institute. And that was brought over. So, and they, they'd already started doing some work on oxygen poisoning, which I never participated in. They did a bit on that. And then when it came to CO<sub>2</sub>, that could all be done at surface level. They hadn't,

they hadn't done much on decompression sickness, but I got interested and did some experiments ... on that and on another problem of... If you're, I'd been on a submarine escape mission to the States, as a sort of tame physiologist of an admiral and some naval officers, and they were looking into a question which had arisen during the war. Some people had been sunk in a submarine – there was one very striking case in a Norwegian fjord – and they'd got out without a breathing apparatus. They'd sort of taken a deep breath and floated to the surface, and the question was now how does this come to be possible? And people thought about it and in fact what emerged, what emerged of course was the air in your lungs expands. Now it's dangerous, because you may burst your lung if you hold your breath. On the other [hand] it's a virtue because it gets rid of CO<sub>2</sub> all the time, and if you start with high oxygen, you see, it's fine. And so I did one or two experiments just confirming, I think they were potentially rather dangerous in retrospect, confirming that if you go down to pressure, and then hold your breath, that means don't inhale, and just follow the air coming out, and you follow its composition, then you do see it. You are in fact, it follows a simple Rinzing(?) equation, a simple logarithmic equation, and you allow your breath-holding time to ... increase by I suppose, oh, a couple of minutes or something like that. Normally you can hold it for about one or two minutes ... and so on.

MB Right.

WP And that's with oxygen as well.

MB And that's just to get to the surface?

WP Just in the time to get to the... So that, that became, that was the start, this Norwegian story, there are some other stories, of what is called free ascent. And, in escape. And then we had this, this expedition to America on, to interest the Americans, who had a great big escape training tower for how to escape from submarines, and explore this. It was a sort of little Admiralty Report on the use of free ascent in submarine escape, which is now universally used. So, that was interesting...

MB So you were deep into that?

WP ...and I would have, I would have gone on with that, and one, I think, with lung properties and so on.

MB Yes. So this accounts for this particular part of the model.

WP So that's, that's the...

MB We've accounted for one...

WP ...that's here, yes, that's right.

MB ...one piece on the, on the board as it were. Yes. How did the swap arise...

WP Well, that was simply...

MB ...to another discipline area?

WP Well that's ... was when MacIntosh was asked by another member of the staff if he would look at the toxicity of an antibiotic they'd found. This, the chap who'd found it was a man called RK Callow who was a biochemist, and the Institute was then very concerned with chemotherapy amongst other things, and they had a unit looking for these products. It was a perfectly good antibiotic. It proved not to be very important, it probably got too protein-bound, I think, but, partly, but also because it was found to have a very characteristic toxicity, you see we recorded toxicity. Of course the routine thing was to anaesthetise a cat and record blood pressure and respiration and use your eyes, see what happened. And MacIntosh had done this, a certain amount of this sort of thing. It wasn't really his great line, but he knew you should inject some histamines, some acetylcholine, some nicotine and things like that, just see, and some adrenaline, just see what effects it had. And we stuck this stuff in. And I still remember these... You stick it in, there's always a little blip because the saline makes a small rise in blood pressure, and then instead of anything happening for the next thirty seconds – normally it would have, acetylcholine sent it down, adrenaline up – nothing happened. And then at about thirty seconds, there was a sudden fast fall in blood pressure, which then presently started recovering with a bit of tachycardia and back to normal, a very sort of funny picture.

MB Mm. Quite unexpected.

WP And ... and then, but as you went on thinking about it, of course MacIntosh knew that, well, we, I don't know how the thought came, suppose it could be releasing something in the periphery, the circulation time's roughly that sort of time, so it's recent... It couldn't be acetylcholine because it's so quickly destroyed, and the only thing possible it could be is histamine. And so you actually looked in the blood, was histamine appearing? And of course on the track back the second time round, there was the histamine, mixed with some adrenaline which had also been released. So it was... But you see, so it's a very, a very simple thing you know, very simple tracing, simple interpretation. And one tracing almost gives it to you if you have some, just pure thought. And then we looked through, then he was intrigued. He knew licheniformin had a guanadine group. And he said 'Well, look here, Harold King upstairs has got some, lots of other compounds' ... and this was part of the chemotherapy effort. So he went up and raided his thing, and we'd asked him for all the basic compounds he had. He had a whole string of dibasic compounds – diamines, diamidines, di-(?)thioureas, di-quaterneries – and ... oh I've left out one. Anyhow, so we plodded through all these, and found that if, if the amine, the two amine groups were separated or whatever the, these two bases(?) were separated by more than about five, six, something like that, steps, they were histamine liberators. Tubocurarine of course is just such a thing and that is a histamine liberator. And so, so we, we were finding all this, very, it was, in a dog it reproduced the signs of anaphylaxis, you get heparin coming out there too, so it was very like a sort of, a very good histamine release. So it's a nice histamine story, and made sense. And ... now that was fun, I think, and one could have done, there were lots of things I wanted to, I'd have liked to have followed that on, just on the structure/action thing. But there was one thing in

particular that happened, which did make a difference. And that is, I think MacIntosh was beginning, he wanted to get back to his old acetylcholine work and so on, and the lab by now, it was about '46/'47 by now, the war was over, they were beginning to get back to acetylcholine or neurological transmission or something. And, but I went on and I thought let's complete the series and let's look at the bis-quaternaries. We'd done all the other basic groups. And the first, the first one I tried was the eight carbon atoms between the two endings, and so far from causing a fall in blood pressure of any sort, there was a steady rise in blood pressure which puzzled me for a moment, but of course was asphyxia. And actually it had occurred with one of the other compounds earlier I'd, which was, I'd put on one side, just toxicity I called it. But this was just a gross asphyxiation and if you just, you, it's very easy, it took about a day to show this was just a curare-like action. But it was a very clean curare-like action, and at that point... It had some interesting properties. It behaved differently from curare. It seemed to stimulate muscles a bit as well as produce this paralysis, was very clean. And there was an interest, the lab anyhow from its chemical transmission was interested in curare. And Bovet I think had, upstairs King had been working on the structure of curare, and Daniel Bovet in Italy had just produced some synthetic curares. So there was a little bit of interest in curare, and people had shown you can use ... curare at the site of operation to relax muscles, and help the surgeon. So, there was, there was an interest in it. And at that point I think ... there was another, I don't really know all that happened because I was very young at this time, very junior, but it was a, Harington<sup>15</sup> I think talked to Harold King about it, and King said 'Well, you know, more of the series should be made.' He'd been doing, making the series most of his life with these compounds, finding things. And somebody, and they needed somebody to do this, and this ... and this is where Madame Zaimis<sup>16</sup> was recruited. She was looking for a job.

MB Right. She came from Bristol?

WP She wasn't very happy at Bristol for some reason. I'm not sure, I think it was the subject she didn't like very much. So she, she was offered this, and she had done some chemistry in the past, and so ... she joined, she joined King to do the chemistry and me with some of the pharmacology. So she made the full series, and then it was just the matter of, well to begin with just the straightforward matter of where the curare maximum was, and we found that it was at the 10-carbon atom – so that's decamethonium. And, in passing I might say that we weren't alone, we weren't alone on this as you probably know. Here in Oxford, a chap called Harold Ing, who was a marvellous chemist, pharmacologist, had been theorising about curare action for years. And he'd decided that he'd, there was a, it was worth making a bis-quaternary source, explore this ... this curare-type structure. And he'd started making some bis-quaternaries deliberately, to explore it. And Burn wasn't very keen on this, but he said that he could have a few rats to, rat, make rat diaphragms of and test on. And unfortunately for him the rat is very resistant to decamethonium, for reasons which aren't very clear. Anyhow, yes, so they, they quite agreed, Barlow and Ing quite agreed with us that C10 was the maximum. But they didn't really get any great impression of potency, while on a, on a cat or on man, the cat is rather close to man in

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<sup>15</sup> Sir Charles Harington.

<sup>16</sup> Eleanor Zaimis.

this, three milligrams would paralyse you. So it's quite active stuff. And it's very free of side effects; no histamine release or anything like that, no ganglion blocking action anywhere. Anyhow, so that was decamethonium, and that had it's run as a synthetic curare. It was displaced, it was a useful run in a way because it introduced anaesthetists to a type of blocking action, curare action, which is different from that of the curare, we now call it depolarising, it's got some different properties. And it paved the way for another more, very widely used stuff called succinylcholine, which is the same thing only it has these two ester linkages, in the middle of it. And that is rapidly destroyed so that makes it transient. But it has, otherwise it's like decamethonium. But the, so that was, there was a lot of work doing, there are lots of peculiarities to decamethonium. It was interesting, the electrophysiology of doing it, and so on. But the, the other thing that happened was ... odd, you test all these series and you get these, down from, if you go below 8 carbon atoms then the others don't, hardly do any neuromuscular block. Could they perhaps interfere, with the other ones, the higher ones? And so it was trying that idea out, first on a bit of frog muscle. It did, they did interfere. And then the test you used, one of the tests you used then for assaying curare-like substances – which we used to have to do because curare wasn't quite pure in those days, for the Therapeutic Substances Act – one of the tests was the so-called 'rabbit head-drop'. If you put a rabbit in a little stock and just infuse curare very slowly into it, it sits there, you know, in its usual way like this, and then presently its head just drops. It's just the neck muscles, his breathing perfectly alright, it's just the first weakness and ... discovered by an American. It makes a very nice end point, you just tap the nose, can he lift his head, no he can't, stop the infusion. Perfectly humane. But doing this test on decamethonium, fine, it just behaves normally. But trying the, it was either the 5 or 6 atom compound, as an antagonist on the rabbit, to see if it worked *in vivo* and not just on a frog's (?), the rabbit's ears flushed bright red. And, now there's no reason for them to, suddenly to flush.

MB Yes, right.

WP But I still remember, this was, it shows I should've...

MB That was a great moment.

WP And I thought, well it was an interesting moment. And the flush, flashed through my mind a lecture by my old professor of physiology – I'm not inventing this, this is all quite true – John Mellanby here, who used to talk about Claude Bernard and how he'd worked on the sympathetic and the control of the blood vessels, and how Claude Bernard showed that if you cut the sympathetic nerve to a rabbit's ear it flushed. Well here was a rabbit's ear flushing, obviously sympathetic to the, to the ear that had been, had been...

MB Blocked.

WP ...blocked. And of course we were, we were in the acetylcholine field already, you see ... so obviously it was blocking another aspect of acetylcholine. So it was, you know, this was luck really. And so there it was, C6, there was another, there was another peak in the series, this incredibly simple series, just ten or six carbon atoms with two basic groups. You know, there are, there are few compounds so simple

actually. And six is a maximum of one and ten for the other. And then we explored in case there were any other properties lurking around, you know. The twelve carbon is faintly antibacterial, actually, and that may in fact have been a pointer, there are some dibasic antiseptics on the market, which I think may have come, flowed from that in the end, this idea of the bifunctional group.

MB So by this time you were deep into pharmacology...

WP And now of course...

MB ...and the chance of a clinical medicine career had gone? I mean...

WP Well you, one...

MB ...it was over.

WP ...one was committed... It was over anyway really, I think. I couldn't have coped with it I think. But I'd begun to meet clinicians, you see, the dec-, the decamethonium thing. Eleanor Zaimis and I, with Geoffrey Organe, the anaesthetist, we were the first to get it, and be paralysed by it. And so you meet anaesthetists and then you experience it yourself, and we tried the antagonism on ourselves and so on, and then when you come to the ganglion block... It's already known that you could ... adrenalectomy and sympathectomy would, could relieve hypertension, though it's a pretty drastic relief, and [Max] Rosenheim for instance was, quickly was brought in on the, on the use of ganglion block as causing hyper-, hypotension, while it's used, and he did the early experiments and so on. And so one came to that group of clinicians. One started meeting anaesthetists, and one had surgeons who were interested with anaesthetists in surgery with minimal bleeding, and this was a nice way of lowering the blood pressure with hexamethonium. And hypertension with John McMichael and Rosenheim and people like that. So in a way I, my wish to sort of be in touch with practical medicine, well I suppose, very luckily I'd amply satisfied really.

MB Right. And you were providing for great needs?

WP And one was, one had... Well, it was very satisfying actually to ... to do something on that. And so it did make one a pharmacologist, and one got interested in structure and what ... what was happening with this drug-receptor interaction.

## **Part Two**

MB This must have been a golden period for pharmacology, the post-war years. And this must have been a great time of opportunity and interest?

WP Well it, it was a, it was a... Yes I, it's an interesting period. I, for instance, when I arri-, I began to get invited, you know I was offered, get offers for a job, although, you know, there were plenty of, lots of room for people then, places were expanding, and there weren't all that many people. And I had a choice between physiology and pharmacology for a start. And physiology ruled the roost in those days; and to be a pharmacologist was rather a hanger-on position, which I... And that lasted a long time. Even when I came here, for instance, I think none of my other colleagues really said 'I am a pharmacologist' ... here, late in the fifties, as late as '59. They'd say 'I'm really, I'm really a physiologist' 'I'm really a biochemist.' 'I'm really a physiologist.' 'I'm really a chemist.' And there was a curious, for a long time there was a reluctance to commit yourself to pharmacology. So when you say it was a golden time, it was, it wasn't a time when pharmacology was held widely in high esteem.

MB I was just thinking after penicillin and streptomycin in the...

WP Well, that's pathology, that's biochemistry, that's pathology, that's chemotherapy. It's not pharmacology, you see. The pharmacology, the great figure to my mind in pharmacology was Gaddum, JH Gaddum in Edinburgh. He was a mo-, he was a very over-modest man, very, very clever man. He'd done, he'd done the first major work in drug antagonism, and he was, he'd worked on DFP [diisopropylfluorophosphate] in the war, and been one of the people who'd take it. He and Adrian<sup>17</sup> took it, and they got enough hydrofluoric acid out of their urine apparently to etch glass, to prove they were, it had really been absorbed, you know, sort of ... what had happened to DFP! So they'd done that. And then he, going back, and he was I think getting on to work on HT<sup>18</sup> and Substance P and these things, which were mere dregs in most peoples minds at that time. And peptides are all the go now, but you ... you would hardly believe the... And I remember I was being (?) about receptors, what about receptors, and I remember there was a meeting in America, which advertised itself as a, just a symposium on receptors, and I thought that looks interesting and discovered what it was about. And it did prove to be drug receptors. And Brown was very indignant. He said 'You can't call a thing ... a receptor is a sensory receptor, and if it's drug receptor they ought to say so!' You know, that attitude. So that in a way there was a... It was interesting, the [British Pharmacological] Society itself had been founded in '31, it was still a little bumbling in a sort of a way, a very nice, friendly society. Ing was one of its more radical, one of its more able members, and he'd founded, got the journal<sup>19</sup> going – they'd got a journal going. Dale had never really helped it. He, in a way, he was a great figure in it in a way and yet he... There was a very interesting exchange between him and, him and Ing in a, in a symposium on drug action, where Dale says well really he doesn't

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<sup>17</sup> Edgar D Adrian.

<sup>18</sup> Sir William is probably referring to Gaddum's work on 5-Hydroxytryptamine (5-HT) here.

<sup>19</sup> The British Journal of Pharmacology and Chemotherapy was started in 1946, with Ing as editor. The title was abbreviated to British Journal of Pharmacology in 1968.

think that the idea of a receptor helps you very much, it just restates the fact that the drug acts somewhere. You see, that's a, it's a way you can say, it was a completely theoretical entity at that time, so he was right. But Ing got up and said 'That's all very well if that is in fact all it does, but by naming it receptor you isolate it as something which needs to be thought about.' Now, which of those is right? You now clone receptors.

MB Mm.

WP But that was the...

MB That was the climate?

WP ... position. That was the sort of climate. And the other climate, the other element which ... element of course of pharmacology as the handmaiden of practical medicine, therapeutics, and all those bits of frog muscle and cats and God knows what, you know. It wasn't really very important. Good practical medicine was the thing. I may say that people like Rosenheim didn't feel like this, but to the general, the general world of medical science was ... was... Physiology was the queen, I think, and then of course with penicillin and the antibiotics of course then pathology and biochemistry was coming up enormously. And that's another thing. Pharmacology was just a side issue, a bit of biochemistry. And the idea, which even now it's, it hasn't really taken all the route I would like, the idea that it is worth taking chemical substances to see what they do to biological systems as a thing in its own right, like you do look to see how ... disease affects the biological system. And I think it may come, and I think it may come if you, if you turn to something like toxicology. That too is a rather despised subject, you know; everybody relies on it, but nobody feels very keen to work on it. It's a bitty subject, just rather a... But actually if you're a toxicologist ... and here is the way I've been sort of thinking about this so it's coming out a bit elaborate probably, but here is the body with something like fifty to a hundred thousand genes, there, that's, those genes are just chemical entities, and a chemical substance can interact with any of those ... if its, and its expression products. Now this is a really general subject that is inevitably going to be ... bitty, the general rules won't be there, so it will be, look as though you are just flitting from one thing to another. But if the human race wants to know if something is going to damage it, your science meeting that need has got to be, has the biggest demand put on it biologically. It's as big as encompassing the whole of biochemistry, so to speak, and...

MB And toxicology is still neglected.

WP And, well it's, it's getting better. I think that people are learning, there's a lot of talk about it. It's financed because the drug firms spend a lot of money on it. And of course it's one of the focuses of anti-vivisection propaganda to try and stop animal testing and replace it with computer models, or bits of chemical reactions or bits of ... amoebae or something like that. And they haven't got the fact that the body consists of fifty thousand vulnerable molecules, and unless your test allows for that then you, you're not really giving the protection you need either to man or animals.

MB Sir William, about 1949, the MRC headquarters moved from Hampstead to Mill Hill and you went...

WP Oh yes.

MB ... you went along there?

WP And I went with them, that's right.

MB You continued the same work?

WP Yes, well the lab changed a lot. F4, Brown, GL Brown went off to University College to be professor of physiology; MacIntosh went to McGill, his old university. Barlow had already gone to train in medicine and then returned to physiology. The, in the mean, since the last thing we were talking about, John Gray I think had joined F4. And Ben Burns, a neurophysiologist, who later ran the F4 lab for a while, had been... Perry had come; he was really in biological standards with Ashley Miles.

MB Walter Perry?

WP Walter Perry. And they, they all came over to Mill Hill.

MB And did the lab keep its name, F4?

WP And Feldberg<sup>20</sup>, who'd been in the old F4, he came back to head the, the new, Brown's place, and he was, he'd been very fond of it. And he, so we called it F4, even in the new, although it wasn't on the first floor and it certainly wasn't the fourth lab! But, no matter.

MB But it stayed, the name stayed.

WP It was called F4. And there was an open lab. It really was, it wasn't quite, well the people had changed, and, but they, we had individual offices and so on where previously we'd had a... Well Hank MacIntosh and my desks were in the, in the open lab, so that ... if someone's experiment wasn't going well you just, and you're bored or something like, you just went to looked at what they were doing or talk to them or something like that.

MB So the new place was...?

WP So it expanded, and as, I always liked the description by a Cambridge neurophysiologist called William Rushton, a great man, who described moving into a new lab as like an 'adiabatic expansion'. Which, an obscure physical term, but it reflects the fact that when you expand a gas the molecules become further apart and the temperature falls.

MB And that happened?

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<sup>20</sup> Wilhelm Siegmund Feldberg.

WP And of course, well, the temperature of the old institute had been very compact, pressed together, friendly, very nice. Everybody knew all the other sections and what was going on, had coffee together, and looked out over the balcony over the barrage balloons and things like that ... at Hampstead. So, but it was still very good. I don't want to be wrong. Harington, the director, used to be rather cross when people compared Mill Hill with Hampstead, and he was justified in a way. But anyhow it was...

MB And your work continued to go on there for another two years?

WP And I went on for another ... three years it went on. Doing, I was, the diving work, I remember there was a, there was a Newcastle Tunnel being driven. Newcastle, that's right, not Dartford. There'd been a preliminary pilot tunnel at Dartford which I and a colleague, Dennis Walder from Bristol, had been... And there was a Newcastle Tunnel being done, and we were able to get a medical officer, data there, and taking all the cases of people getting bends and so on. And that turned into a sort of MRC report on the natural history of decompression sickness in the field'. That was...

MB Because that was a major tunnelling development at that time.

WP And that was, it was quite, it was the first time anybody had really looked at it, I think, seriously. Well ... well, more or less. Anyhow, that took some time. And I was, there was still some things on, working with Burns<sup>21</sup> on the motor endplate, and so on and so forth. But I was, I think I was getting restless, and wanting a show of my own in a way. I just had an office, and I couldn't organise anything much. So ... and so actually the next, that's in '51 or '2, the reader in pharmacology at UCH – this is the applied pharmacology – called Andrew Wilson, he went away to a chair in Liverpool I think, so they had a vacancy. And because it was UCH and Harington the director was a UCH man, Max Rosenheim was at UCH, and so on and so forth, and Brown was at UCH, or University College rather, then I ... there was the invitation to follow Wilson as a reader in applied pharmacology.

MB And you couldn't have had any doubts about the next step?

WP Well it was ... it was obvious. It was, it was ... actually it wasn't all that good a move really. I could have got a chair somewhere I think probably, but it was a, it was a good place. So I moved into a nice office and a lab, and then across the road in University College there was a lab, which taught me that laboratories separated by a main road have half the value of the same number not separated by a main road! Anyhow...

MB And there you started to do a good deal more teaching?

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<sup>21</sup> Benedict Delisle Burns.

WP And then I had to teach. I had to organise a course in applied pharmacology. It was a bridge between the basic stuff Schild<sup>22</sup> taught and the fundamental, the practical medicine which Max and others taught. I had to organise the therapeutics courses, so I had to get these different clinicians to give lectures on the subjects I thought they ought to give them on, and so on. That was quite...

MB That you enjoyed? Yes.

WP I ... I quite amused the unit; just for once the consultants were doing what, you know, this mere pharmacologist asked them to do!

MB Mmm. That's good.

WP Just for once.

MB What about the research?

WP And the research... Well, I had £200 as research allowance, which was... And so there was a bit of histamine work still to finish off. I, the only place I think where you'll find a dist-, an account of the histamine content of the human leg is in an amputated leg which ... I analysed the histamine content from top to toe. This was all a question of how it's distributed; you know, the places with the biggest contact with the outside world have the highest histamine and so on. And there was an important, actually there was one significant thing. It was a null result in the end, but a man called Rimington<sup>23</sup> and ... a pathologist interested in porphyria, had recruited the help of a colleague of Charles Dent in biochemical medicine who'd isolated stuff called porphobilinogen from patients with porphyria. It was a very good bit of work, and of course Rimington hoped it would be, account for the symptoms and so on. And he asked me and John Thompson, who is now ... professor of pharmacology now at Newcastle, if, who'd come to me out of the RAF, if we could study the pharmacology, which we did. And unfortunately it proved to be very, about as interesting as an amino acid, you know, a rather inactive material. It's on the way to something else. But we, during that we teamed up with Abe Goldberg, who went to Glasgow later. And that was, it was an interesting episode; even if it was negative it was interesting doing it and exploring its properties and so on. And then, and then one was teaching. And I think I was getting involved ... well, the decompression work was going on and so on. But then, while I, I think I, again physiology was a possible option. But a chap called Cyril Keele, who was professor of pharmacology at [The] Middlesex, was also helping the surgeons ... in developing their postgraduate work. It was about the only serious graduate, postgraduate teaching in medicine going on, I think, was the, the surgeons' courses for FRCS [Fellowship of the Royal College of Surgeons], the primary, you see, and the anaesthetists were getting something of the same sort. And he said they wanted, they'd got the money from a motor engineering man called Vandervell to set up a lab for five years, and would I care to try and come to get this lab going at the College of Surgeons. And I had seen enough of clinicians by then over hexamethonium and decamethonium to feel they really did need ... you, a doctor

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<sup>22</sup> Heinz Otto Schild.

<sup>23</sup> Claude Rimington.

needed to be educated after he qualifies. He shouldn't be restricted just to that period. Sometime later he should be introduced right back to the ... to the early fundamentals, not just the latest thing in the *BMJ* or something like that. And I, and Keele was persuasive, and it gave me a nice little lab of my own, offered me that, and so I accepted. The price was I had to start lecturing to the embryo surgeons straightaway, actually. You know, before I went there I was already giving another course of lectures. Although they're interesting, with a medical student, they're mad keen to lay hands of healing, and they don't really want to learn about the basics very much once they've got into medicine a bit. They're all right to begin with but they lose interest in basics, they want to lay hands of healing. But the qualified doctor, he's laid hands of healing and actually he's seen some problems he didn't quite understand, you know, that sort of thing, and he'd rather like to know a bit more about the basics. So I found actually that the lecturing to the embryo surgeon and the, not so embryo, sort of pract-, sort of beginning surgeon, beginning anaesthetist, was really rather good actually. No practical classes, but ... and so on, but really good actually, worthwhile. So, I never regretted that.

MB Just talking about your move to the, to the College of Surgeons. That might not have seemed such a good career move at the time? I suspect that a number of colleagues...

WP No, well...

MB ...thought that was a down step?

WP ...no, absolutely so, absolutely so. I consulted four of them and I think one of them thought it would be rather interesting, all the others advised me against it! But...

MB So, it was quite a, quite a step on you part to make, that decision was quite ... quite a heavy one?

WP Well, I don't remember agonising over it very much.

MB And you went to Queen Elizabeth Square?

WP And that's Queen...

MB Not Queen Elizabeth Square...

WP It's Queen Square.

MB Queen Square.

WP That's Queen Square, opposite the National Hospital. The surgeons and the physicians had a joint, they owned it jointly, for conducting, this examination hall where conjoint exams were held. The top floor had been a ... a cancer, one of the cancer research charities I think had had it as an animal house, and so my later, my office later, was, it was, later I found had been mouse breeding centre or something!

And so on and so forth. Anyhow, I was allowed to turn this into a lab. I was allowed, I was allowed to gather together one, two, three, a staff of three, which I required, I insisted one should be chemically trained and the other two come what may. And ... well, that was, and that was, that was another very happy period really, I think. I also became secretary of the Physiological Society, around that time. Physiological Society.

MB This was about '54/'55?

WP Which was '54, right now. Yes

MB Right, yes. And you attracted, but going back to attracting people to the team? That was rather an important team?

WP Well it, in a way, I don't know, I was so green behind the ears I don't think I ever felt us, we were a time, we were a team or anything. I just thought well now, I, we need some, we need some people, and the jobs were advertised, and I couldn't find, and I couldn't find quite what I thought would go. John Thompson was with me. He'd been with me at the College of Surgeons. And he was a very solid character with some neurophysiological skills. The chemist turned out to be a man called John Gardiner who'd been down at Porton, and elsewhere. He was really a biochemist, but he'd worked on acetylcholine and choline uptake and transport, which was good. He'd been with Whittaker<sup>24</sup> at Cincinnati. And then he went on later to ... to be professor of pharmacology at Hong Kong, and then, at Singapore and then at Hong Kong, the other way round. And now he's retired and lives in Australia. He married an Australian wife, who was a technician at Hammersmith. So that was... And then the, the other member was John Vane, who had trained with Burn<sup>25</sup>. He'd been out with Welch<sup>26</sup> over in Yale, and was looking for a job and he saw this. And he ... I forget how it started, whether I asked him or he wrote in and said what about it. Anyhow, that, he came. And that was the little group. And then later... We were awfully lucky, I think. We recruited two Medical Research Council clinical research scholars. One was a man called Marley, Ted Marley, who was an awfully nice psychiatrist. He wanted to do some basic stuff. So he came and we worked together on ... adrenaline, the fate of adrenaline and things like that. And that was quite significant work as it turned out. And the other man was a man called Greig Murray<sup>27</sup>, a surgeon, who went off to be professor of surgery at King's, and he'd worked with John Young on counting nerve fibres, he wanted some general things, and I forget, and he... So John Vane ... I think we all worked with each other more or less. And Murray worked with Thompson on something to do with the superior cervical ganglion-nictitating membrane. Marley worked with Vane on some HT and amine uptakes and so on and so forth. It was, and then there was George Clark<sup>28</sup> who was later professor of surgery at ... at UCH. He was one of those... And another person in ... in the group was a man called Jimmy Payne who was just an anaesthetist at Hammersmith, who was one, and he wanted to get some basic knowledge and so he

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<sup>24</sup> Sir William is probably referring to VP Whittaker here.

<sup>25</sup> Harold Burn.

<sup>26</sup> Arnold Welch.

<sup>27</sup> James Greig Murray.

<sup>28</sup> Sir William might be referring to Charles Grant Clark here.

came along once a week to do work on neuromuscle block with me. And they all, and it was a, it was, it had an open lab and I had an office and John Vane had a mini office, and they all had mini offices, but the, fundamentally it was rather an open lab and ... and so on. And it was a very good time actually.

MB Produced a lot of results?

WP It started John Vane in the sort of lines he was, he was going. It, John Thompson didn't get so... The one I was sorry about in a way is John Gardiner. Somehow we couldn't meet him properly. I still feel that John Gardiner had a capacity for research which somehow didn't get its outlet. We ... we didn't know how to exploit him. We were a very small group. And I don't think he, you know, that with the chemical skill he made some things... We couldn't, I feel that was, he was the one who I think a little bit lost out. But John Vane really went famously, he had various colleagues and so on, and that went very well. And that sort of grouping fitted him, I think. Not very well off. Quite high spirits and cheerful. Not bogged down with teaching, there was very, not much admin. And John Thompson I think had a, he was, he went ahead in his, rather a different way, solid way.

MB Did that, did that unit go on and is it, is it still in existence?

WP Well at the end of the five years... Well, that coincided just about with the, that's right, exactly more or less, with the Oxford chair becoming vacant. And so the, in a way, everybody had come to assume I'd go back to Oxford. It was, it was taken too much for granted really, I think, in retrospect. Anyhow, that's what did happen. I did ... come. And then the ... the money had then run out, but I can't remember how the later finance, I think the university was satisfied that this deserved support, and the College's own funds together with some university money got it recognised. To begin with, you see, it wasn't even recognised by the university. It became a recognised place. And then John Vane stayed there. Gustav Born, who was a great friend of his, came from Cambridge. And then John got ... got more, you know, got more and more of his own thing. They had more, they got, they moved into the College of Surgeons, had more room, more money and everything. And then after Gustav Born went, I forget where, I forget his movements, whether he went to Cambridge from there or to King's from there, then, you know, a chap called Graham Lewis took it over. I believe now its future is more problematic. The surgeons are always a sort of place in a bit of a state of flux, and there's so much better provision for graduate teaching now that I think it maybe the original... But I simply don't know what's happening now.

MB Right. I was going to just ask you, in the years, five years you spent there, did you, well perhaps you'd like to go back over and ... crystallise out for me the things that you felt were achieved in terms of research. You've talked about the excitement of the teaching for you. What do you think were the great ... great rewards of the, of the research of that period? From a research achievement point of view.

WP Well, I think the thing I remember most vividly is a thing called 'the stimulated gut', which I think did matter. It's a, it's childish in a way, but I think it mattered. It was, I was asked to ... I was asked to lecture in the, in the States, or go,

attend a, give to, contribute to a symposium on the pharmacology of the small intestine. And I didn't know much about it. I think this was because ganglion block was being used then, I knew about ganglia, so let's get involved in it. And I thought well really one ought to know more about how the intestine is ... I'd worked on striated muscle, and of course you take a muscle, there's a nerve runs into it there, and you can stimulate that, you can stimulate that and analyse it. But with the (?) intestine the nerve network is in the wall of the intestine. And a chap called Ambache<sup>29</sup> had shown that you, if you put electrodes on the intestine it, alright it'll twitch, it just moves away and your point of stimulation has changed ... it's completely out of control. And the idea occurred to me well if you, if the damned thing is going to move all the time, and all the, the whole nerves going, suppose you put a, an electrode up the middle of the whole thing and pass a current from inside to outside, then even if it does move the electric field will be the same. And I still remember trying it one night. It was, I'd probably been doing some histamine assays or something on, I don't know, some ganglionic work or drug receptor stuff. But I tried it one, late one night, and got the one bit of platinum in the lab, and an alligator clip, to dip into the bath(?), and I put this strip of aluminium up through the intestine, and I got my stimulator and passed a shock between these two things, I was sat in the (?). And bang, lovely twitch. Just ping, ping, like that. And so ... beautiful, just like a nerve muscle preparation.

MB A great moment.

WP And it was splendid. Then, so then you were saying 'Well, well if...' People in fact then weren't confident as to what the transmitter was. Feldberg had actually suggested it wasn't acetylcholine because there were some odd (?) results he got, and so on. So there was a genuine uncertainty. And of course we know now there are many, but there was, even that acetylcholine was the dominant one was uncertain. But pop in some atropine(?), bingo, gone, off in, you know... It's a, collect acetylcholine out of it, you know, it was a lovely thing. And of course it showed that you can, it showed a way in which you can take a thing where the nerve network is in this structure, in the tissue, and put in an electric field, and you can get nerve-evoked responses. So it'd become, it, I'm, I think people were delighted, I showed it at society meetings and so on, and you know people were just delighted because here was a hitherto very refractory bit of smooth muscle, the small intestine, which normally just goes like this, you know, twitch, twitch, you could make a quantitative assay out of it and so on. And, so that was a, I went on with that when I came to Oxford...

MB That led to important work, yes.

WP ...so that led to a lot, lots of miscellaneous things. So, I was also in a way partly linked with that, partly with the histamine work, anaphylaxis, problems with anaphylaxis. I did get interested in drug receptor interactions. I did, I'd always wondered why hexamethonium is a blocking agent, competitive blocking agent, while decamethonium when it comes to work on your muscle is if anything a stimulant. Agonist, antagonist. Now, what on earth is going on? How, why on earth is

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<sup>29</sup> Nachman Ambache.

something a stimulant and why not? And thinking about this and doing experiments of various sorts, I cooked up a theory of drug action, called the rate theory of drug action, which essentially says that you don't get a stimulant effect unless the drug is such that it can turn over at the receptor. The turn over time is essential for stimulant action. And I tied this in with the rate constant of dissociation rates and so on, which proved not to hold water in the end, but at the time it ... it was a, it was a very, a remarkably economical, effective theory. You looked through all the drugs and you see if they, if they sort of stuck to their place. They might do something at first, but then they occluded the receptor.

MB So they blocked further stimulation.

WP Only a thing which go on and... They could do a trace, there might be a trace of, but they, they might do an initial trace of action in the first unit, but I, then I think it's fairly doubtful. But they ... they block any agonist. While the things, all the things that could stimulate were always small molecules, lively little things, which go on and off like that. And that sort of took quite a lot of time, trying to shape that and so on, and argue about that.

MB That was exciting pioneering.

WP So it was...

MB Nowadays these things are taken for granted, but that was, that was very good indeed.

WP Well, receptors ... receptors were just beginning to be serious. A man, a man called Ariëns<sup>30</sup> in Holland had begun to talk about why a thing is efficacious, why it's effective, and he just gave it a name and how to estimate it. And Stephenson<sup>31</sup> in Edinburgh had also wondered why is a thing an agonist. He decided it was because it had a property called efficacy, and he showed how to handle this idea. But none of them had a model of why it was efficacious, why it is that fatty things are antagonists and some are not. And so my suggestion was that turnover, it still is actually, is the, is the key. And although the high priests of the receptor church I may say now dub this a heresy, the rate theory, I still think there's something right about it. Turnover, it's rather like enzymology in that, you know, if you, interaction of an enzyme, it's, the things which are split are those which go on, something happens and they leave, there's a great interest in leaving them, while the antagonists are things which are firmly bound.

MB There's a nice elegance about the model that ... that recommends it. There's a nice elegance about it.

WP Well it ... the, a thing that does relieve my conscience... I mean I think if one's wrong, it's a, it's a bad thing. I don't think one should be wrong. I don't know if I am wrong or not. But the thing I do like about it, if you teach it to students, it

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<sup>30</sup> Everhardus Jacobus Ariëns.

<sup>31</sup> RP Stephenson.

doesn't mislead them. Because the drugs are, they will find in fact that the, it's the smaller drugs which tend to be agonists and the large, big things with lots of things stuck on them are the antagonists. The higher the affinity is, the more it sticks, the slower its action will be, and things like that, you know. They're, all these things are true.

MB ... Sir William, we're getting to the point at which we can view your move to Oxford and perhaps that will be part largely of a, of a further interview. Perhaps we can just talk about how that move came about, and that will bring us to the end of today's ... today's...

WP Well, I...

MB ...talk.

WP I don't altogether ... know. I think that it, I, the lab had gone well, and if, and Burn was retiring, so if you look around for who could follow him, I was an obvious possible. That I'd been an Oxford man, and obviously I used to examine at Oxford sometimes and so on, I think made people feel that it was a rather foregone conclusion. So, I think I also had been very happy at Oxford, and I thought it would be rather fun being at a place I'd, that people I knew I liked and so on. And ... so, it, I don't remember it's being very much problematic. I think there may have been more things than I knew in the background, from what I... For instance, I know the electors didn't agree at their first meeting who, that I should be approached. And I ... but there were other things (?) there which...

MB Did you apply or were you invited?

WP I wondered should I apply, or not? Well, I didn't even wonder that, I thought it was, if you want to go for a role you should apply. And I think I, as a matter of fact I don't think it ever crossed my mind that I wouldn't apply if I wanted to go. Now, that's correct. It would never cross my, if you express, I was not wanting to be a sort of tease and to be asked and therefore increase my hand. It was an idea which was strange to me then, I understand it better now. Krebs<sup>32</sup> later told me I should not have applied. But no, I was very innocent. I'd never held a grant at that time. All I'd done was try to make good labs with what, the authorities around me were sort of saying 'Well, here's a room and here's some money and off you go' and so on. And so that's what I'd been doing. So, I was very innocent.

MB So you put in an application?

WP So I put in an application.

MB And the first, and the first look at it, it didn't go?

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<sup>32</sup> Sir Hans Adolf Krebs. Whitley professor of biochemistry at Oxford 1954-67. Awarded the Nobel Prize in Physiology or Medicine with Fritz Lipmann in 1953.

WP I think I was the only applicant. I'm not sure about this, I believe I was. And, you know, if I'd been on the board of electors I'd have thought well, that's a bit odd. Surely there must be somebody else to think about. And of course if you've been on [the] electors, you get papers, you get sort of a great dossier of, I don't know, fifteen, twenty, ten, whatever it is, people, and the thing is to be confronted with no choice, well, must have been odd. So I, I don't ... and so I think they then said 'Well what about so and so, what about so and so?' I remember Brian(?)<sup>33</sup> ringing me up saying – he said he'd ring me up after the, he was one of the electors – saying 'I'm sorry, Bill, we're going to have another meeting, so don't, but don't worry too much!'

MB But, it all went right in the end?

WP Anyhow, so it... But in the end, that's right, they did settle on, on me and ... and...

MB And you came to Oxford?

WP And so one came here with the ... with a, with a... Again I was, it was very un-Krebs like, I wanted to bring nobody with me, I wanted to, you know, to set up a place with, and help people along, like that, so that... I can hardly believe my naivety now, actually. It's a different world in some ways. But anyhow, I had, there was an assignment, I had an assignment straightaway. And that is that Burn ... the lab was, before, was rather a small one, it was only enough, it could only hold a practical class of about twenty or thirty at a time, so they ran it to ... in series. And the intake was only about fifty or something like that. And it was run as a sort of extra course on top of the, after finals before you, before you went on to clinical school, you know it's, they went on slightly late to clinical school. Two months; a two terms course I suppose it was, I think that's right, it's a long time ago now. And so it was, the lab had been a small personal research laboratory for Burn and Blaschko<sup>34</sup> and Ing and Bülbring<sup>35</sup>, that's really what it was. But Burn had asked for a wider lab, particularly for a classroom, and so the first thing... And the university had agreed this. He'd asked for it about ten years before and at last it was coming. And my job, first task was to implement this, so that ... I settled down, started to settle down and looked for plans and things like that. I never discovered some of the details Burn ... I was passed on two files, one was about the University of Glasgow, and the other was about promoting Blaschko to a readership. These were the two files I was passed. I didn't... There were some plans but they were found on top of a cupboard after it...! But I got plans from the architect and so on.

MB Sir William, this is the point...

WP I went through this all, went through all this again with my things, and ... and so, and then, and then, so there's a hyphen in my research and things where I get this going, and get this extension built and begin to settle into Oxford.

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<sup>33</sup> Sir William might be referring to Dr Eric Brian Smith here.

<sup>34</sup> Hermann Karl Felix Blaschko.

<sup>35</sup> Edith Bülbring.

MB Marvellous. This is a point where we can ... close, for today, our conversation, and move to look at the whole Oxford story as it unfolded when we talk next time.

WP Yes, I think so. It's a good hyphen really, semicolon!

MB Great. Thank you for talking to me today.