The Royal College of Physicians and Oxford Brookes University
Medical Sciences Video Archive MSVA 107

Sir Stanley Peart FRS in interview with Dr Max Blythe
Oxford, 16 June 1994, Interview Two

MB Sir Stanley, towards the end of your time at St Mary's, working with Fleming, you were making plans to go to work in Edinburgh on a new project. But before we do, can we just tie the Fleming story up and, can I ask, there's been a lot said about Fleming and his contribution, whether he really was a Nobel Prize-winner, and just how much he contributed to the penicillin story. Can I ask your view on that? How significant a figure he was?

SP Oh, I think, yes. I would recommend that anybody that doubts it should read Macfarlane's book on Fleming,[1] because he started off, I'm quite sure, being an Oxford man, somewhat prejudiced in favour of the Oxford team, but he ended up by giving the appropriate division of the laurels to Fleming and to [Ernst] Chain and to [Howard] Florey.

MB So he came out on a balanced scorecard.

SP He really did. And it's very obvious, you see, that Fleming made the original observation, and, you know, without the original observation, Chain, whose job it was to comb the literature for Florey at that time – Chain being the chemist that Florey had taken on, thanks again to Dale,[2] whose name comes up in every direction you can think of. But he was combing the literature, and he came across this reference to the effects of penicillin. Now, it's very obvious that as you look at Fleming's career, as a very practically minded bacteriologist, the story really starts with lysozyme. And this is a beautiful story, because Fleming was curious about what it was in tears, or nasal secretions, when you had a cold, as to what might inhibit bacterial growth. And he was very interested in the influenza virus at that time, too. More of that later.

MB This is the 1920s?

SP Yes, that's right. And so that when he grew this organism, which was [*Micrococcus?*] *lysodeikticus* – unfortunately, it was the only bacillus which seems to be killed by lysozyme – he observed that when he let a tear, or nasal secretion when he had a cold, fall on the plate, covered with a growth of bacteria, that he got a clear ring around the drop. And he said, 'Well, that's interesting, it's knocking off these bacteria, so that might be important.' He tried to put it into wider use, but, unfortunately, it seemed to only kill one particular type of bacillus. But now it's very difficult to resist the idea that when he was subsequently, in 1928, looking at the plate of *Staphylococcus*, covering the plate, bar the places where the fungus, the *Penicillium* fungus, *notatum*, was growing, and the clear ring around the fungus

[1] Macfarlane, G., 1984. *Alexander Fleming, the man and the myth.* London: Chatto and Windus, Hogarth Press.
[2] Sir Henry Hallett Dale (1875-1968) British physiologist.

showing that the bacteria were being destroyed, that the two things didn't immediately ring a bell, and…

MB A reawakening…

SP It had to be. And that's, that was really how it was.

MB There was a big argument, then, that for ten years this didn't really go anywhere. He didn't try to extract anything, and…

SP He did, he did try. But his efforts were, unfortunately, not successful. He actually gave the task of trying to purify it to… who was perhaps the best fungal chemist in Britain at the time, actually, but whose name now escapes me at the moment. He died not too long ago, actually. And he laboured at it for a long time. And Chain's great contribution was that he looked at it, he looked at what had been done, and he tried one simple experiment to extract penicillin from the mould culture. He just changed the pH of extraction. Previously, penicillin, which is an acid, had been destroyed by an alkaline condition. All you need do is keep it acidic, and penicillin was stable. And that was a major contribution and it was at the back of all subsequent efforts to purify penicillin. And, of course, what Florey and Chain did was to extract it and to show, without any doubt whatsoever, that you could kill off bacteria which would otherwise – pneumococcal bacteria, for example – which would otherwise kill off a group of mice. And that was their great contribution, so that…

MB You've got a wide spectrum of bacterial action.

SP Absolutely. So that you've got that whole… without the initial seminal discovery, the rest wouldn't have followed, because Chain picked it out of the literature as being an interesting substance, or action, to follow up.

MB How did it come about, this controversy though, about Oxford versus St Mary's?

SP Well, the bad blood came because Almroth Wright[3] wrote a letter to *The Times*, laying claim to the fame for Fleming, you know, because it was Florey and Chain… Florey and Chain had gone off to the United States to interest some pharmaceutical companies there, because they couldn't – remembering it was the beginning of the war – they couldn't get the interest of British pharmaceutical companies at that time, to take it up seriously. They had other things on their mind, like the war, you know, and other drugs that they had to produce, so they weren't prepared to do it, whereas the American firms were, and did. And so you got the very large-scale cultivation of the mould and the production of crude penicillin, which was, of course, very effective during the war, during the later stages of the war, and of course, used on Churchill, too, when he had pneumonia. So Almroth Wright laid too much claim to Fleming. He sort of pushed the Oxford contribution almost out. Well, you can't do that. It must be a balanced contribution. So I think it's a non-conflict, myself, but it was engendered…

MB But it was…

[3] Sir Almroth Edward Wright (1861-1947).

SP Yes. And [Lord] Moran, who then was Sir Charles Wilson, actually added to it, you know, by making more claim. I suppose he felt that Fleming, perhaps, was being pushed too much into the background. But, as it happens, Fleming, who became a world traveller after this, he was the famous figure. Now, it's very interesting. Maybe it's a personality difference between Florey, who was, again, not a flamboyant figure, you know… in many ways his sort of persona was somewhat like Fleming's. Chain was very different. Chain was ebullient and so on, and, of course…

MB Mid-European energies!

SP Absolutely, yes! And he was in no doubt, in my opinion, as to who had discovered penicillin. But, you know, that was… that was it. Because I got to know Chain later and he was a tremendous chap. Could have been a professional pianist, you know, he was good, actually. Excellent, actually. So that… and, of course, I see his son now, who is also a scientist, which is… which is interesting.

MB So, getting towards the end of your days at St Mary's, with the Fleming registrarship in… looking after penicillin affairs, as it were. Getting to that point, did you feel that controversy going on around you in those years? Was that something you directly felt?

SP It didn't emerge so strongly at that time, you know. It started to emerge later. It became… it gradually, like a lot of vendettas, almost… and because people took sides, you know, and claimed the total picture for themselves, you see. So the Oxford group resented what had happened at St Mary's, and so they said, 'We'll push them on one side,' so that when they went to receive the Nobel Prize between them, they didn't really speak to one another. Not that Fleming did talk a lot, actually, you know, but I mean, he just went his quiet way and was quite happy, because he was the chap receiving more of the plaudits than anybody else. And, of course, he had some interesting traits. He liked having his photograph taken, you know, tremendously actually, so there are a lot of photographs of Fleming about. Of course, there are a lot of Fleming Streets around the world, in most of the major capital cities, you know, and wherever he went, he was feted.

MB He enjoyed that publicity?

SP Oh, he did! He enjoyed it.

MB He even thrived on it?

SP Not surprising, perhaps, in view of his background, and in view of the fact he'd lived through his life with Almroth Wright in the background, you know, who was, as I say, a very domineering and dominating figure, in actual fact. But I think you've got to look at that aspect.

MB You actually were working with him as well?

SP Oh, I did, yes. Yes. Well…

MB Worked with…

SP Yes, well, you know, I mean, I did six months, really, and it was very interesting, you know, and he sort of asked me whether I was interested in a career in bacteriology, and I said, 'Not really.' But I was full of admiration for his observational powers, actually.

MB And his nitty-gritty kind of tabletop (inaudible).

SP Well, he did… he could do things with his hands, and he showed me how to draw up the bacteriologist's pipettes, you know, so that they were calibrated, how to calibrate them, weighing them with mercury drawn up into the stems. He showed me how to do accurate counts of the number of organisms in blood that you took off – you see, we had a lot of patients with septicaemia. He drew the blood off. You could say, 'Well, this person has 100 million organisms per cubic millilitre of blood,' actually. You could dilute it out and culture it, and just count them [bacterial colonies].

MB It's incredible assaying…

SP Yes.

MB …which we don't think about these days. It's more automated.

SP No, not at all. But, you know, all that sort of thing appealed to me, you know, I liked that aspect of bacteriology.

MB So that was an important formative part of the job.

SP Absolutely.

MB You're going to go to Edinburgh next, and I'm coming to the reasons for that. And I think [George] Pickering[4] was part of the story?

SP Well, Pickering, I'd always kept in touch with him, because, of course, I did his house job as part of a joint job that I did between paediatrics and the medical unit then, you see. And you remember, I'd had contact with Pickering before, when I was a student, you see, and I was very anxious to do his job, you know, because I'd got a great admiration for him. And I was lucky enough to do it. And at the end of my house jobs, he suggested to me, you know, was I interested… well, he asked me, was I interested in doing research? Now, of course, I'd become very interested in doing research. It didn't matter what the research was, but I wanted it to be, somehow, linked very closely to clinical medicine. And he said, 'Well, what will do a lot of good is if you go and work with a real scientist, like [John] Gaddum,[5] and I'll see if I can get you an MRC [Medical Research Council] studentship to go and do that'. And, you know, he did that.

MB And you got your two or three hundred a year?

[4] Sir George White Pickering (1904-1980).
[5] Sir John Henry Gaddum (1900-1965).

SP So I got… yes, I got my three hundred a year.

MB It was three hundred a year?

SP Yes, it was three hundred a year and which, I suppose, is not bad, actually.

MB And you went that far north for the first time?

SP Oh, absolutely. You must remember, I was born in South Shields, but, you know, across the border was quite unknown to me! Though, of course, a lot of my ancestors were Scottish, of course, you know, and my grandfathers were, actually, you see. So that though I had obvious roots there, they weren't obvious to me! So that…

MB Had you met Gaddum before you went there?

SP Never. Never.

MB Did you go and see him? Did you have an interview, or you just went?

SP No. No. I just went.

MB It was all happening.

SP That was it. Yeah, I mean, they… Pickering knew Gaddum, of course, very well, I mean, they'd met through the MRC or something like that, you know. I never enquired about that, you know, it was all new to me. And so I went. And there I went to live in Leith, and I remember the hoar coming up from the river and it rolled over Leith, and I used to cycle up to the University, the new building.

MB The mist coming. It really is wonderful, isn't it?

SP Oh yes, yes, except when you have to cycle through it, actually, you know!

MB So you were cycling, in those days…

SP Yes.

MB …from Leith into Edinburgh.

SP Into Edinburgh, yes.

MB Into the new building.

SP Into the so-called new building, yes, that's right. It was quite old, the new building, actually, you know! But it's got a long history to it. And they were, the laboratories were, you know, those typical high old laboratories. And, of course…

MB And cold?

SP Oh boy! They were cold, yes! They didn't have any heating, of course. You must remember, you know, it was 1946, you see, and heating was not something that was encouraged, particularly in Scotland. You know, they were short of fuel. People were very short… they were short of food, you remember, it's still rationing. You know, they still had food kitchens where, you know, for a shilling, you could get a meal. And I would occasionally go there and have a meal, you know, and that was, that was it.

MB I remember, in an earlier conversation, you were saying something about wearing a coat in the lab to keep warm, basically.

SP Oh well, the laboratories were very very cold, because, you know, my first encounter with those great high laboratories, and they were sort of rather dark, and dark teak benches, you know. And we used to teach the students there, of course, the elements of practical pharmacology, which I enjoyed doing, in actual fact.

MB So you were in some corner of a teaching lab?

SP I was, yes. Yes, that's right. I took part in all the activities of the lab, you see, as well as doing my research, you see. So that's when I really had to learn the basic pharmacology. And, of course, to me, at that time, you see, pharmacology was… as it was to most medical students, was not something they took very very seriously, because, you know, when you think about it, at that time, the number of drugs available to treat anybody with, were not many, actually, you see. So it didn't loom large in the medical curriculum, you know.

MB So you remember the days of exciting receptors and…

SP Oh well, nothing like that, you see, because you've got to remember, I was taught how to make pills in the pharmacy course, you know. We actually used to take powdered *Digitalis* leaf, put it into a die and stamp the pills out, you know! And that was what we were… that was what we were taught! And in one corner of the pharmacy, there were long beakers with leeches in them. I mean, you know, I know it makes me sound archaic, but I mean that was the truth of the matter, you see. And they were used, those leeches, it wasn't that they weren't used. They weren't there for show.

MB And that was in the original training period?

SP Yes, that's right.

MB Was this still very much the picture when you got to Scotland? It wasn't all that different?

SP Oh well, there was a big difference in the… pharmacology was real pharmacology, you see. When you met Gaddum and Marthe Vogt,[6] you see, as the leaders of the Pharmacology Department there, that was very different.

[6] Dr Marthe Louise Vogt (1903-) Lecturer, later reader in pharmacology, University of Edinburgh, 1947-60.

MB These were giant figures as well.

SP Oh, they really were. I mean, you know, they were, for me, of course, frightening, in the sense that they knew all about pharmacology and I knew nothing.

MB Tell me about Gaddum.

SP Well, Gaddum, a shy, gangling figure… glasses… and he sort of… his arms and legs seemed slightly disconnected. He used to be leaning up against a… you know, a wall, and he sort of moved around in a very sort of peculiar, gangly way, actually. And he was very shy, basically, that's what people, perhaps, didn't understand about him.

MB So gangling, and awkward in conversation?

SP Yeah, awkward in conversation. He would sort of listen, and then he would come out, you know… slightly, you know, explosively, on occasions, you see. It was difficult. But, you know, there it was, and you could see him, because he had a large domed forehead, actually, and there was a lot of brain behind it too, actually, which was working. And he was very critically… he never let you get away with a loose statement, no more did Marthe Vogt, you see. They always were asking you, 'Justify that statement,' you know, and they taught me, you know, how to think clearly.

MB From the start, was able to take you aside, and talk to you about issues?

SP Yeah, well, he asked me what, what I wanted to do, and suggested was I interested in this topic, you see, and, you know, which was really about sympathins. And, of course, then when I read up about it, of course, I was fascinated. What I wanted to do from an early time was to make my own little mark. I wanted desperately to do something, you know, which was unique and really made an advance, you know. That was my ambition. There was no doubt about that, from an early time.

MB And Gaddum introduced you to…

SP And he gave… what he gave me, yes, what he gave me, of course, was a very important question. And that's been with me throughout the rest of my life when I advise people. Give people, when they're young, important questions. If you can be sure that they're really important, that's the thing to give them. Don't let them work away at something which is sort of interesting, but, you know, not attacking the main theme, because far better to be working away at a very difficult problem, and you either crack it or you don't, of course. But, whatever, you get more satisfaction out of it in the long run. And that was the problem I was confronted by, because sympathin, which had been around, basically, since the start of the century, in terms of the chemical transmission of sympathetic nerve impulses, versus electrical, of course, was… it was still unknown. I mean…

MB A confused story at that stage.

SP It was very confused. I mean, when I entered it, it was that… the field was, perhaps, dominated by the views of [Walter B] Cannon and [Arturo] Rosenblueth: Cannon, W B Cannon, who invented the term 'homeostasis', for which he's perhaps best known. But the idea was, then, that adrenaline, from the work of [T R] Elliott in 1902 and 1904, where Elliott had first suggested that, perhaps – and he never carried it further – perhaps the activity of the sympathetic nervous system is exerted through the release of adrenaline, at or close to the nerve endings.

MB So that was really exciting, then.

SP It was. But it lay fallow, because nobody quite accepted, until [Otto] Loewi took it on and showed that, in those two hearts which he had in tandem, that acceleransstoff, which caused the heart, the next second heart, to beat faster when you stimulated the nerves to the first heart – acceleransstoff. And vagustoff, which slowed the heart, you see. [And] that the acceleranststoff, which we now know is noradrenaline, actually, so that it… among a few other things, perhaps, liberated as well, but principally noradrenaline. And it wasn't known until the 1920s, you see, and that was when [Henry] Dale really seized on it, and really believed fully and finally in the chemical transmission of the nervous system. And [John] Eccles[7], an Australian working in Britain, believed just as passionately that it was electrical, and that the chemical things were just a passing phenomenon. And that, of course, led on to the controversy with Feldberg[8] about acetylcholine.

MB It went on for quite a long time?

SP It just extended. And this was the background in which I was precipitated, you see.

MB Was that a time when there was a thought that adrenaline might go two ways, to a kind of sympathin A, sympathin…

SP Well, this was, this was Cannon and Rosenblueth, and that was sympathin E, excitatory, sympathin I, inhibitory. The idea that they put out was that adrenaline combined with a substance and became sympathin E, and [with] another substance and became sympathin I, and appeared in the circulation. You remember, a lot of…

MB Having different effects according to different effective needs.

SP Yeah. A long time ago, Dale had shown that ergot would reverse the action of adrenaline on the blood pressure. If you gave ergot, instead of a pressor effect, you got a purely depressor effect. Now, he never completely explained that at the time, but remember that was about 1910, actually.

MB You've mentioned him several times. This was a giant of a man.

SP Oh yes. He bestrode the whole area of pharmacology, and all his pupils; you've got to talk of the whole Dale school, including all those that came from Germany in the 1930s, because of Hitler… Hitler's…

[7] Sir John Carew Eccles (1903-1997) Australian physiologist.
[8] Wilhelm Siegmund Feldberg (1900-1993).

MB There was an enormous ability of helping the, helping the Germans into really important…

SP Because he'd always taken an interest in German pharmacology and so he knew what was going on there. He knew that Feldberg had an assay which would be very useful in determining what was released at the neuromuscular junction. And, of course, he invited him over when he knew that he was in desperate straits, because Feldberg was sacked at a moment, literally, a moment's notice, in the middle of an experiment. His professor said, 'You're out,' basically. And so he had to leave, and he left. And it was difficult for him to obtain a passage and admission to Britain, at that time, but Dale had made the arrangements that he would be admitted. And so… so many of those people, Marthe Vogt, the people that came to work with Dale, and then moved on to other places, in some cases. British pharmacology owes a tremendous amount, both to Hitler and to Dale! So that this was very…

MB Things were never going to be the same again.

SP That whole [Dale] school was very very important. And Gaddum, of course, having worked with Dale, with Feldberg, with Marthe Vogt, you see…

MB Was Gaddum also a product of this?

SP No. No, he wasn't. No, he wasn't. He came earlier. He was different. His parents were of German origin, but he'd been in this country a long time before.

MB Was he brought up in the North?

SP No, no, he wasn't. No, he was unusual, you see. I mean, that department was unusual, because the Scottish departments didn't sort of, perhaps, welcome, you know, the Sassenachs, or anybody else at that time. But, I mean, not only was there Gaddum and Marthe Vogt, but there was Dekanski(?), who was a Pole, in there, you see. There were two sort of what you might call 'card carrying Scots', actually! Crawford was one and Henry Adam was the other! Henry Adam, bless him, is still alive, and Henry Adam was working on histamine at the time I was there.

MB But not…

SP No, but he's still, he's still around. He's very full of beans.

MB Who else was there? Let's just run through them.

SP Well, Miles Weatherall was a lecturer in pharmacology, and Miles Weatherall subsequently became the director of research for the Wellcome Foundation, you know, and… and he, again, was one of those people that seemed to me, to know so much more about pharmacology than I'd ever dreamed of! I was terrified, initially, of what was going on, but I learned subsequently to stand up for myself. But that was a tremendous experience for me, because, you know, to be shown how to operate, by somebody with the skills of Marthe Vogt.

MB Have we said enough about Marthe Vogt and her background?

SP Oh, Marthe Vogt, again, was a refugee from Germany, you see, and she…

MB And done so much…

SP Oh yes. But she was a tremendous person, actually. A really… a tremendous experimenter. She could operate beautifully. I mean, she would have made an absolutely wonderful surgeon on man, actually, but she was very beautiful in surgery, but she was also so simple and clear thinking in her approach to problems. I mean, you know, she stuck to it and achieved. And she was very good chemically, too, you see. She had good ideas about things. For example, she was the first person to demonstrate noradrenaline in the brain, which, when you think about it, was a rather important discovery, actually, you see. And she was one of the earliest in endocrinology, pharmacological endocrinology. So she got a number of firsts, and she was very very helpful to me.

MB She befriended you quite early on.

SP Yes. She showed me, she showed me how to do things, you see, and…

MB She was easy to talk to? Nice to talk to?

SP Yes. Oh, very. Very very easy to talk to. Slightly frightening, because she was, you know, she was always putting this direct question to you, and, you know, you never quite knew whether you were pleasing her with your responses or not. You know, when you knew so little, it was not too easy, because she knew such a lot! But, experimentally, what good fortune I had to be taught by those people. And, of course, equally, talking of experiments, there was [J R] Learmonth,[9] who was the professor of surgery, next door. And he saw me struggling with an attempt to do a cervical ganglionectomy on a cat, you see, and he said, 'Well, you know, you're not in quite the right place,' leaning over me. 'I'll show you how to do this.' And so he showed me how to do this cervical ganglionectomy, because, of course, he spent a lot of his time removing bits of the sympathetic nervous system in man, to achieve, you know, good results.

MB Learmonth sat on two chairs at that time, didn't he?

SP Well, he had the… he was the professor of clinical surgery as well as the professor of experimental surgery, you know. Not everybody was too happy about the fact that he was occupying two chairs, but he again was a man of real substance and personality, and I was again, you know, I was lucky to have him show me these things. But that was it, you know, people just showed you them. And so the whole atmosphere of that department was… was one of the turning points in my life, anyway in terms of experimental work. And, you know, struggling as I was, with the task that Gaddum had given me, knowing very little, of course, I had to find out… well, all right, if we do get substances liberated in the blood, how can I assay them? How can I differentiate between adrenaline and anything else? So I was looking, you see, for methods of distinguishing on bioassay – you must remember it was bioassay at that

[9] Sir James Rognvald Learmonth (1895-1967).

time, because Gaddum's contribution, of course, was the pharmacological assay of substances. He was very very hot in that area.

MB And this was a very hot area in pharmacology at that time?

SP He was very interested in parallel assays on different substances with different responses. You know, you could distinguish between adrenaline and histamine by their different actions on smooth muscle. And, of course, what he said, you know, 'Maybe you'll be able to distinguish between adrenaline and noradrenaline,' because noradrenaline was in the news at that time, 'by an appropriate parallel assay.' And so I set to to find discriminating smooth muscle. And I came up with the rat colon, which was… you know, don't ask me why! But, I mean, I just thought I would look.

MB That was just a shot in the…?

SP A shot, yeah.

MB And… just framing the question, very very tightly, and say that what he really said to you, was asking you to look, really, at sympathin. But it was really sympathin coming out of the liver. It was hepatic sympathin…

SP Oh yes. Well, that was what he'd worked on before, you see. And others had worked on it. In other words, when you stimulate the sympathetic nerves going into the liver, around the hepatic artery, you stimulated the nerves, and then, with a delay, if you had a distant smooth muscle, like the nictitating membrane of the cat, it would then slowly contract. And that was sympathin. A sympathetic action. That showed you that there was a substance circulating in the blood, which took the circulation time to get there and then cause the contraction. And you sensitised it using cocaine. Cocaine would… it had been known for some time that cocaine would sensitise a nictitating membrane to the actions of adrenaline. So people said, 'Well, this must be adrenaline, mustn't it.' But, you know, because we're still with Elliott, you see, in 1902, you see. And that was it.

MB And this was a really tough first year.

SP Oh, very.

MB Because I know you'll probably be covering it in a nice way, but it was a really hard year. You were having to drain blood from the liver in the way, I think, that Gaddum had suggested, that was going to turn out to be pretty bad news?

SP Oh well, it was bad news, because, of course, now, I wouldn't dream of doing this, because he… he liked what I think is a pretty crude approach. You put a glass tube up the [vena] cava to just below the exit of the hepatic veins, as they went through the… just as they left the liver to go through the diaphragm. And then you had a ligature around that, so you would then divert the blood coming out of the liver in the hepatic veins down through the tube, and you'd collect it. But, of course, the real problem with that was, of course, as soon as you pulled on the top ligature, the blood pressure dropped out of sight! So it was a thoroughly bad preparation. But he

insisted that I kept at that, you see. And I kept saying, 'Well, look, I cannot get these animals to survive and collect the blood properly.'

MB This is cat you were working on?

SP Yes, that's right. I couldn't get it to work properly. And I was pretty desperate, you know, I was really close to feeling, you know, that I was completely incompetent, and that…

MB You did this…

SP And he just said to me, 'Well, look, you're not just… you're not doing very well with this, are you?' And eventually, you see, a year had passed and I had found how to assay substances in blood. I was ahead on that, because, you know, to assay these very small quantities of substances in shed blood, I ran into all sorts of problems with shed blood, and how could I avoid them.

MB And this is a material on the change all the time.

SP Well… well, it was, actually. It had plagued pharmacologists for years, you see, because they knew that shed blood was bad news for smooth muscle, because they couldn't control all the contractions and depressions that occurred when you applied shed blood to smooth muscle, you see.

MB How did you cope with all that?

SP You know, in the [C A L] Evans [E H] Starling era, you see, they were doing the heart lung perfusion, and they said… going back to the literature at that time, you see, I was struck by the fact they said, 'Well, if you can actually perfuse the lung with this blood, you may then be able to continue the experiment. But often, you can't.' Now, then there was the argument, was it because they were filtering out microthrombi out of the blood, because, you know, anti-coagulants at that stage were not… you know, heparin hadn't been invented, you see, so they were often using defibrinated blood, you know. Anti-coagulants were in a very primitive stage when I was a student, you see. Heparin, [J E] Jorpes hadn't got heparin out of mast cells, you know, at that time. So that this was difficult. Well, this was known …

MB What (inaudible).

SP Evans, well, they just perfused it through organs. Now, they found that there'd be a period of intense vasoconstriction in the lungs, and if they could just manage to get past that initial phase, they could then continue the experiment. But all the original descriptions of Starling and co., of the heart lung preparation, are full of that sort of description. And it was… all about… was it embolisation, or was it some other substances that the lung was removing? It was probably microemboli, I suspect, myself. But, nevertheless, that was in my mind, you see, and I thought, 'Well, how can I get round this problem of blood? What is it that's actually happening?' Because I would put blood, the plasma, which I'd separated, and put it on to the smooth muscle, and, of course, the thing would go off the scale, you see. And I couldn't…and I said, 'Well, you know, this is going to be impossible to assay

substances like adrenaline and noradrenaline, in the presence of all this. How can I do it?' And so I worked away at this and examined the blood and the properties of plasma to see what it was that was doing it, and could I pharmacologically antagonise, or did I have to extract the substances I was interested in, out of the blood? I wasn't fully aware of the effects of potassium at that time, for example, you know, and I'm sure a lot of the effects I was observing, the depressional effects on smooth muscle, were due to potassium. But eventually, I came up with the fact that, miraculously, when I was perfusing a rabbit ear to measure the vasoconstrictor effects of what I was producing, that when I gave ergot – it was dihydroergotomine – that this abolished the nasty vasoconstriction in the control blood. So I could get a nice flat background and stimulate the nerves, and I would get, I would be able to assay vasoconstrictor substances appearing in the blood perfusing… perfusing the spleen, as it happened, which I was collecting blood from.

MB (Inaudible) had the stable background for the work?

SP Well, so I… but, of course, what I didn't realise, because I marked… I said to myself, 'Well, that's interesting,' because Gaddum didn't believe me at first, actually. He said, 'It's not possible'. And I said, 'Well, look, you know, here it is. Ergot blocks these actions. I don't know why it does it.' But then, a couple of years later, there was a report by [Irvine Heinly] Page and [Arda] Green of a substance which they'd extracted from shed blood, known as serotonin, which was 5-hydroxytryptamine. And, of course, we know that ergot blocks 5-hydroxytryptamine. So it's almost sure that that's what it was, you see. So I got through all that, which took me rather a long time, lots of setbacks as well, before I…

MB You were well into your first year before that.

SP So I was. Then I remember going to Gaddum. You see, I hadn't solved the problem, of course, and you know, I said, 'Well, look…' He said, 'Well, this is your year, isn't it.' I said, 'Look, I haven't solved this problem. I cannot go and leave it, without…

MB Did he feel that you might pack in at that stage?

SP Oh yes, yes.

MB You did?

SP Oh well, he felt, you know, he'd given me a year, but I hadn't solved the problem, so he thought, 'Well, you know, maybe it wasn't going to be solved.' And I said, 'Look, I can't be happy with this, so can I have another year?' And so he said, 'All right.' And he gave me another year! So he applied to the MRC for another year, so that I got my extra year, during which time, of course, I got married in London. But that was in '47, you see.

MB If we can put that in place, I think, while we're going on there. You had a rather exciting trip down and got married to Peggy.

SP Yes, yes, that's right. Well, it was… oh yes, it was very nice, actually. Well, of course, it was the first train across… it was frozen solid, actually, at that time, you see.

MB It was a bad year for winter, wasn't it?

SP Well, that was the year, I think I've mentioned to you before that the preparations in the laboratory that I left up overnight, even though they were saline, were frozen solid in the morning! It would freeze saline, so that you can guess that it was cold! And I used to work at night, you see, wearing a coat, you know. I mean, an overcoat! I mean that's when I took to smoking Woodbines, you know, for something to do while I assayed things every two minutes. But those were things that came later. But, oh yes, it was an exciting trip down. I was pleased, you know, because Fleming came to the wedding as well.

MB And Wilson?

SP And Wilson, yes, that's right. So it was… it was nice.

MB And was Peggy going to go back with you to Scotland?

SP Yes, she was. We went…

MB Right away?

SP We went back to Scotland and I introduced this poor, unsuspecting girl to life in… you know, in an apartment there. And we lived… every year, we lived in about four or five different apartments, because we had to keep moving on because they kept letting it for more money to somebody else, actually. And it was very hard until we arrived, finally, in George Square, which was lovely. Now, that's an interesting story, because this was an apartment which hadn't been lived in for fourteen years. There was a sort of dead bird in the sink, you know, desiccated. And then I saw, on the mantelpiece in this apartment, which was above the old Women's Union in George Square, behind the new buildings in Edinburgh, a portrait of Harvey Cushing. And we'd rented this place from somebody called a Miss Fitzgerald, who lived in Oxford. And I thought, 'Well, that's interesting. Harvey? What's she doing with a picture of Harvey Cushing on the mantelpiece?' And so I went into it, and, of course, she was a friend of Harvey Cushing's. He used to visit her. And she'd worked with the elder Haldane,[10] doing physiology with the elder Haldane. And I looked up her papers, which dated from about 1900, and she died at the age of a hundred, and she was admitted as a member of the Physiological Society when she was about ninety-five, because she hadn't been a member of the Physiological Society even though she'd been working with the elder Haldane. But she'd gone to live in Oxford. I always remember it because she was insistent on the inventory, when we left this wonderful apartment, with all her wonderful antique furniture and her … sort of Meissen dinner sets and all that sort of thing, and she said, 'Well, the inventory, these five items I'm interested in. There's the knife sharpener, the tin opener…' and there were all these things! And we'd been living surrounded by her rather nice

[10] John Scott Haldane (1860-1936) British physiologist, father of John Burdon Sanderson Haldane.

possessions, actually, for all this time. But that was George Square, and that was a nice, it was just a nice little side issue of somebody who was important.

MB So you were married. And things were beginning to get better at the laboratory?

SP Yes, they did when I changed. I said, 'Look, I'm going to do it. I'm going to do this. And I'm not going to persist with this liver, it's killing me. Why don't I try the spleen?' So I just…on my own…

MB What made you think of the spleen?

SP Well, because the spleen has its own independent sympathetic nerve supply, it's got a good inflow and outflow, it's easy to collect the blood without doing any harm to the circulation, you see, so you could stimulate the nerves, collect the splenic vein blood, which drains into the portal vein directly, and so I just cannulated that, dead easy, stimulated the nerves… you take the nerves off the outer coat of the artery…

MB This is the splenic…

SP And so I just switched to splenic sympathin, and lo and behold as soon as I started to do this, of course, I started to get results, you know, they started to flow. And I…

MB (inaudible) results…

SP Well, I started … well, the exciting result was when I showed that there was something coming out which inhibited the rat colon, as well as caused vasoconstriction in the rabbit ear, and also stimulated the nictitating membrane of the cat. And so I was set up then to do a parallel pharmacological assay, you see. And the first experiment said, 'This can't be adrenaline. Could it be noradrenaline?' And the experiment said, 'Yes, it could be,' because the ratio of activity was such that it couldn't be adrenaline, but it could be noradrenaline, you see. Now, of course, latter day work says that, of course, a lot of substances liberated from sympathetic nerve endings, there's co-location, for example, not just of noradrenaline, with peptides of different sorts, with adenosine and so on - the work of Geoff Burnstock. So that there were a lot of other substances, no doubt, coming up. But the predominant effect could be explicable on the basis of it being noradrenaline. So I just went on and accumulated the results as fast as I possibly could, and it started to work very well indeed. And I…

MB Some marvellous traces.

SP Yes, well, these are the traces in the paper I wrote subsequently, which was *The Nature of Splenic Sympathin*.[11] But, you know, just reverting back to Peggy, the thing was, I said… we'd been walking down the main street in Edinburgh and I stopped in front of a jeweller's shop, and there were some rather nice small, pearl-handled knives and forks. They were very nice, dessert knives and forks, they were

[11] Peart, W.S., 1949. The nature of splenic sympathin. *J. Physiol*., 108, 491-501.

beautiful, and to our eyes, they were beyond reach. And I said to her, 'Look, if I ever get this problem solved, I'll buy those for you.' And so I'd been working all night, doing assays – and she often used to come up to the lab to bring me fish and chips, actually, you know. So that there was one night when I knew that we'd got it right, all the experiments worked in the right way and that completed a series of experiments and I knew we were all right. So the next day, I went out and bought them and didn't say anything to her. And then I came back in the early hours of the morning and put it by the side of the bed, you see, then when she woke up in the morning, she said, 'What on earth's this?' And so she knew…

MB The breakthrough.

SP …the breakthrough had occurred, actually. So that was it. It reminded me very much of that story I've told you about Feldberg. You know, Feldberg, when he was working with Dale, he was standing with his wife in front of a fishmonger's shop, and he… Lady Dale passed and she said, 'What are you standing there looking at?' And he said, 'Well, we're looking at the lobsters in the window, because, you see, whenever I do an important experiment which I think really advances the subject a bit, then we have a lobster supper.' So that after that, you see, it became known as a 'lobster experiment', you see, and Henry Dale took that aboard too. And so it was very like that and I rather appreciated it.

MB How did that breakthrough change your relationship with Gaddum?

SP Oh, quite a lot! Quite a lot! Oh yes! I mean, he eventually said, 'Had you considered a career in pharmacology?' Yes! No, no, that did make a big difference, because he appreciated success, actually. After all, the kindest thing he did for me was letting me publish it myself, you know, because he'd…

MB You did publish work with him, though?

SP Yes, I did. And with Marthe Vogt. That was on the assay of these different substances in blood. But he let me…

MB But you were (inaudible).

SP Oh, that's right. I fought hard to keep that, because it had nearly killed me, actually, you see, experimentally, and also as a test of my stickability, you know.

MB You didn't write up for a PhD or anything, this work?

SP No, no. No, no. No, I didn't do that.

MB You never went into that?

SP Well, I never thought that PhD's matter, actually, you see! What matters, and I do, I'm very serious about this, now that we're into an area where taught PhDs are becoming the rule, and I'm very dubious about that because, sure, a lot of students haven't got a broad biological background, therefore they need to be taught rather more about it. And with molecular biology becoming very much more concentrated,

they often, in my experience of interviewing them for fellowships and things, their lack of biological breadth is very outstanding, I'm afraid. And so there may be something to be said for that. This is one great virtue of having a medical education, actually, you're bound to be broad in your approach, actually. And even in my primitive days, it gave you breadth, actually, and I think that's very important in tackling problems. All I would say, really, is that if you're given an important problem, what could be more educational than that? What could be more testing of your general character, actually, than that?

MB Absolutely. But, thinking of 1947, which was a special year, there's marriage.

SP Yes. Absolutely.

MB When did the actual…

SP I also broke my jaw in that…

MB …breakage of the jaw take place! I was just about to ask that, because you were into rugger in Scotland in an interesting way, playing at Murrayfield.

SP Oh yes. Yes, I was. Yes, I first played for the University, and then a chap called [Micky] Steel Bodger, who came up from England, who was actually an English international, and he displaced me from the Edinburgh team, not surprisingly! So I looked around and I joined Edinburgh Wanderers. And Edinburgh Wanderers had as their home, Murrayfield, you see. So I can lightly say, 'Well, I was playing in the sevens at Murrayfield, actually…'

MB Cold day, hard ground.

SP It was a hard ground, boy, it was hard! And I tackled somebody and hit the ground with my jaw, and broke it and that was that. Mind you, it had an advantage. I'll tell you why it had an advantage, because my wife used to take me around… because I was wired up, you see, and bound all round, and she used to take me round to the fruitmonger, you know, fruit and food, as I told you, was very scarce, you see. So she used to take me round, looking like this, you see, you know, with a sort of straw between my lips, you see. And say, 'Well, look…' – bananas were very scarce - 'and I can put bananas through this.' And so we used to get better food than either of us would have otherwise had, you know! So it was an advantage. Nobody in the laboratory could understand why one earth I ever played rugby, because rugby was not something they'd ever had anything to do with, you know. It was sort of one of those nasty rough games, but I loved it, because we got all round the Borders on a Saturday, you see. We used to play all these teams down on the Borders. Wonderful, wonderful, it was good!

MB How did that period in Scotland affect you, generally? I mean, you became very fond of Scotland?

SP Yes, I did. Oh yes, I did. I also grew to hate certain aspects of it, like the cold wind blowing up the Edinburgh steps, actually, you know. And it was a funny time to be in Scotland. Of course, I've returned to it, you know; I've been lucky enough to be

given the DSc of Edinburgh University, subsequently, which was nice. And it made me think very hard of life in those times, you know. But it… yeah, I've got a sort of… still got a slight love hate relationship with Scotland, I guess, actually. But I can't deny, of course, that it was, perhaps, one of the most formative periods of my life, actually. I knew then that I wanted to do research and that I could do it, no matter what.

MB You stacked up…

SP Yes, that's right. And then, so then I… when I left, I came back.

MB You were clutched back by the Forces?

SP Yes, well, that's right. Well, that had been deferred because I went to… as you know, I've always felt slightly guilty about the fact that I was a medical student in the war, and I'd deferred it to do this research. Then I went into the RAF Medical Service.

MB Before we clutch you back, though, for that service, these were produced in that period, weren't they?

SP Oh yes.

MB Can we have a peek?

SP Yeah, well, you've seen the original paper on splenic sympathin, but a lot of young students will not be familiar with how we had to project our slides, you know, 2 by 2 is not… that is a projection slide 3¼ by 3¼, double glass sides.

MB And you had to carry whole boxes of them?

SP And you had to carry boxes around. These are the slides I first projected my results at a Physiological Society meeting, actually. So I'm rather proud of these. But they're the original smoked drum slides, you can see them there. But they really do weigh rather a lot, actually.

MB But they're treasure from that time.

SP Oh, they are, yes. Now, I love them. That's why I've always kept them.

MB Yes. It's nice to have them on film as well.

SP That's right.

MB Thanks very much for bringing them in. Now, you are clutched back and you go to rather a nice part of the country.

SP Oh yes.

MB RAF.

SP Yes. Oh, yes, RAF. We went to Ely. And it was rather nice, because the RAF Hospital in Ely, just about a mile outside, and we survived there in a very nice apartment there, and Ely, of course, very quiet cathedral town, really very quiet indeed. But we made lots of good friends there. And the RAF Medical Service was quite an eye-opener to me, actually, you see, because I'd already got my MRCP, you know, before, and so I was graded as a medical specialist, which… as I look back upon it, I think what an injustice was done there, really, because, you know, I was still very green, actually, but, you know, willing to learn.

MB And fresh from cat surgery!

SP Oh, fresh… yes, I fancied myself in that way! But the medical problems of a bunch of young RAF recruits, though, they varied, and could be quite considerable. There were people doing extraordinary things, like doing partial gastrectomies on nineteen-year old recruits, you know. And I used to complain about it.

MB What, really?

SP Yes. You know, because peptic ulcer being quite common, and surgeons, perhaps, fancying themselves as… you know, in this respect. They would, perhaps, you know, very likely do these sorts of operations which…

MB What, on the basis of dyspepsia or something?

SP Yeah. There was an awful lot of… there was an awful lot of dyspepsia around in these recruits, you know! But it was, it was quite remarkable.

MB That must have been rather frightening, people doing that…

SP Oh well, it was frightening.

MB …bizarre intervention work.

SP Very, very unusual. And nobody could get away with it now, actually, of course. I mean, it just wouldn't be done. But, you know, that's the sort of thing that could happen. But, of course, I then… I made a lot of friends with the local GPs around Ely.

MB Because they had referrals, I guess.

SP And so we used to act, function as a district general hospital for Ely, actually. And so all the patients they wanted an opinion on, I used to go round and see them, or bring them in if they were ill, so we could… this was, I never asked anybody actually, in the higher command of the RAF whether I could do it. One just did it, you know! So we were running a sort of private hospital service for the inhabitants around Ely and a few of the villages beyond, actually. And I used to be called in to give an opinion on those people.

MB It sounds a unique opportunity though. I mean, you've come from quite rarefied research, and you land up having a very general medical brief, seeing a lot of cases.

SP Oh yes. That's right. And my colleagues there were very interesting, you know, a lot of them knew a lot more medicine than I did, I have to say, actually, at that time.

MB It was a good re-equilibration process.

SP Oh, it was. It was excellent.

MB How did you like the RAF generally, though? I mean, that was good to have that attachment for a time?

SP Oh yes. Yes, indeed. I mean, it… I think it's one of the best services, actually. I mean, you know… if you're young…

MB And you stayed in Ely?

SP And we stayed in Ely, and that was it.

MB Two years?

SP Yeah, two years. They wanted me there as a medical specialist, and so they stuck me there and that was it, you know.

MB And Peggy got rather used to moving?

SP Oh, oh, she… oh, she got a very nice life, you know, in Ely. I mean, made a tremendous number of friends.

MB Did Peggy continue her career throughout the period at Edinburgh and Ely?

SP Yeah, she continued nursing, but when she was in Ely she didn't need to do that, and that was… the opportunities weren't there. But the opportunities to live a better life than she'd encountered in Edinburgh, when she, you know, really had a tough time, you know, keeping me going there.

MB They were tough years.

SP They were tough, but, you know… in retrospect, they were very good. I think I've told you, the example, moving from one apartment to another after midnight, carrying a sack containing coals and a black cat on my back, plus some other… you know, household pieces. A long black car drew up alongside us and it was the police saying, 'And what have you got in that sack?' And I said, 'Well, coal and a cat!' Because, really, we were moving from one apartment to the next. And that was it, you know, that was the sort of life you remember.

MB At this particular moment, we're going to move from one reel to another. I'm going to close this part of the interview down for a moment.

SP Yes, sure.

MB The reel's running and we're able to continue that story. But to move from Ely, and that rather curious two years, back to working with Pickering, which is the next big part of the story.

SP Yes. Yes, because he offered me a position in the department then, towards the end of my time in the RAF.

MB You'd kept in close touch, I think?

SP Yes, I'd been in touch. Not very close, you know. But he, he offered me a post, actually, you know, and I eagerly accepted it, just what I wanted.

MB This is clinician and lecturer?

SP It was a sort of… well, it was a sort of assistant on the medical unit, it wasn't dignified by the term 'lecturer'.

MB Back at [St] Mary's.

SP Oh yes, this is back in the medical unit. And there were a lot of interesting people working there then. A lot of post-war registrars, senior registrars still around, who'd…

MB Anybody worthy of mention at this stage?

SP Well, I suppose [Richard] Lovell,[12] who was the first professor of medicine in Melbourne, for example. He emigrated to Melbourne and he was working on rheumatoid arthritis at that time. And Brian Hudson, who subsequently became the President of the Royal Australasian College of Physicians, a very eminent endocrinologist at the Howard Florey was there. He changed from doing cardiology to becoming, ultimately, an endocrinologist. Tony James, who was the first person to distinguish between people with duodenal ulcer who secreted a lot of acid at night, versus those with gastric ulcer, who didn't. Now, of course, at that time, that was quite important, because people with duodenal ulcers got pain at night. Now, it was not known, and it still isn't absolutely sure why they do, but now that we know that there's this well-known *Helicobacter [pylorii]* infection at the bottom of an ulcer, maybe that makes more sense. It may well make more sense, actually. But that was what he was doing. But that was… somebody was doing something original all over the place. And Peter Sanderson, who was the reader in medicine at that time, in the department, was busy doing work on calcium, when people were not in the position of measuring calcium in the blood, he was doing the early work on measuring calcium and ionised calcium in blood. So everywhere you looked, it was interesting. And

[12] Professor Richard Lovell (1918-2000). Interviewed by Dr Bryan Gandevia for the Medical Sciences Video Archive of the Royal College of Physicians and Oxford Brookes University, 28 March 1996. MSVA 126.

there was Harold Scarborough, who was a professor of medicine in Cardiff, and who was a Scotsman, and who subsequently went to Nigeria to run a department of medicine there.

MB Was this the Bell, Davidson and Scarborough?[13]

SP Yes, absolutely. That was the next best thing to ascorbic acid – you remember that he thought he'd discovered a new substance which was like ascorbic acid, it never sort of really came to anything. But he was the first chap there that taught me how to do plethysmography, you know, and measure blood flow through the hand, using a hand calorimeter, you know. You had a great big thermometer, graduated in hundredths of a degree, you see, and if you put your hand in the water, and measure the change in temperature of the water… it's an enormous calorimeter, really.

MB Yes, this is kind of Beckmann thermometry in a way?

SP Yes. You could actually tell, and if somebody walked into the room, you would actually shut off the blood flow through the hand, and you could do it, because the temperature rise, which was steady, would then stop. And that's one of the methods of measuring blood flow that I first became acquainted with. I hadn't realised that later in my life I would have to become acquainted with a lot of other methods of measuring blood flow. But that was, that was what was going on there. And so I used to help him in his experiments. But, of course, because of my background in looking at catecholamines, one of the things that we rapidly encountered was the fact that there were one or two patients around who had that rather rare tumour, phaeochromocytoma, and so I set to to try and find more of them. And we became a collecting centre for these rare tumours, because I could assay the stuff in the urine, for example. They put out a lot of noradrenaline in the urine from the tumours. It's a tumour of the adrenal glands or the sympathetic chain, in essence. And you could assay it. And a lot of… including one of our house physicians, we diagnosed as having phaechromocytoma. That was unusual because he was thought to be getting scared before his final exam, actually, but, in actual fact, he was having attacks due to release of noradrenaline into his circulation, you know, so that he went pale and then flushed, and they thought he was nervous. But he was an Irish international footballer and he wasn't the sort of chap to become nervous like that. But we showed that he'd got phaechromocytoma.

MB Was the prognosis pretty bad?

SP Well, it would have been if he hadn't had it removed, because…

MB But removal, was it pretty successful?

SP Oh, yes. But it wasn't easy then, you see, the surgery of this, because the circulation would often drop and the blood pressure would drop right down into their boots, actually, and people would die during operation. But what we used to do was infuse them with noradrenaline to keep the pressure up, at that time. We now know, of course, that what you do is, you block the alpha receptors. But we didn't know that

[13] Bell, G.H., Davidson, J.N., Scarborough, H., 1950. *Textbook of Physiology and Biochemistry*. Edinburgh; London: E&S Livingstone.

then, of course, you know, because receptors were not talked about at that stage, you see. But then I did all right with that and did some work on that. But it wasn't my main… you know, I could see that wasn't going to be my major work in life. And Pickering, who'd been working on renin at that time… he'd worked on it before the war, in 1938, you see, and the interest in the whole subject… you remember that…

MB This was the link with blood…

SP Well, Tigerstedt… it goes back a long way, you see, because [R] Tigerstedt and [P G] Bergman had extracted rabbit kidneys and shown that there was a substance there which raised the blood pressure, which was destroyed by heating, and which they named renin. They did a lot of the early work, which quite clearly stated what it was. And they knew that it was proteinaceous.

MB They knew the location in the kidney as well, did they?

SP Oh no, not the slightest idea. They just extracted. There was a big vogue in the latter part of the nineteenth century for injecting extracts of various organs, you know, because that was how the endocrinology of some of the organs was discovered. You cut them out, saw what happened, put it back, or an extract back, and see whether you restore function, you see. And that was how the adrenal function was discovered, you see, way back to… you know, Addison, in about 1850, you see. And [Charles E] Brown-Sequard did the same experiments in animals, and showed that the blood pressure dropped and they died within a day or two, and if you gave back an injection, they'd survive a bit longer. But he didn't take that any further. But it took a rather long time before we got the composition, that better established. But, of course, in the case of adrenaline, that was the first hormone to be crystallised, you see, and that was in 1904. And, of course, [George] Oliver and [Albert Edward Sharpey-] Schäffer, using injections of extracts of adrenal… you see, remember that Oliver was a general practitioner, just interested in various subjects. He brought an extract to Schäffer, eminent professor of physiology, and said, 'Would you please inject this into an animal preparation.' So Schäffer had a greyhound set up, measuring its blood pressure, injected this extract in, and stood back amazed, while the blood pressure went right up into the skies, actually. That was how adrenaline was discovered, you see. And then it was crystallised. You see, those experiments were done in about 1894. Ten years later, it had been crystallised and you could buy crystalline adrenaline off the shelf, you know. So it was the first hormone to be described, you see. So then Tigerstedt and Bergman, you see, in 1898, had been doing similar experiments with the kidney, and found another pressor substance. Then nobody took any interest in it, seriously, until [Harry] Goldblatt, who thought that the kidney was the source of high blood pressure, because he was a pathologist, you see, and he used to see narrowing of the little intra-renal blood vessels, you see, under the microscope. And he said, 'Well, look, what's happening here is that the blood supply of the kidney is reduced, that causes the kidney to raise the blood pressure to maintain its blood flow.' So what he did was, he put a clip on the main renal artery in the dog and lo and behold, the blood pressure went up. And that excited everybody's attention. So there was a big return to the experiments of Tigerstedt and Bergman. They looked through the literature and they came up with that. And among these, Pickering was one of the people. He was working with Thomas Lewis at University College at that time, you see. And he showed that, yes, surely you could extract the material, just like

Tigerstedt and Bergman had said, out of the rabbit kidney. Then the war came, so that's about where it stood.

MB And into the early fifties, when you came back to this, he was back on target?

SP Yes. Well, he was interested, but his interest at that time was… he didn't want to take that any further, particularly, himself, but he said to me, 'Well, why don't you find out what it is that causes this…' Because two groups of people had been at it in the meantime, [Irvine Heinly] Page and his colleagues in Indianapolis, [O M] Helmer and Page, initially, and Braun-Menendez and his colleagues in South America, in Buenos Aires, in the Argentine. And their pharmacology, in the Argentine, was very good indeed. It was a sort of Germanic influence, you know.

MB Yes, but that was Menendez.

SP Yes. And very good. But that was, you know, [Bernardo Alberto] Houssay) who got a Nobel Prize, being an endocrinologist, he got the Nobel Prize for his endocrinological work,[14] he was subsequently protected against Peron, the Peronist regime, by Braun-Menendez. Braun-Menendez came from a very wealthy family. They owned masses, you know, haciendas galore, and masses of countryside and masses of cattle, you see. But he was able, because he had the influence. He didn't go along with the Peronist regime, but he was able to protect Houssay from being thrown out or killed, you know. One of the two it could have been. But he was a phenomenal man, Braun-Menendez. They were, in their different ways, quite remarkable. They were working on what they called hypertensin, that was the activity produced by the action of renin, and Page and Helmer were working on what they called angiotonin. Now, I liked the South American group's work, I thought it was extremely good work. And actually, I stuck with the name hypertensin, you see, hence my early papers are all about the isolation of hypertensin. Then these two groups came together and decided that they'd have a compromise, and so the name angiotensin came out of hypertensin and angiotonin.

MB So that's how it arose?

SP That's how it arose. That was a compromise and they agreed that's what it would be called.

MB Did you meet these people at international conferences?

SP Oh yes. Oh yes.

MB You had a chance to talk with Menendez and colleagues?

SP Oh yes. Yes. Yes. Braun-Menendez had a very sad end, you know. He was… there were a group of them, Braun-Menendez, [L F] Leloir and [J M] Munoz they're all well-known names, actually, in the area, and one day they were… there was a flight inside South America, and thunder and lightning and rain, and they didn't want to fly, but Braun-Menendez, being a sort of swashbuckling sort of chap he was, said, 'No, we're going to fly.' And they didn't. He did, and the plane crashed, and

[14] Bernardo Alberto Houssay shared the Nobel Prize for Physiology or Medicine in 1947.

that killed him. And that was a shame, because, you know… it was a great loss, actually. A great loss. He was one…

MB A great charismatic figure.

SP He really was a tremendous chap. And Page – who, you know, we had the celebrations of his ninetieth birthday, you see, and we've got the volume, which I'll show you next time, of that – was working, and they came, eventually, to the same conclusion, that it was likely that renin would be an enzyme working on a substrate in the plasma to produce a peptide. So the race was, of course, I was given the task, find out what this is. So Pickering said, you know, 'There you are. Go for it.' And that, of course, attracted me, because it was just right in the area… well, right in the area that I would, you know, naturally take to.

MB And this was going to be five, six, seven years of your life?

SP Who knows? Well, it turned out, it turned out to be that, yes.

MB And you were going to take it to Mill Hill in due course?

SP In due course. Well, it was, that's right. That's where it ended up, actually. But I worked away first, you know… how do I get enough of this material, and what was it, really? And how labile was it? How could I make it in sufficient quantity? And initially, we stuck with the rabbit kidneys, largely because Pickering had worked with the rabbits. If I had any sense, I'd have turned to use pig extracts, rather closer at hand. At that time, you know, rabbits ran over the whole of Britain, but there were particularly large areas of Northumberland, from where both Pickering and I came, that were… they trapped a thousand rabbits a night, and sent them down to the market, you see, in London, for consumption. So we went up there and we used to go and spend about three days there and take part in the… when they brought the rabbits back to the sheds, they used to gut them and we used to take the kidneys out, put them into a big Thermos flask, you see. We came with great buckets of dry cold and everything else, you see, and froze them. And we ended up, you see, with two thousand kidneys, you know, from one night, and, you know, we came back with a tremendous amount of rabbit kidney, you see. And I used to then have to spend the next few days and nights extracting these kidneys, you see, because we could dry them, you see. You could cut them up and dry them in alcohol, because when they were crude, the alcohol didn't knock the renin off, it didn't destroy it. And so you would do that, you see. And you had an alcoholic haze, where you got these masses of drying renal extracts, you know, and then you'd take the powder, then you ground it up, then you'd have a nice powder, you'd get your uniform powder, which was your standard preparation, and so you could then go further with it, you see, and use it. You'd extract it, I used to precipitate it out with ammonium sulphate and all those sorts of steps, you know, to get a usable…

MB So there was quite a lot of cookery to get…

SP Oh well, I became a sort of… in various ways, just a cookbook biochemist, you know.

MB But it worked, you got the material.

SP Oh yes. So I got the renin.

MB And it was in fairly pure form?

SP Well, not at that stage, no. That was my crude preparation, which I could use for my preparation of angiotensin. So I set to. Then I had the problem, well, what blood? Well, what blood is easily available in large amounts? And, of course, ox blood, cow blood was the stuff that you could get in large amounts from the slaughterhouse. So I set to, and I used to start off, you know, with ten, twenty litres worth, and spin it down in great big sort of centrifuges. And it was really ridiculous! But the… it took so long, you know, because the blood's defibrinated. They used to defibrinate the blood in the slaughterhouse, you know, using a besom broom. You know, that's how they used to do it. I mean, they didn't do… they'd just take a broom, and just… that was a very old traditional method of defibrinating blood, you see. And if they did it well, you didn't get it full of haemoglobin, you know. That was bad news. If the plasma's full of haemoglobin, your recovery of material, finally, was going to be very poor. We knew that. So that the aim was to get nice clear plasma. Anyway, that went on for a while and I said, 'Look…,' one day I went to Pickering and said, 'Look, I've done a few investigations and I think I can do better with separating this blood. You know, I can get a milk separator for thirty-five pounds.'

MB With the plates in?

SP With the plates in, the stainless steel plates, a handle, and an electric motor, just in case… the handle was there just in case the electric motor broke down, you see. So, as you go along the entrance to the A40, you pass the centrifuge firm that used to make these…

MB Alfa Laval.

SP It's Alfa Laval. Alfa Laval are a Swedish firm, you see, full of milk separators. So I went down there, you see, one day and I went into the shop and saw just what I needed, you see, a nice little device with plates, stainless steel plates, and you put the blood in through the top, through the centre came the concentrated red cells, through the outside came the plasma. And you could just watch it spurting out! It was one of the great days of my life, you see, because it was terrific! You just separated the blood.

MB But you were getting buckets full, you needed…

SP Oh well, I was dealing with a hundred litres, you know. That was how I did that. So that I would then up with a dustbin full of plasma. And the problem was, now, okay, I could, on a small scale… you see, I was good at putting up rat blood pressure assays, you see, that was easy, that would take me about five minutes to do that, you see. And I, from my Edinburgh experience, you see, I could do that, so that I could assay what I was making, on a small scale. And so I did the usual industrial method. You start on a small scale, get a method which would work, and then up the

scale and see if you can still make it work on a big enough scale. Well, that took me a long time. It really did, because I didn't know… how could I extract what I was… I added the renin to the plasma, that would then make the pressor substance. And then the problem was, how do I get it out of that great mass of plasma, you see. Now, you must remember the time that we're talking about, you know, ion exchange resins had not been invented.

MB This was the early fifties.

SP That's right. Adsorption was a method ranging from charcoal to some aluminas and so on. It was known that you could adsorb things, the catecholamines on alumina surfaces, for example. All the rest was really terribly cookbook. And I took to charcoal, you see, because I went into Sutcliffe and Speakman, well known names in charcoal circles! But, you know, they're used for so many things, you see. They were used for clarifying beer, for clarifying maple syrup. They're used for a lot of things, actually, you see. And I read all the literature I could get my hands on, you see, about how to adsorb, because I thought adsorption. I went through a period when… it was the time of the introduction of the early dialysis machines for renal failure patients, you know, and there was a great big drum with slats, and you wrapped the sausage skin round and round this, and you put the patient's blood in at one end, and it was going, revolving through a bath of fluid, which was moving in the opposite direction, and so the urea and everything else was coming out of the patient's blood, and the blood was, having been washed, was returned to the patient. That was the original Kolff machine. Now, I knew they'd got one at Hammersmith Hospital that they weren't using, you know, because they'd gone on to better things. So I borrowed this and I set to, and I incubated my mixture and then passed it through this. But, of course, one of the troubles with this thing is that the loops get looser and looser and they rupture, you see. Now, of course, in the case of a patient, that was not good news. But in my case it wasn't good news either, because by the time I'd done all this in the cold room - I'd set it up in the cold laboratory – by the time I'd done this, I'd lost everything, you know, there was nothing coming, because I then still had to concentrate, out of all that vast volume of bath fluid, the substance I was looking for. So I rapidly gave that up. But, I mean, you know, it gives you some idea of the extent to which I went.

MB (Inaudible).

SP Yes. So I investigated charcoal. Now, I showed that you could easily pick up the pressor substance on charcoal, but then I couldn't get it off! So I said, 'Well, it …'

MB So by stirring with charcoal, or over charcoal you could take out the active…

SP Activity, yes. Oh, absolutely, yes. It adsorbed it nicely, and you could then… then the problem was how to get the charcoal out of the mixture, you see. However, I'll come to that in a minute. First, you have to find the right charcoal. And after a lot of experiments, I came up with the fact that what's called 'animal charcoal', which has still got some calcium in it, was ideal. And I could get the… you know, if you use fatty acids, you can actually get peptides, as I discovered subsequently, you get peptides off charcoal, they're desorbants, very good desorbants for charcoal, actually,

for some reason. Must be just the shape of the fatty acid. Now, I chose the simplest fatty acid, acetic acid, actually, not as strong as formic, obviously, but it was good. And I used acetic acid to get it off the charcoal. Then the problem was, okay, we've got it on the charcoal, how do we get the charcoal out of that mixture, you see. Because I worked out how much was the optimum quantity of charcoal. You stirred the charcoal with the incubation mixture as it was occurring, on a hundred litre scale, you see. So I said, 'Well, I've separated blood once. Why can't I separate the charcoal?' you see. So I just, you know, I did it that way, initially. But then again, that became so cumbersome because everything clogged up. So then I went into… 'Well, what about filter aids?' That's when I discovered filter aids, which are kieselghur. And kieselghurs, of course, have been used for filtering all sorts of mucky materials, you see, and this was sort of slightly mucky, actually, when you got down to it – plasma with charcoal in – a very glutinous sort of mess. So what I then discovered was high flows, high flows, Cellite, the name of the stuff. And that, you just mix that in with your final mixture, in the right proportions, and then filter it. And you end up with a cake on a filter funnel like that. And you don't have to use enormous quantities, but it enables you to filter through, so you've got a mixture of charcoal and Cellite, as a cake, and then you just put the acetic acid on top… you wash it with saline first, get rid of the gunk, and then when it's clear, you put the acetic acid on, and off comes, into whatever volume you need, you can elute all your active material. So that was step one, you see. That took me quite a while to work that out.

MB A couple of years?

SP Oh yes, it was going on for that, actually, yes. Then I, then I had the problem, 'Well, okay, you've got it in the acetic acid, how do you get it out of it?' you see. And that was when I had to learn about how to push this activity out of a watery phase into an organic phase, because it was going to be easier to handle in an organic phase, you see. And I discovered how to do that, by adding salt to the… if you add salt and put an alcohol on top, like butanol, you can push it into butanol. That's the basis of a lot of that… what was then very much in vogue, was what's called the Craig apparatus, you know, partition coefficient separation. If you got a partition coefficient in favour of either the water or the organic phase, you can make the organic phase move. He had an enormous apparatus full of, you know, about a hundred tubes, and each… it rocked automatically, it mixed the two phases, then it settled, then it pushed the top phase on to the next tube. They all moved on. And that was Craig's apparatus, you see. And that was very much used. Some of my competitors were using that, actually. Skeggs in Cleveland used it.

MB So you finished up – we've got about two minutes at the most – you finished up at that stage, with your active principle, in a fairly pure…

SP Oh, a fairly impure phase! Oh, it was still very impure, actually, you see. And then I was struggling to find out how to get it… I could isolate it. And, of course, I got as far … as we'll go into later, as various steps to get a pure product. And so I got it as far as the isolation of hypertensin, and I knew the amino acids in the peptide, because I'd found out how to separate it in different ways. But it required lots of adsorption/desorption steps before I could arrive with anything that was remotely pure.

MB Next time, we're going to go on to those particular steps and also go on to Mill Hill.

SP Yes. Because that's where I took the… that's where I took the material.

MB This material went on there to be researched further?

SP Further, that's right.

MB So that's our next conversation.

SP That's the next step.

MB I've enjoyed today. Thank you very much.

SP No, it's a pleasure. Yes. Good.