Patricia Jacobs

Personal Details

Name	Patricia Jacobs
Dates	1934
Place of Birth	London
Main work places	Edinburgh, Honolulu, Salisbury (UK)
Principal field of work	Human cytogenetics
Short biography	See below

Interview

Recorded interview made	Yes
Interviewer	Peter Harper
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Edited transcript available	See below

Personal Scientific Records

Significant Record sets exists
Records catalogued
Permanent place of archive
Summary of archive

Biography

Patricia Jacobs was born in London but moved to Scotland at an early age, studying zoology and botany at St Andrew's University. After a year in America she joined the newly formed Medical Research Council Clinical Effects of Radiation unit under Michael Court Brown in 1958, and was responsible for a series of the key early discoveries of human chromosome abnormalities, particularly the XXY Klinefelter syndrome and the other sex chromosome abnormalities. In 1970 she moved to America and joined the University of Hawaii in 1972, working particularly on the cytogenetics of spontaneous abortion. In 1988 she returned to Britain as head of the Wessex Genetics Laboratory Service, Salisbury.

INTERVIEW WITH PROFESSOR PATRICIA JACOBS, 13th FEBRUARY, 2004

PSH. Can I just start off by saying it's Friday 13 February 2004 and I am at Salisbury District Hospital talking with Professor Patricia Jacobs; Pat, what I would like to do, if I may, is perhaps to start a bit at the beginning and ask, am I right that you were born and brought up in Scotland?

PJ. I was not born in Scotland. I was born in London but I was brought up in Scotland. My father was evacuated from London on the very first day of what the Americans call World War II and at that time people thought that the war would be over very quickly. I don't know on what basis. I was four years old and a whole group of people, who worked in Nobel for ICI, Imperial Chemical Industries, in the Nobel division, were moved en mass to a little place on the west coast of Scotland and all dumped in a hotel. They all stayed in the hotel, because it was thought that very soon the war would be over and they would all be going back to London. The reason they were all in this very small place on the West coast of Scotland was it was very near a site with a lot of sand dunes and under the sand dunes was the largest explosives factory on our side in World War II. My father wasn't a chemist but he was an accountant attached to this division and was moved with everybody else.

PSH. Am I allowed to ask where that was, after so many years?

PJ. Yes, Stevenson. We lived in Saltcoats which is next door to Stevenson, which was where the factory was, on the west coast of Scotland in Ayrshire. So it was north of Ayr. About 30 miles south west of Glasgow.

PSH. And then you went to school and stayed on for the rest of your childhood in Scotland.

PJ. Oh yes. They never moved back. That was the thing. After a year it became obvious that they couldn't all go on living in this hotel. Which was an interesting thing for a child. I was four. Everybody then got rented accommodation one way or another in Saltcoats, and I of course was going to school there. And we stayed there for the duration of the war and then, to my mother's especial horror, they were told they were never going back to London and eventually they moved the division to Glasgow. Now by that time I was 18 so I was grown up. I don't remember anything about London. So I consider myself Scottish. Whenever I go back across the border I feel at home. But in actual fact I was born in London, but I was brought up and spent all my formative years in Scotland.

PSH. How did you get interested in science in general and in genetics in particular?

PJ. I went to school and I did OK but I could not do languages. This was in the days of the Scottish highers when you had to sit a bunch of highers and pass them all together or you failed the lot. So I was good at science at school and very bad at languages so my streaming was guaranteed from the word go. I was going into science, which I did. I very nearly didn't get to University at all because I couldn't pass lower French. In those days you had to have a foreign language, even if you were doing science, to get into university anywhere in Scotland. Probably anywhere in England as well, but I don't know that. And eventually, with a great deal of difficulty, I passed lower French, and lower French at that time was very low. So I then went to university to study science. I had no huge ambition to do this but I couldn't study anything else, because I was hopeless at languages.

PSH. Which university is this.

PJ. I went to St Andrew's University.

PSH. St Andrew's.

PJ. Yes. and the science I studied at school was chemistry and physics. I didn't particularly like either of them, but I was quite good at them, especially physics. So I went to University and I decided that I didn't really want to study chemistry or physics. What I really wanted to study was botany, because I loved wild flowers and this was my huge compelling hobby all through my childhood, and I don't know what led to that, because I didn't know anybody who was interested in botany. I wasn't encouraged. It was something I developed myself. Anyway I got to University and decided I would do botany, and so that's what I did, because I thought it would be very nice to wander around for the rest of my life looking for wild flowers. It seemed a very agreeable way of passing the time. And then I had botany at University, and remember I had never had botany at school. I had never done it, but in those days they were keen that you should have chemistry, physics and maths and they would graft on botany. And the first term consisted of fossil ferns and I lost a lot of interest in botany there and then. And with botany I had to take zoology, and I was very fortunate, because the zoology department was headed by Mick Callan and he was a superb teacher. Also very hard on anybody that didn't arrive on time, leave on time, all the rest of it.

Anyway, so I switched basically from botany to zoology, but it wasn't all that much of a shift, because we had to take two subjects at St Andrews for three years, so I took botany and zoology, but my heart was in zoology. And specifically this is where I first met cytogenetics, because of course Callan's great area of expertise was lamp brush chromosomes. In the Scottish system in those days, you could take an ordinary degree in three years, which I did, and if you wanted to do an honours degree you came back and did an additional fourth year which most people didn't. But that's what I did and in zoology, unlike some other subjects, Callan insisted you went ahead and sat and passed the ordinary degree before he would allow you to come back and do the honours degree, so that's what I did. And then I came back for a year to do an honours degree under him and this was an entirely research degree. There were no lectures, there was no nothing. Now whether that was a good or a bad thing, it would now be considered to be a very bad thing. I consider it

to be a terribly good thing and I got plunged into research at a very early and very green stage. He decided I would do a project on centipedes. There was something very interesting, which I can't remember now, about centipedes' chromosomes. But before you could do a project on centipedes, you had to find centipedes. And this was one of the very, very rare, very hot summers in Scotland. And I came back to University early to find centipedes for my project which was starting September/October. And I have to tell you, the only thing I discovered was that in a very hot summer, centipedes go somewhere else, and I spent two months looking for centipedes and only found about three. It was dreadful.

I went to Callan who I found very strict and I was actually scared of him, I admired him but I was scared of him. And I eventually made an appointment. You never dropped in to see him. You made an appointment through his secretary and you knew when you were to come and you knew when you were to leave and I said I haven't been able to find any centipedes you know, and time is marching on. So he said "Oh. Oh". And he said "perhaps you can work on the praying mantis instead". And I thought, oh my God, if I can't find centipedes how in the world am I going to find praying mantises.

PSH. Yes in Scotland.

PJ. They don't even live in this country. And then he got a little pot, and I can still see that little pot, and he said, here you are, and he gave me this little pot and it had 17 testicles of praying mantises in it which he had brought back from Italy. His wife was Italian and he went every summer to Italy. Her father was quite a famous man called Dorn who ran a research station on some island near Naples, and he went there every summer. So from this island he had brought back these 17 testes of praying mantises, and he said you can work on these instead.

PSH. Were they in formalin?

PJ. They were in some preservative. I don't know if they were in formalin or 3 and 1, but they were in fixative anyway. So I went off and I looked at them and I thought, this is all I've got you know, and I've got a whole year and I don't know how to do any of the techniques I need. I don't know anything about anything. Anyway, to cut a very long story very short, and I was very much on my own, because in St Andrew's there was also a marine research station and it was also part of the zoology department, but it was spatially quite a long way away from the actual zoology department. It was right on the coast and everybody else who was doing honours in my year had chosen to do a project based at the Gatty Marine Laboratory, so not only was I doing research, I was the only honours student there. So I was very much on my own which was, I think in retrospect, good.

PSH. Did you get chromosomes out at the end of the day?

PJ. I certainly did. And it was fascinating because they had a very interesting sex determining mechanism and it was XXY, these praying mantises, and I ended up getting chromosomes out and publishing a paper with Callan.

PSH. Really?

PJ. Which I thought was very good, because interestingly enough, the paper was about non-disjunction.

PSH. Gosh.

PJ. In the praying mantis. That's very funny. Isn't that funny?

PSH I didn't pick that paper up, but the citation indices only started in the later part of the '50s so probably that would have been earlier.

PJ. No, 1957. It was published in 1957.

PSH. Not to worry, but can I then ask, did you go on, after you had done your honours degree, what was the next step after that? Was it direct to Edinburgh or was there something in between?

PJ. No. After that I decided the time had come for me to earn some money I didn't know what to do. I didn't have this burning desire to do anything, but I had enjoyed my research here, so I went to America with a friend, just for a fun year, and we got jobs, both of us, as research assistants in a place called Mount Holyoake College which is one of the swanky all-girls colleges in the eastern part of the United States and I did not enjoy it. I don't think I even knew why we went there. We picked it out of a book. I don't think we even knew it was all girls and it was in a very little place in Massachusetts. It had a very good academic reputation and I worked there for a lady, called Dr Kathleen Stein, who was lovely. And she was head of the zoology department or whatever it was called and she worked on mice and on day one she said "Right you are in charge of the mouse house". Well number one, I am terrified of mice and number two, I have never picked up a mouse before. How could I possibly be in charge of a mouse house. The nearest I had got to animals in my zoology degree was 17 pickled testicles, so I really didn't enjoy it and then I discovered there were also rats in the mouse house which I also was responsible for. I ended up coming to terms with them, but barely. She was a lovely woman but she was scatty and she did research projects which would have taken maybe two or three years to do and she would just come and ask me to do them. Then two weeks later she would come and ask me to do another one, which also should have taken two or three years and suddenly I got very worried and then I realised she never came and asked for any results. It was a very odd year. Anyway.

PSH. It was a year was it?

PJ. A whole year. A whole academic year and anyway, I got to see a lot of the States. In those days, going to the States was a big adventure and we went the cheapest way, which was by boat, not by flying, and so we were there and we thought we will never ever be back so while we are here, we had better go and see the States. And we bought a very old car with another couple of people and we travelled all over the States. It was amazing, on practically no money at all. And while I was there, towards the end of my time there, I got a letter from Mick Callan, the man I had done the honours thesis

with. He had had a request from Michael Court Brown, saying he was setting up a unit in Edinburgh to look at human chromosomes and he had written to Mick asking him if he had anybody who could do that kind of thing, and he thought of me and my praying mantis days. And he said, you know if you are interested, write to him, so I did and I got the job without being seen because I was in the States and nobody would ever have come back to be interviewed.

PSH. Which year was that Pat?

PJ. It must have been, when I started it was 1958.

PSH. So the human chromosome number had already been got right by then.

PJ. Exactly. Very much so. By Tjio and Levan

PSH. And techniques made it possible to look at human chromosomes?

PJ. Well that's a whole other question. My job was in a newly instituted MRC Group. It wasn't called a unit, it was a group because it was small. And it was called I think, Group for Studying the Clinical Effects of Radiation Research, or something like that, and my remit was to look at the chromosomes of people with radiation induced
leukaemia and see if they were any different from the chromosomes of people with non radiation induced leukaemia. So, we were using bone marrow, and when I started I went down to Oxford and Harwell to learn two things. From Harwell and from Charles Ford, I was to learn how to look at chromosomes, but he didn't really do human chromosomes, he did mouse chromosomes; and from a man called Lajtha in Oxford who was a haematologist who grew bone marrow. So I, as you know Harwell and Oxford are close together, I went between those two individuals learning what was to be the two aspects of my research project I suppose. What I should tell you then is, because people forget. I didn't have a PhD, I only had an honours degree. In those days, if you had a first class honours degree, it was exactly the same as having a PhD as far as the MRC were concerned. You were a scientist and you were at the same level so there was no incentive whatsoever to do a PhD. That was good, because I didn't have any money and didn't see how I would do it anyway, and I had what looked like a good job. So I stayed in Harwell and went between these two labs I have just spoken of for about, I think it was three months towards, was it 1957, I can't remember now. Anyway I was there for three months

PSH. And you published a paper with Charles Ford on human chromosomes.

PJ. And Lajtha. That's right, I did that when I was there. But it was basically a technical paper on how you could use bone marrow and Charles' techniques, very beautiful techniques for looking at marrow chromosomes in mice, which was what he was doing at that time and how you could apply it to humans, using Lazlo's technique which was for growing bone marrow and nothing to do with chromosomes. So I was the person that linked those two together, this very young and very naive creature.

PSH. Charles must have been really quite an inspiring person to work with. I get the feeling that a lot of people have interacted with him but it is just very sad that he is not here to interview; you must have learned a lot during that six months.

PJ. I learned a lot. There was no question, I had nowhere to go but up. Let's face it I had to learn a lot. First of all, I had to use techniques that I had never used before, and secondly I was young and naive. I did learn a lot. I learned a lot from both of them.

PSH. Am I right, that one of the things Paul Polani told me was that Charles Ford was initially rather reluctant to work on human chromosomes and he had to be a bit enticed to do that.

PJ. I think that's true, and its easy for me to say this now, and I think it was a mistake. This is what I think. I think he was superbly good. He did this T6 translocation, which was a fantastic cytogenetic handle on a whole variety of things in mice. And I think he was incredibly good and here he was, I mean it is difficult to imagine how isolated Harwell was in those days. It really was. If you missed the bus to go to Harwell, there was no way you could get there that day. There was a bus that toured round all the places. It was amazingly isolated, and most people just didn't have cars. And I think myself what Paul said is probably true. I think Charles was a superbly good cytogeneticist, but I think all of his really major work was done on mice.

PSH. Yes.

PJ. I really do. In terms of mammalian work. I'm not sure what happened before that. He worked on plants and I don't know anything about that.

PSH. So when you got back to Edinburgh, this must be now coming up to the end of 1958 or something.

PJ. Now the beginning of 1958 I think. Yes the beginning I believe.

PSH. And what were you put on to do when . . .

PJ. Exactly what my job had been. I had to now look at marrow chromosomes in the cases of leukaemia that were radiation induced versus those that weren't radiation induced. Now in retrospect it's easy to stop and think about it but I knew nothing about this field whatsoever. A case that is radiation induced is rarer than hen's teeth. So I got up there and I think I practiced the technique OK on people with leukaemia, because, remember it is bone marrow all the time, and with people with leukaemia which was not radiation induced, and that was the majority. And at that time, this MRC Group was situated right in the radiotherapy department and had its own beds. So we had patients, we had everything we needed to do this and from that point of view it was very well set up. So we had our own three beds and we could get marrow with facility and easily. So I developed the technique and I felt a little bit comfortable that I could probably do the technique and I could look at chromosomes of marrow, but nobody really wanted me to look at the chromosomes of ordinary leukaemia; I was supposed to compare them

with these radiation induced leukaemias, which were few and far between and see if there was anything significant. What we were there to look at was radiation effects, which of course was Michael Court Brown's, one of his big research interests.

PSH. So your leukaemia series was sort of built up as a control series.

PJ. Exactly, and you can't go on looking at controls and not looking at any, so to speak, subjects, research subjects. So I was getting bored stiff because there wasn't any of this project I was supposed to do, I was offered a Klinefelter patient by a very nice, far-sighted endocrinologist called John Strong.

PSH. Yes.

PJ. So I thought well I might as well do this. I had done one in Harwell, which was the one that was published and it was just a kind of practice one, and that was a funny story in itself. So John Strong said alright, would you be interested and I said "Sure. Why not". So he got me marrow and I always used to go along. This was one of my jobs and I discovered very early on, and all of this marrow astonishingly enough was taken from the sternum, which I understand carries a small but measurable risk, while taking it from the iliac crest doesn't. Nonetheless it was. And the first thing I discovered, we had to go there and stand and get the marrow straight into the relevant culture media. And the first thing I discovered was, that the technique had a funny effect on people. There is a very significant proportion, about 50% of people just pass out cold, and it is something to do with seeing a needle stuck in a sternum. It really is.

PSH. Well it's not very nice.

PJ. It's not very nice . Luckily I was in the 50% it had no effect. I just used to catch people. Anyway, on we went and I looked at the Klinefelter and the preparations were really very bad. Even though I had practiced. And I thought there were 47 chromosomes and there were two Xs and a Y, and remember we couldn't separately identify any of them, couldn't even tell the Y. But I did and I couldn't believe it. And this was not the perceived wisdom of what Klinefelters were in that day and age. There were two kinds of Klinefelters, called chromatin positive and chromatin negative and nobody had clearly made any distinction between them except in their sex chromatin body; and everybody assumed that they were sex-reversed females, so everybody expected them to be XX and I thought I could see 47 chromosomes. And I thought I could see something that was compatible with being a Y, which means there was 5 acrocentrics rather than 4. So I thought, well that's very funny. So anyway I didn't know. So I went on holiday and I asked my technician to prepare a tray of slides with the Klinefelter in it and lots of other things in it too, and I would come back and score them blind, and I did. I came back from my holiday and I scored them blind and I thought, well that's funny because there seemed to be two that seemed to have 47 chromosomes, not just one as I had expected. So I said to her, I've got two that I really think might have 47 chromosomes and she broke into a big grin, because she had put two from the Klinefelter's in the tray. So I thought, well

that may be true. So that's it. So we told Michael Court Brown, who saw the significance of it. We didn't. I mean I was 22 years old or something and I knew nothing about how Y wasn't supposed to do anything, because we were all supposed to be like Drosophila and it didn't have any effect whatsoever on sex, and he seemed to think it was very important and so I wrote and I remember it clearly. He said well you had better go and write it up. Now while I had published one paper before, I have to say, most of it was written by Mick Callan. It was based on my work, but he wrote it. So I went off and wrote this paper, with great difficulty I have to say, and brought it back and showed it to Michael Court Brown and I have never forgotten that. He tore it in shreds and I stood there nearly in tears, and I said "But it is the first paper I have ever written" and he sort of held it like this. And he said, that is exactly what it looks like. Anyway, so I had another go with his help and that was it. So we published that paper and this was the famous Jacobs and Strong.

PSH. And this was very early 1959.

PJ. We could have done it in '58 but I didn't bother. I didn't honestly, I was so naïve. I was so young, it just seemed to me that was interesting, but I didn't realise how interesting it was. But I bless that naivety if you like, because I had no idea that this wasn't supposed to be possible.

PSH. Can I ask Pat, had you had any contact at this point with Malcolm Ferguson-Smith over in Glasgow.

PJ. I don't think so, because I wasn't there to study these things. I was there to study leukaemias. And I believe I didn't. I had contact of course with him later on, when my leukaemic remit sort of fell by the wayside, it never did completely, but you know, it became obvious that the original thing I was supposed to do was very impracticable.

PSH. Because in a way Malcolm was quite isolated over in Glasgow and had been beavering away on the sex chromatin and things, but it's interesting to me to see how the different strands of work either do or don't come together.

PJ. But he knew a lot about Klinefelter's while I knew nothing beyond what the gentleman I studied looked like who was ascertained because of his endocrinological problems.

PSH. One of the things which I find absolutely fascinating, both reading and talking to people, is that everything happened in this tremendous rush in the first part around 1959, and there was Klinefelter's and Turners, and Down's and everything kind of happened and, did you already know, when you were doing your Klinefelter work, about Lejeune's Down's work?

PJ. No. I didn't know about Lejeune's at all and I independently discovered the additional chromosome in Down's

PSH. I was going to ask you about that.

PJ. Why did we look at Down's? Because they had an increased risk of leukaemia. That was the only reason we looked at them. I had nobody in my

milieu who was interested in congenital abnormalities or who was interested in genetics per se. They were interested in leukaemia. We went to a local institute for the mentally retarded and we explained what we wanted to do. They said yes, we could. Shows you how things were done in those days, because remember we were looking at bone marrow.

PSH. Yes.

PJ. We went, this was in 1959 or 1958, and we went and we got bone marrow from, I think it was something like 20, anyway it was a not inconsiderable number of patients who the institution told us were Down's. We came back and we looked at the chromosomes and most, but by no means all, I decided, had an extra chromosome - 47. This was true whether they were males or females, but all of them didn't. So there was, let's see out of those 20, something like 6 that didn't. So we went back to the institution and we said "well, most of them seem to have an extra chromosome but they don't all. And what can this mean. And have they all got Down's syndrome". And the institution assured us that they did. So I thought, well I wonder. So we thought the only thing we can do is get an expert on Down's to come up and look at them blind. So we got Penrose to come up. So Lionel Penrose came all the way from London, and we all went out to this Institution and I was there too just to look. These 20 patients we looked at or whatever number, all paraded in front of Lionel and it was an education to me to see how he dealt with these patients. He was my hero ever since that day. He almost identified with them, and the way they responded to him. It was great and he went right through, and he told us which ones were Down's, and which ones were Down's plus something else, and which ones didn't have Down's. He said it so nicely that even the people in the institution were willing to accept it. And of course he got it completely right, and all the ones he said were Down's we'd got the extra chromosome in, and the ones that we hadn't found the extra chromosome in he had absolutely no doubt, didn't have Down's.

PSH. So there wasn't a translocation Down's in that group?

PJ. None. Not a single translocation Down's in that group. We might have expected to find one, but we didn't, because we certainly were by no means the first to describe that. That was done by other people. So that was that, but by that time all this had dragged on you know, one thing and another. Then we knew about, and I can't remember how we knew about Lejeune. We hadn't actually seen the publication, but we did know. But it was interesting because we came to it through the leukaemic angle.

PSH. And then, I mean, you published a lot of papers on chromosome abnormalities in Down's, in relation to leukaemia, partly related to Down's and the connection with leukaemia. Am I right, that at that time, there was absolutely no way of telling the difference between chromosomes 21 or 22, or did you have some inkling that . . .

PJ. None at all. If you have 5 things, let me assure you, when you classify them, you see two that definitely look bigger, two that definitely look smaller and one in the middle and that's how you always split them up. We hadn't got the faintest idea. And somebody must have said they thought it was 21 and it

wasn't. But it was really the smallest one, but this was because of this problem that you always have, if you group any things that you don't really know the difference, you do two big, two small and one in the middle.

PSH. You were also then involved with the extra chromosome fragment in chronic myeloid. Was that known as a finding at all before your work or was again, that something that came quite independently from yourself?

PJ. Again independently. The first people that published on that were Nowell and Hungerford and they had the bad luck. It was no more than bad luck to look at two male patients.

PSH. Yes, Y's

PJ. And they thought they were Ys you see, they thought they were small Ys. By that time I think we had looked at that and wondered. So we looked at some that were also males next to females. And immediately, saw that it was a small chromosome in all of them. So it couldn't possibly be the Y, and we published independently and it was published after Nowell and Hungerford who undoubtedly made the first observations, but it was unfortunate that their two patients were males. It was a little bit of bad luck but I think we again did it independently.

PSH. And then, presumably at that time, everybody thought the chromosome abnormality in chronic myeloid was somehow the same or related to the changes in Down's. Is that it?

PJ. Some people thought that, but some people knew it wasn't.

PSH. What did you think?

PJ I knew it wasn't because I was working with haematologists and they said, but that's not the kind of leukaemia Down's get. Just that simple, because they, you see the other people thought "Oh Down's. Leukaemia. They've got this chromosome'. And it immediately became obvious. Down's as you know get

PSH. Acute leukaemia

PJ. Acute leukaemia. Now it turns out to be a very specific one involving the megakaryocytes by and large, but it is not chronic myeloid leukaemia.

PSH. That's fascinating.

PJ. So we realised that when a lot of people didn't. But it was only because you have got to see people in the context in which they are in, and I was in a haematological context.

PSH. Can I bring you on a year or so to the whole population studies, which you were very much involved with. Am I right that these were started also as a kind of control in terms of radiation studies.

PJ. Yes. I can't remember how we came to do that. We were never involved in what I call clinical genetics because we didn't, again, have that kind of background. We had people who did huge population studies. Michael Court Brown, who was an epidemiologist and Albert Baikie was our haematologist. I mean it was a very small group and these were our two areas of expertise. We didn't have expertise in anything that could be called dysmorphology or knowing anything about those kind of things or for that matter in genetics. So we started doing population studies because we needed them as a kind of control, you are right. And at that time I started to be fairly horrified by the amount of rubbish that was being published – maybe a little bit later than that - on cytogenetics. Where every polymorphism was thought to be, you know, like a large heterochromatic block on chromosome 9 which is my bête noir, was associated with more clinical conditions than any of us have had hot dinners. Nobody ever bothered looking at normal people. Now that wasn't possible when we were doing bone marrow. When I look back on what we did on bone marrow I'm fairly horrified. But it immediately became possible when you could do blood. Blood opened up this whole thing.

PSH. That was 1960 or thereabouts.

PJ. 1960. It was published by Moorehead and his colleagues in Philadelphia. I brought the blood culture to Europe. It is a trivially easy technique, but you know at the beginning we thought we needed 20 cc of blood. Now 20 cc of blood from an adult isn't a problem. It was a nightmare from babies. People had to go through their heads to get this 20 cc of blood that we insisted on. It was absurd. Isn't it absurd.? But we did.

PSH. You wouldn't have got it through any ethics committees these days.

PJ. Do you think we'd have got through an ethics committee taking bone marrow from Down's syndrome patients? You know, of course not. The thing was absurd, but I have to tell you that's what we did. I took the blood culture technique, lock, stock and barrel, from Mellman and the people who developed it in Philadelphia, Noel, Hungerford, Mellman, these people who themselves, to their credit, got there by actually following word for word the person who first did it, whose name just for a moment escapes me. He was a haematologist from Oregon, who actually first did the blood culture technique and nobody had ever been able to duplicate what he did. Nobody had used the same red cell agglutinins as he did, because they thought that red cell agglutinin was just used for getting rid of the red cells, which it was. But it was a very obscure one he'd used, and it was this phytohemagglutinin and nobody else ever used for that. They all used whatever, I can't remember what it's called now, the red cell agglutinator that every haematology lab had, and nobody had never been able to get the dividing cells that he had. And what Mellman, and the rest of them did in Philadelphia was actually go back and duplicate his technique, word for word, and that's how they rediscovered, and they were the first people to say that, if you read their papers.

The blood culture technique, and what really mattered was phytohemagglutinin and nobody knew why it mattered. Not terribly sure that they still do, and that's a very good historical point and that taught me something else. It taught me that if you are going to follow somebody's

technique you had better follow it, absolutely meticulously. Once you had got it to work you could start changing things, but you can't change them first of all, no matter how trivial you think one ingredient is as that's what everybody thought. Phytohemagglutinin. What was that, you couldn't get it. So we actually made our own. We went out and just bought a pound of kidney beans at the grocers and made our own phytohemagglutinin. With that we then very easily set up the blood culture. Everybody else said they couldn't do it. We used to run courses and we had people from all over Europe come to our twice yearly courses to learn how to do the blood culture, which wasn't our blood culture at all. And we eventually got, phytohemagglutinin wasn't difficult to make but it was messy. In the end some pharmaceutical company made it and must have made a bomb. We were the people who tested it for them and we got it free because we did all the testing, the quality control, and we just used to set up the cultures and told them whether it was any good or not.

PSH. Am I right then, the studies of whole populations were what led you to your estimates of frequency of chromosome abnormalities in the population, because really nobody had a clue before then how common these things were.

PJ. Absolutely not, and I mean it just became obvious. They were astonishingly common. It was amazing. You have to remember that about 5 years before then, nobody thought that people could live with these kind of abnormalities, and then we have all the structural abnormalities which as you know, are orders of magnitude more than you see in any other population of any other organism that has been looked at in the world. And I don't think anybody knows why that is. If you stop and think about the translocations, the inversions etc that you could see just looking down a microscope, which is all we had then, microscopes weren't that great and the techniques weren't that great either. So we must only have picked up a very small proportion of what would now be visible using good banding techniques.

PSH. At what point did the XYY study come in, because you had studied patients from mental handicap institutions for Down's, but presumably that wasn't a total survey, so how did one kind of lead to the next?

Pat Oh, we studied a lot of patients in mental retarded institutions using sex chromatin. We were very, very fortunate to have a superbly good pathologist called Neil McLean in the Western General Hospital and he got very interested in doing our sex chromatin for us and he did that and he was terribly good. And so we did huge surveys of people for sex chromatin abnormalities. And of course by that time we were also interested in triple X women, the first one of which we stumbled upon while looking at patients who had presented in local clinics for menstrual abnormalities. So the first triple X patient actually had that. She had premature ovarian failure and that was, and she had two sex chromatin bodies and that was thanks to Neil McLean's very astute observation. And that was the first patient who had two sex chromatin bodies and it was realised soon after that they must represent two X chromosomes.

PSH. I had forgotten that.

PJ. So it was interesting. Anyway where was I?

PSH. XYY.

PJ. So we did mentally retarded institutions, we did sex chromatin first and then we went back and looked at the chromosomes. So when we looked at the chromosomes we had a very clear idea of how many of these population studies were XXY or XXYY and there were vanishingly few of the latter category. But then I went to a meeting somewhere or other, and I sat next to somebody called Mike Creasy who had done a survey of retarded patients in special hospitals, as they were called. You know, these are where they had been very naughty and gone into these hospitals for being very naughty, but considered not to be responsible for their actions, so they were either mentally retarded or with a serious mental disease. And amongst the mentally retarded he found 2% who were chromatin positive. Now that is 1% more than you get in ordinary mentally retarded institutions. Now that, whether on the basis of the figures that was significant, but there was a very solid 1% of male patients in institutions for the mentally retarded were chromatin positive, and he was finding 2. Well it doesn't sound a big deal. Not at all. But when he went back and looked at the chromosomes, a very significant proportion were XXYY. A far greater proportion than you would get in ordinary retarded institutions, and I said that to him. That's far too many XXYYs. I am sure it is. I can only remember seeing one in all the patients we've done and he said "No it's just chance". I thought, I don't think it is. I went back and I looked up our data to be sure what I was saying was right, and I found my one and only XXYY was also held under conditions of high security, but in an ordinary institution for the retarded. So I thought well that's very funny isn't it? Maybe the Y is affecting their behaviour. So I thought, well that's quite likely isn't it? If you stop and think about it 98% of the prison population are males. So you can't say the Y has got nothing to do with behaviour, because why would you get this astounding figure, which is incontrovertible.

PSH. Always been the main risk factor, being male.

PJ. Exactly, so I went back I told Michael Court Brown. He said "Well that's very interesting. Let's see if we can go and look at special hospitals". Only one in Scotland and we got permission to do this from the Scottish Office, and we went back and we looked at these male inmates, of which there were several hundred, I think 3 or 4 hundred, I can't remember, and 15 females were in that same institution. That was the ratio there. And they try to tell me the Y has got nothing to do with it. Absurd. And we were not allowed to see the patients, this was part of the thing, and for reasons I simply don't know. We used to go along, the medical service for these patients was done by the local GP. He was a lovely man, and he would be in one room with the patients, and we were next door with our bottles. We would give him one and he would bring us back the thing and a tiny piece of paper, that size, that had a number, a coded number on it, the patient's date of birth and for no reason I can think of, the patient's height. We didn't want the patient's height. We never asked for it, but it was there. We took these back and we looked at them in the lab. We only got about 10 a week. Week two, and I have never

forgotten this, my technician who had been with me right from the beginning . . .

PSH. Is that Muriel?

PJ. Muriel. Muriel Brunton. She flung open my door she said, “Well here we go” she says “we’ve either got an XYY or a 6 ft 4 Down’s syndrome patient”. Because of course we were still counting small chromosomes, pre-banding, but we could pick out the Y really, but she said that. And I thought that was marvellous, because remember we had a hypothesis that we would find these people there. That was our hypothesis, so I kept very calm and I said “Muriel, the first one doesn’t count, it’s the second one that counts. This could be chance”. And the next week we found another one.

PSH. That’s fascinating, so I’d not realised you had the height information to go with it.

PJ. Exactly at the beginning. And the next one was also over 6 ft. So straight away, on those first two. Why we got the height information, I still don’t know.

PSH. I genuinely can’t remember, did you put anything about the association with height in that first paper.

PJ. Yes. Yes we did. It was striking. If you looked at the people there who were over 6 feet it was something like 70% of them or some ridiculous number. Of course this is a squashed Scottish population in those days, when being over 6 ft was quite unusual shall we say.

PSH. Can I ask you Pat? You were in this ‘Effects of Radiation on Genetics Unit’, how was all this other work kind of tolerated? It must have required quite a broad vision when you were going off doing these things which would seem quite unrelated, to let you do that rather than say, no let’s just stick to the leukaemias.

PJ. Well for one thing, in those days, an MRC group or unit was set up under a director. Normally it was closed down at the end of the scientific lifetime of that director and that was it. So while he was there, everything that went on in that unit depended entirely on the director. Presumably, I suppose, he must have reported from time-to-time to Head Office what was going on. But it was so different. The MRC was so broad in those days, and of course nothing was said because this was exciting work and it must have been obvious, and you were in the care of a senior person from the MRC and it was the same person the whole 14 years I worked there. It was wonderful, he came up, and knew everything that was going on, presumably he took it back and the MRC didn’t object. Why would they, it wasn’t radiation research, but it was very good research I think and very interesting and the director didn’t mind, so really the direction of the unit changed and eventually they changed the name to ‘Population Cytogenetics Research Unit’.

PSH. Was that already at that point before Michael Court Brown died, that it had changed and enlarged

PJ. Oh long before. Yes. It changed its remit and enlarged. All of that happened before. So the MRC obviously had to agree with this, so they must have known what we were doing and they didn't mind. People were given so much freedom in those days. I presume they thought we were doing well, but I think everybody got much more freedom and we were all treated like adults.

PSH. Yes. Yes. What year was it you moved from Edinburgh?

PJ. '72.

PSH. And where was it in America that you went to first, was it straight to Hawaii or was there a stage in between.

PJ. I had a sabbatical year which the MRC, very unusually, paid for. They paid me to go on sabbatical for a year, which as you know, we don't do in this country and I went to California. I decided to change my organism and I went to work on Drosophila, and I had a lovely year working on Drosophila with Dan Lindsay for whom I had the highest regard. A superb man and I have even published a paper on Drosophila.

PSH. I saw it in the list.

PJ. Wasn't that tremendous. I think there were more researchers than there were flies in that, huge massive experiment that went on. And it was lovely. It was very nice for me, I needed it at that time. And then I came back, was that 1970? Probably not, '71. And then I came back and then I went to Hawaii in '72 and the reason I went to Hawaii permanently was, by that time I had met Newton and actually I had married him. And he was in Hawaii and I was still in Edinburgh and it wasn't working out very well.

PSH. No cheap flights .

PJ. No cheap flights in those days. And even if there were, the distance is horrific and the time change is worse. So I upped sticks and went to Hawaii, still doing human research. And I set up a research group in the Medical School and it was independent of Newton, because one of the little things I have in my life is that I think it's very bad, I think it's actually appalling, for people to work in the same place as their spouse. I think it's appalling for them and I think it's even worse for the people who work with them. Sometimes it can work out depending on the people, but not often.

PSH. Not easy.

PJ. But most of the time it doesn't, and I said one of my conditions for going to Hawaii was that I worked in a completely different set-up from Newton. And I did. I was in the Medical School and he was in the School of Biology. So we were completely physically and administratively separated, which was good.

PSH. Yes indeed.

PJ. And we always have been ever since. And that has been terribly difficult when you are looking as you know, two jobs for relatively senior people, and then say that you won't work in the same place, in the same department. Anyway, so that's what I did and then I had the loveliest time in Hawaii and that's when I went to work on spontaneous abortion. We haven't mentioned this and David Carr, who did this wonderful work, the first work on spontaneous abortion, often gets left out.

PSH. Yes.

PJ. If you are a cytogeneticist and you are used to doing, population studies which is what I had done, while you are astonished at the frequency of cytogenetic abnormalities in populations, but still they are not every second one. If you are interested in studying the population genetics of chromosome abnormalities, it was quite clear the thing to do was spontaneous abortions, and so for 5 years we did a survey of spontaneous abortion, which I have to tell you we have never written up properly, I always said I would do it when I retired. It was a good study, in Hawaii, and the incidence of chromosome abnormalities in spontaneous abortions is 50% and to suddenly find that every second preparation you looked at was abnormal, it was like I had died and gone to heaven. And it was a terrific experience, and we also did a very good, and never published, epidemiology study at the same time. And the great thing about that is we got all the epidemiological information, before anybody knew, if the person who had the spontaneous abortion was the 50% with the normal chromosomes or the 50% with the chromosome abnormality. So it was a superbly good, built-in-with-your-own-controls study. And that's what we have never published.

PSH. Am I right that you kept strong links in that area back with the folk in Edinburgh.

PJ. Oh yes, we have always kept strong links with Edinburgh.

PSH. Because I saw, looking at the papers, that there was a whole series of papers coming out in during the '70s involving you but also Edinburgh.

PJ. Yes, but a lot of that was work that I was wrapping up that I did in Edinburgh before I left. A lot of that was. Some of it was stuff that Newton helped me to analyse. Edinburgh data that he helped me to analyse in Hawaii, so that was mostly tidying because when I started in Hawaii it was with institutions for the mentally retarded. That was kind of my thing, and after that I went onto the spontaneous abortions. I found it very difficult. Well, I hadn't been used to writing grants, because we were privileged people if you remember in those days

PSH. MRC Units

PJ. MRC Units didn't write grants, unlike now when they are supposed to. So I had never written a grant before. So I wrote a grant to NIH and was horrified having to do this and horrified by the complexity and I didn't get it, so it was quite a long time before I could start. But the great thing about NIH grants is you can re-write them and re-write them and re-write them until in the end you

get the money I think, because people get tired of reading them. In those days. I'm not sure it's like that now. So I got money that way, because I had no money. I had no salary when I started. I had to get, as one did in America, get my own salary, but what I did have was a very nice lab. So that was that. So I had lots of time, since I had no money and I couldn't do any research, to write up all the stuff I hadn't written up in Edinburgh and I went back quite a lot. Back and forth.

PSH. Am I right that it was in these early Hawaii days that you started on X-linked mental retardation and then Fragile X?

PJ. I don't think it was the early, yes it was the Hawaii days definitely and I know how I got onto that, because I read these very interesting publications on this Fragile X. Not so much the first one, which I think I missed, the Herb Lubs one in the 60s wasn't it, but the ones from Australia, the Grant Sutherland ones. And I thought that's a very funny thing. I'm a cytogeneticist. I know about gaps on chromosomes. I remember what I learned at Mick Callan's knee kind of thing. I'll sort this out. Cold shock. That's what it is. So I started out just to sort out the fragile site, and of course it turned out to be not quite so easy as I had again naively thought, because I never sorted out what caused this fragile site, but it got me into X-linked mental retardation and at that time, I don't know how this came about but Ros Evans, Ros Evans as is but Ros Angel as was at that time, came to work with me from Australia in my lab. She was very friendly with Gill Turner, who used to come and stay with Ros in Honolulu, so I met Gill Turner, who was at that time was doctor X-linked mental retardation par excellence. So that was how it kind of came about and we did do these surveys using of course, as everybody did, the cytogenetic techniques and we were into surveys. I have always been into surveys. Never into single patients, perhaps until I came here. And that's how we got into Fragile X and it is still as you know, one of my main research interests.

PSH. Absolutely.

PJ. Love it.

PSH. When did you first meet Stephanie Sherman? Because you published quite a few early things together.

PJ. Stephanie Sherman, 'Sherman Paradox'. Oh yes, Stephanie came to Hawaii as Newton's post doc. So she worked with Newton. She never technically worked with me but we worked together, and that's how she got into it. She got into it because of us. She didn't bring it with her, as I recall. I'm sure I'm right. And so we published a lot together. We had loads and loads of fun doing that you know, and then we realised all these funny things. It was called the Sherman Paradox, the anticipation in this disease, and it was great and we had a lovely time. Then I got quite friendly with Jean Louis Mandel
through the Fragile X thing, and that's one of the lovely scientific contacts I have had in my life. So that's how that happened. So of course, the two things we did really in a big way when I was in Hawaii, where I think I was for 12 or 13 years, were Fragile X and spontaneous abortions. I was very happy.

PSH. And which year was it you moved from Hawaii.

PJ. First of all we went to New York City and that was in the very end of 1985. We moved to New York City because we decided Hawaii was isolated. Everybody says 'how could you move from Hawaii.' Well Hawaii is gorgeous, we had a lovely time there, but it is extremely isolated. And most people in this country have no idea how big the Pacific Ocean is, as far as I can see. They think the Pacific Ocean is the same size as the Atlantic and it isn't. It's over 2 ½ times bigger and Hawaii is right in the middle. It's the furthest place from a major land mass of anywhere in the World, except for Easter Island. We had to fly 5 hours before we got anywhere, and that was only California, so there you go. So we decided we needed a change, and it was isolated intellectually as well. Then we made the great mistake of our lives. We had to get two jobs, still won't work in the same Institution, and we did it in New York City and we hated it. We were there for two years, most of which was spent finding another job. Anyway but there were lovely things about New York City but both of us happened to hate working there and we are not city people. We should have known that before we went at our age, wouldn't you think? Anyway there were lots of good things. I mean I still find New York one of the best, most vibrant cities in the United States and I love going back to visit there, but to work there was a nightmare. I think the only people who can work in New York City are people who were born there. Quite different from the rest of us. So we worked there. I worked in Cornell and Newton worked in Sloane Kettering for two and a bit years and then we left on January 1st 1988. Very good day if you are changing jobs to do that. You never forget if you start on January 1st. We moved back here and I got the position of Director of a diagnostic lab, and I had never ever done any diagnostic work before, ever, and Newton started a cancer epidemiology unit. Genetic epidemiology unit in Southampton.

PSH. I was wondering what made you come here. I knew Marina Seabright very well and she laid fantastic foundations.

PJ. She decided I would come here.

PSH. I remember her saying that.

PJ. An amazing woman. I got this letter and I thought, me? Heading a diagnostic unit? I'm a researcher. I don't want to do that and I had never been anywhere near Salisbury. I didn't even know where it was. I knew it was in England, but I was very vague as to where it was. Anyway I was very unhappy in the States and I came back here, en route from some meeting or other in Germany, and it was the most beautiful, beautiful autumnal day, I have never forgotten it. And the spire was going up to heaven and it was just gorgeous and I thought, why am I in New York City. I could be in a place like this. And I mean, she not only talked me into it, but she really went a long way into fixing up Newton's job in Southampton. So what can I tell you. It was amazing. And I came here and one of the reasons I came here was not to run a diagnostic unit, which I think I am not very good at. It was because I suddenly realised that this very large, as it

was, diagnostic cytogenetic unit had never done, with all due respect, a day's research in its life. It had this huge amount of data, that had never been worked up, or even looked at really, and it was exactly the sort of data that I wanted at that time. Huge numbers of Klinefelter's, because now I was interested in looking at the origin. The actual parental origin. What caused chromosomes to go wrong, and for that you need a population of people in whom chromosomes have gone wrong.

PSH. It must have been a big wrench for both you and Newton though, leaving America. After all you had had the Allan award and I think you were about to be president of ASHG.

PJ. Not very many people know about that. Created such a furore. They asked me to be President which I thought was very kind of, I felt very honoured and flattered. And you see I thought well that's fine, and nobody knew I was moving. I was trying to move. Nobody knew. So I knew if you want to keep something secret you don't tell anybody. That's the only way to keep something quiet. And I knew the reactions there would be in both our institutions if they found this out. And I was right as it happened. So you tell nobody. And then I thought, well that's fine. I'll accept this, it was very nice of them to ask me. I feel very flattered. It will make no difference. If I am in Britain, I am closer to the scene of things, which was Washington where the main office was than I ever was in Hawaii. You know it is much closer. Britain is much closer to the east coast of the United States than Hawaii is, and that would have been perfectly alright. So I thought there's nothing to stop me being - I am a member of the society – to stop me being the President, even if I happen to go to Britain. And I hadn't decided yet, so I told nobody. And then they discovered. When it came out. And I said well, you know, I am still very happy to be – I pointed out I was closer to America than I ever was in Hawaii and they nearly had a fit. I couldn't, everybody said, you won't be able to contact your senators because you won't have one and it never occurred to me that the President of the American Society would ever involve contacting senators for various things and they were horrified and they had to have another election. This is what happened and it was very embarrassing and it cost them a lot of money, because they had to then circulate all the membership. And I felt so embarrassed. But I didn't really think I had done anything wrong.

PSH. And after all

PJ. But they obviously did.

PSH. It is a society that covers Canada and Mexico as well.

PJ. Well, I think if I had been in Canada or Mexico I would have been alright, but it was Britain.

PSH. You wouldn't have had senators.

PJ. I wouldn't have had senators. Exactly. But anyway it was funny, so you are right. I then kept very quiet and sort of crept about and didn't tell anybody,

but I felt I had done something terribly wrong, inadvertently because I didn't feel it was wrong at the time.

PSH. Coming back now, as you did, it was more or less at the time when you had started to link molecular with cytogenetic techniques and . . .

PJ. That's right yes. We did that in New York City.

PSH. And the Fragile X must be the best example of that I would guess.

PJ. Well I don't think I had any credit whatsoever for doing that, the people who did that as you now, were certainly nothing to do with me, but I was just so excited when I discovered what was the basis of this thing. This was the first, as you know, tri-nucleotide repeat disease.

PSH. In terms of the pre-mutations and the effects there, now you have been very directly involved.

PJ. Oh yes very. I mean the Sherman Paradox and all the stuff.

PSH. And the premature ovarian failure and now the other effects in males.

PJ. Yes it's astonishing isn't it? Well that is still, we have got two major things that I am still doing on Fragile X. One, you may remember, we did a survey of Wessex, always seem to be doing surveys, of all the Wessex people with so-called special educational needs. This was the first really big molecular study to find out what the frequency of the disease was, because as you know it was wrongly hyped up on the basis of cytogenetics.

PSH. Chromosomes. Yes.

PJ. Exactly. And we did this, and we found to our utter astonishment something we didn't expect to find, which was that, we had a control population of course, that the number of what we call intermediate alleles that was between 40 and 60 was significantly higher in these special educational needs boys than our control. So we thought that's interesting. And we found that when we analysed the first half of the population. So we thought, well we can check this by analysing the second half of the population you know, that we haven't done yet, because it was a five year study, and see if we can repeat it and we did. So we found it both in the first half. So in a sense we had repeated our own results, but nobody else has ever repeated them. We thought well, what does special educational needs mean. We didn't know. The schools chose them, so it was sloppy and we said if you are in any doubt include them, please include them because we are also interested now in Frax E and we all know, if that has an effect at all, it is a very much lesser effect on intellectual development. So we wanted to, if in doubt include them and we did that. So it was the schools who chose them. So God knows and I should think it was different. We know it was different from all over the region. So it doesn't necessarily surprise us that other people can't repeat it, because I doubt if we could repeat it, because we don't really know what the population was but, however, it was a demonstrable effect and we knew nothing. The schools wouldn't let us go back and look at the patients. So we

had to do it the other way round and that is what we are in the middle of now. We had to find a population that was very well documented phenotypically. We would then look at the size of the Frax A and E in this.

PSH. Yes.

PJ. So we'd have the phenotype, so we had to go out and get the genotype. What we had before was the genotype and no phenotype. And we have done that now. We have just finished doing the ALSPAC boys; we are only doing boys, because if we can't figure this out in boys we'll never sort it out.

PSH. This is the Bristol cohort.

PJ. The Bristol cohort of all children born in a year and a half, whenever it was, so they are about 10 or 11 now. So we have been doing that for 5 years.

PSH. That is very interesting.

PJ. And we have now finished. We finished about 4 months ago doing this. So blind you can't believe it. All we got was plates of DNA and anyway, it doesn't matter. So we are in the middle of sorting it out now and Newton and a girl called Sarah Ennis, who has been a great joy in my life, who was a PhD student, has now got her PhD and is extraordinarily good, are analysing the data now. So they have got the data from ALSPAC and the data from us and it is very complex.

PSH. I won't ask about it Pat.

PJ. No. It hasn't been analysed yet.

PSH. I think we, like I was saying to Paul Polani, I have probably started to wear you out, but I mean there are other things we haven't talked about, the origin of the Down's chromosome, which I could have asked about. I can't resist though asking about Barra. You still go there don't you?

PJ. Yes.

PSH. When did you first get your place on Barra?

PJ. I did it when I was in Hawaii, and everybody thought I was mental, including me. How could I live in Hawaii and purchase a property - from one remote island to another remote island that's on the other side of the world. I have been going to Barra for a lot of years. I love the place and it's extremely difficult to buy a property on it and I was very friendly with the doctor in Barra at that time, and he told me that this particular property that I now have was coming up for sale and was I interested. And it is, in my biased opinion, the most beautiful property on the island. It was much bigger than anything I intended, which I wanted what we call in Scotland a but and ben, you know two rooms and that was it. And it is the most gorgeous situation and to cut a long story short, I've got it.

PSH. I have seen it. I have cycled round Barra with my camera.

PJ. Oh that's right. I had forgotten that. Well you will have to then agree with my . . .

PSH. I do. It's a beautiful island.

PJ. You see this postcard which is wrongly . . . That there is the corner of my garden. That is my garden post.

PSH. My!

PJ. That's the post at the corner of my garden. That's my view.

PSH. Pat, that is wonderful and I am going to finish there. Thank you very much indeed.

PJ. Thank you, I have quite enjoyed it.

(End of recording)