Kay Davies

Personal Details

Name	Kay Davies
Dates	Born 1951
Place of Birth	Stourbridge, UK
Main work places	Oxford, London
Principal field of work	Human Molecular Genetics

Short biography

After studying biochemistry at Oxford University and in Paris, she joined the lab of Bob Williamson in London, developing molecular research on Duchenne muscular dystrophy and other genetic disorders that she has continued in both Oxford and London. She is now head of the Oxford Centre for Gene Function.

Interview

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INTERVIEW WITH PROFESSOR KAY DAVIES, 22/02/2011

I = Interviewer (Peter Harper)

D = Kay Davies

I It's Tuesday, 22 February, 2011, and I'm talking with Professor Kay Davies in her office at Oxford Centre for Gene Function

D Henry Wellcome Building of Gene Function

I Henry Wellcome Building of Gene Function. Kay, can I start off very simply and ask where were you born?

D I was born in the West Midlands, in a town called Stourbridge, which is about 5 miles from Kidderminster.

I And did you come from a family with scientific or medical background at all?

D No; my father was a tool maker in British Leyland, at Longbridge; and my mother didn't work when we were small, and then had a part time job taking people round the Stuart Crystal Glass Factory, so that she could be home for us in the evening when we came home from school..

I What do you reckon it was that took you in the direction of science?

D Well, in retrospect, I think as I've grown older I've realised, I was very good at Maths, , and I really inherited that from my father. And he hid that pretty well, but yes, it came from him.

I And was there any particular point that decided you to go in the direction of chemistry, because that was what you did your undergraduate degree in, chemistry, wasn't it?

D No, but I think I was always biologically biased, and that again is because my mother is a mad gardener; right down to the Latin names of plants and has a huge interest in biology. But I wasn't allowed to do biology at school, because the way the curriculum was structured, you either had to do biology or Latin; and if you didn't do Latin, you couldn't get into Oxbridge. And so I had to do Latin; I didn't want to do Latin, but they made me do Latin in my last year before O levels, as they were then called. So I then had to drop biology.

I Right. Then am I right in that you came here to Somerville College to do chemistry?

D Yes, yes. I was best at Maths but I didn't want to do Maths as a further degree. I couldn't do biology because I didn't have biology at A level, and I thought the next best thing was to do something like chemistry because that might give me a good grounding to do biology later on.

I Right. Was Somerville an all women's college then? How do you feel about most of the, Oxford and most other colleges, having abandoned being all women, and sort of gone over? What do you think about it?

D I think overall it's been very good. I think initially it was quite difficult because some of the male fellows in women's colleges found it quite difficult and vice versa. But in fact overall I think it's been enriching. Yes, I think it has.

I You don't think it's been perhaps good for the men but bad for the women?

D No, I don't. I think the general feedback is that it's been a good thing overall.

I Now, your degree was chemistry: did you have the chance in that degree to do a fair bit of

biochemistry?

D I was certainly pushed in that direction. I was very lucky to have a tutor called Jo Peach at Somerville who was a bioorganic chemist, and she spotted right away that I was interested in the biological aspects of the subject, rather than the physical chemistry, and therefore she encouraged me to do more and more of that. And you could do options and so I did the biological chemistry options. And then of course the final year of the chemistry degree is one year's research and so she encouraged me to do that in biochemistry, and that was the real turning point because, you know, I never looked back after that.

I Remind me, oh, I've got it here: what did you choose for the topic of that research year?

D I did it on the structure of chromatin. That was before the nucleosome was discovered, so we were doing chromatin preps in collaboration with people in Searle, just down the road in High Wycombe in fact. They were doing the x-ray analyses of some of the things we were interested in.

I Was this purely, well, I say purely biochemical; it wasn't microscopical at all in terms of chromosome structure in any way?

D No it wasn't; it had nothing to do with genetics. So at that stage, you know, I was not really aware of genetics. I was aware of cell biology but not genetics.

I After your undergraduate degree, did you go straight on a do a DPhil?

D Yes, I did.

I And again, what was the main area of -

D Well, fortunately, my supervisor, the late Ian Walker, tried to persuade me to do a DPhil and I thought that it would not be a good thing for me to do a doctorate because I would not be able to follow my husband around; so I went and applied for a DipEd (teaching training course), as it was called. I went to the DipEd interview and a very kind person interviewed me and I sadly can't remember his name. He said, "Kay, first what you need to do is you need to do a PhD ; and then come back and do a DipEd, because you'll always regret not doing a research degree." So I thought about that for a bit and Ian had some funding so I stayed on to do a DPhil and that turned out to be extremely fortunate because I enjoyed it so much; and I never went back to teaching.

I And this was still in the chromatin field?

D No, not directly chromatin structure. It was looking at RNA polymerase; transcriptional activity in relation to chromatin structure.

I Did you feel that, at that point, you were kind of into molecular biology, or wasn't there such a divide between molecular biology and the biochemistry as there had been at least in some places?

D Well, George Brownlee, who had just come to Oxford, recruited by Rodney Porter, was in the floor below, so they were beginning to do gene cloning, but that was preparing your own enzymes to do it, and so it didn't really touch our group at all. So I never did any molecular cloning. So in fact when we moved to France, I was determined to go to a lab that would teach me how to prepare proteins, and teach me how to clone; which is why I chose a lab outside Paris which clones yeast RNA polymerase genes, because I could do both.

I Right, because I was going to ask you then about the move to France. Was this specifically, so to speak, for you, or was it for your husband's career as well.

D No, in fact Steve went to France a year before me, and I actually had to write a letter [laughs] to Wolfson College to say I wouldn't follow him, in order to get the JRF; the junior research fellowship [laughs] which wouldn't have been allowed now, of course. That was done in good

faith. I then moved to Paris when Steve settled in his chemistry lab and I decided then that I would try and learn some cloning and purification of proteins, because that was the gap I had in my knowledge; that was the direction in which the field was going.

I How did you find the time in France?

D I loved every minute of it. Paris is just a lovely city and everyone was so collaborative. I mean, you could go into the Pasteur and Margaret Buckingham, who used to be in Oxford and I knew her vaguely, introduced me to the people in Pasteur who could prepare DNA ligase, and EcoR1, the restriction enzymes. So if you had those key enzymes, you could start doing your own cloning. And so it was very much a spirit of working together, which I really enjoyed, let alone Paris being a beautiful city with the art and the music, so I really enjoyed it.

I You weren't stuck on the outskirts too much?

D Well, we lived in the outskirts but those were the days when you could park. So you could drive your car into Paris in 20 minutes and park on the pavement and leave the car. Of course you can't do that anymore so it was a completely different experience.

I And then I saw, well you've got quite a few publications and that was really where you were doing the RNA polymerases.

D That's right; yes.

I Now, what made you then come back and particularly end up at St. Mary's?

D Well, because actually Bob Williamson was doing a sabbatical in Margaret Buckingham's lab at the time and I was just beginning to think what this cloning could do. And that was the same time that Walter Bodmer and Ellen Solomon published their paper and Y.W. Kan published his Sickle Cell Anaemia diagnosis using DNA probes, followed by the paper by Botstein et al. My husband had a lectureship in chemistry at Oxford and I didn't really want to come back to Oxford straight away; there weren't the opportunities for me. So I felt that if I went to London and learnt some genetics, I might be able to see what I could do. And I'd always wanted to work adjacent to clinicians trying to do something with disease. I was quite motivated by that; I didn't really want to just do basic science, and that particular post doc fellowship gave me the opportunity.

I Yes, this is 1979 to 80?

D It was 1980 when I came back.

I Which was really when everything started to happen, wasn't it, in terms of human molecular genetics. Am I right that the specific project you were involved with at the beginning was the CF work?

D Yes, I was employed as a CF post doctoral fellow, but in fact from the start Bob had the foresight to see that you couldn't do CF because you didn't know what chromosome it was on; so it was Bob that set up the collaboration with you; and it was Bob that had the foresight to think, "You've got to purify X chromosomes." So he said, you know, "Kay, you've got to purify X chromosomes; go and see Brian Young in Glasgow." And so that's how that collaboration came up.

I I was wondering that, and I suppose Bob having been in Glasgow would have known Brian Young.

D Exactly.

I Did you move very rapidly across from CF to Duchenne? Because I remember when you first appeared in Bob's lab and I'd rather forgotten that you were involved with CF.

D I almost didn't do any work on CF. We immediately persuaded the CF Foundation, CF Trust as

it was, that we could use DMD as a model for CF; and so we did.

I Yes. Remind me: what was the very first, before you did the chromosome sorting, what was the very first DNA library that you used?

D I don't think we made any library before the X chromosome library.

I You weren't working with the Maniatis library or anything like that.

D We might have done to get new RFLPs for C3; things with myotonic dystrophy; the early markers. But no, I hadn't made a library, nor had I used one.

I So tell me a bit about the link up with Glasgow, because I remember being at one removed from that, and you'd be sort of going up there and coming down, and it was all very exciting. Tell me a bit about it.

D Well, Bryan was an expert, as you know, of coming up with this profile of this 4X cell line; and he was very interested in the Philadelphia chromosome which is chromosome 22, and the same cell line very nicely separated chromosome 21 from 22, that's at the smaller end of the spectrum. And then because it was a 4X peak, we could easily look at the shoulder next to chromosome 7 and 8 in size to isolate the X chromosomes. We used to go up to Glasgow regularly and sit all night, you know, adjusting the cathode ray oscilloscope to make sure the chromosomes all went down the tubes in the right order. So quite different from the automated way of doing it today..

I [laughs] Yes.

D We didn't know whether we'd be able to clone such a small amount of material, so there were quite a lot of false starts where Bryan would send us some material and we'd try and clone it, but we couldn't get enough material to get it to go into the phage. And eventually, of course, we did, but it was very hard for the first year; and Jo Murray was there helping us do it. Yes.

I I seem to remember the very first probe that appeared was that the one that Marian Hill was involved with? It wasn't near Duchenne, but I can't even remember where it was in the end -

D I can't remember its name either. But it was again a proof of principle; it's one probe that you could isolate and with somatic cell hybrids you could identify that it was uniquely on the X chromosome. Yes.

I And then after that there was RC8, which I mean, looking back on it I'm really rather amazed that so much came out of that, because it wasn't exactly a very easy probe, was it?

D No, because it had lots of repeated sequences in it and we weren't clever enough in those days to work out how to get rid of that repetitive signal. So it was quite difficult to use, yes. It was also quite difficult to prepare those phages in those days in very large quantities.

I Yes. I mean that was a very exciting time and it, for me seeing it as a bit of a bystander and contributing in a small way, it was pretty amazing. Do you think you realised at the time just how important it was?

D I didn't, but I think you know, interacting with you, and it's not because you're just sitting there, I mean you did remind us about how important it could be; because you had the same vision as Bob about how if you got a marker that was even a little bit close, you could get the proof of principle of an RFLP being able to say where the gene was. Okay, it wasn't close enough for accurate prenatal diagnosis, but it was certainly accurate enough to be the first opportunity where an RFLP was linked to an unknown location, although we knew it was on the X chromosome. And it was good enough to show that Becker was allelic with Duchenne. And that was also the second important result that came out of that.

I I guess I was pretty naïve about it; I think Bob was too. It was probably a good thing. I always felt you were the kind of fairly hard headed one that made sure that things actually worked, rather than just… I mean, you got enthusiastic as well, but you didn't just get enthusiastic.

D No, no, no, because I was fairly obsessive about getting… because I had to work at the coal face, on the bench. [laughs] And of course it was also fortunate that Peter Pearson liked to play squash with Bob, so he came through with the probe 754, so we were able to go on and do more on that. But you're right, the first proof of principle was RC8. So that was a turning point.

I Yes. I remember one thing at one time when I was talking with both you and Bob and I saw that there were unambiguously two bands in a female heterozygote; and saying, you know, "look there are two bands." And neither of you were terribly impressed by that -

D [laughs]

I - but it was for me, because every test that was protein or something else based, on X linked carriers had always failed to pick up a proportion of them because of X inactivation. And to see this, but I remember both of you said, "Well, obviously there are two bands because it's DNA, not protein."

D But it was particularly important for that very reason, of course, because there wasn't any carrier detection at all; actually there wasn't any prenatal diagnosis. So it was very important for Duchenne; that particular moment.

I Now you've stuck with Duchenne over a long time. I mean, would you like to just give me an idea thinking over the subsequent years, which areas of the Duchenne work do you think have really been both exciting and most important.

D I think the first one was the characterisation of the deletions, and it was having a lot of those patients from yourself and the late Sarah Bundey, and just… I remember thinking, "This is going to be easy. You'll be able to predict severity: the most severely affected phenotypes will be this; and the milder affected patients will be this; and Tony Monaco came out with his reading frame theory, and we thought that would be simple, and it wasn't. And I remember identifying that patient with the large deletion; there he was age 43, he could still have walked up a cliff, and I still tell that story today, and he had half his gene missing. And that was a moment because his gene is really the basis of all these gene therapy protocols now. I mean, I didn't invent his gene, but it was that collaboration between the clinical geneticist and the basic biologist that said, "Well, okay, you can take 50% of this gene away; you can put it into an AAV Vector, and you can tease it around a little bit more, and you can get mini genes they use today; and now we're having gene therapy trials, based on his gene.

I And I right that that was a patient of Sarah Bundey?

D Yes it was. Yes.

I I thought it was.

D And she wrote to us and she said… I've still got the letter… "I'm sure this patient, he's got a slightly abnormal presentation but I'm sure he's just got a little deletion" is what she wrote. [laughter]

I She must have been surprised.

D Yes, she was.

I That's the sort of letter, by the way, you want to save it for posterity; and don't -

D I know exactly where it is; it's in a filing cabinet in anatomy building.

I Be careful nobody tidies things up. Tell me a bit about the utrophin work, because that was something, for me anyway, very unexpected.

D And it was unexpected for us. So Don Love who was then the post doc in the lab. I mean actually Lou Kunkel had not cloned the whole of dystrophin gene; he'd done the lovely work on Pert 87 and the cDNA, but nobody had cloned the full length kb dystrophin gene. Nobody was giving it out, so in order to do prenatal diagnosis of some of the deletions, we needed to clone the whole gene. So we were screening like mad all of these genomic libraries, and so we were very surprised when a particular sequence came out that didn't seem to hybridise to the X chromosome. It didn't map on the X chromosome. And we were then very fortunate that Diana Hill came through the lab from New Zealand, who was a DNA sequencer. And she said she'd take the sequence back to New Zealand and just find out what it was. And of course I remember, it was Boxing Day that year; she faxed back the sequence and she said, "You can't believe this; this is 83% identical to dystrophin." And then we realised, "Wow, this could be really interesting." And as we cloned it, you know, and did the Northern blot and showed it was 13 kb, we realised that potentially this could be an ortholog; and that's exactly what it turned out to be.

I How do people understand the role of utrophin now, because I haven't really kept up with it at all.

D Well, if you knock it out in the mouse, if you remove it, you get almost no phenotype. I mean you get subtle changes at the neuromuscular junction, so we're still not quite sure why it's so highly conserved; why it should be so big like dystrophin; in other words why has it been conserved in evolution. It clearly has this structural role at the NMJ, but the NMJs actually develop normally even without utrophin; they just don't function quite as well, but well enough for most. So we're still not quite sure what it does.

I Well, that's interesting because I thought it was just me not being -

D No, because of course we don't know what a human utrophin knock out would look like, or even a mutated utrophin, because we probably wouldn't see it because it would be a recessive disease, and it would be relatively rare presumably.

I Nobody's accidentally come across -

D No.

I - anyone with a -

D No. I mean, muscle levels of utrophin in muscle are relatively low in the adult, but there are huge amounts of utrophin in your kidney, your lung, and your spleen; even your fat cells actually; why you should generate such a large protein at such high levels?

I Do people then have any idea about the evolutionary basis, you know; the two molecules, or maybe there are more than two in that family?

D Well now we've got dystrobrevin, which is closely related to it, but clearly dystrophin and utrophin are related by an ancient duplication event, but not of the cDNA and a retro insertion, but a duplication of the whole locus which is why you can line up the 79 exons of both of them; utrophin is a bit shorter than dystrophin in genomic terms, but essentially the structure is the same. So, and that's quite unusual. And of course dystrophin has a very high new mutation rate; and again I don't know what utrophin does. If the phenotype's lethal we'd never pick it up.

I What year was it that you moved from London to Oxford?

D That was 1984.

I And am I right that, I mean, you really joined David Weatherall's group, and was that

already in, was the IMM [Institute for Molecular Medicine] already open then, or was it before?

D So the story there is that I went for an interview for an MRC Senior Fellowship and Sydney Brenner was the chairman. And Sydney Brenner at the end of the interview said, actually I think Malcolm Ferguson Smith was on the panel because Malcolm kept answering the questions when I couldn't answer them. [laughs] And Sydney said, "We must do something about getting you back to Oxford because this commuting's a nonsense" because I used to commute every day. "And in any case, if you're going to have a senior fellowship now you should become more independent. I'll fix it." And so he rang up Henry Harris and David Weatherall and I went to see Henry Harris and David Weatherall, and talked about my research in molecular genetics. Although I wasn't interested in thalassemia per se, I was interested in the general approach that David was using. And so he was kind enough to offer me a small lab and an office, which was on the top, the 7th floor, of the John Radcliffe Hospital.

I Yes, I seem to remember things were virtually, had got to an impossible state in terms of having a lab with enough space to function.

D That's exactly right.

I And was the building, was the new building going up then?

D It was clearly something that was planned, but it hadn't started, and then John Clegg and David worked together to put that up.

I Yes. Just thinking beyond Duchenne a bit, a number of other diseases had crossed the horizon by then. One that occurs to me particularly is the spinal muscular atrophies.

D Yes, and that was Don Wood of the Muscular Dystrophy Association in the States persuaded me that it was a good idea to do the same thing we'd done with DMD with SMA. But of course SMA was rather difficult because the diagnosis of mild cases was hard and in the case of the Type 1s, a lot of babies go home to die, sadly. Don put me in touch with Martin Bobrow who had worked with Victor Dubowitz for a little bit on SMA and Conrad Gilliam was working in the States on SMA; and he'd worked in Bob's lab so I, you know, we were colleagues in that sense. So we said to Don, "If we could bleed every patient in the UK and Conrad could do as many in the States maybe we could try and map spinal muscular atrophy."

I Was there any hint of a chromosomal location at that point?

D None whatsoever.

I And I'm trying to remember, I mean, it was unlike CF, purely mapped by DNA rather than anything protein based.

D Yes, it was. And so that had to be done by consanguineous pedigrees as well because it was so difficult to find more than one affected child in a family that was still alive.

I I mean, that turned out to be an unusual set of mechanisms, and at what point did you start to suspect that, I suppose I wouldn't call it a dosage effect, that something involving, missing different numbers of -

D I think that that was only when we knew that, from our pulse field electrophoresis work that we'd done, that Louise Tinsley did, we could see that the amount of DNA in that locus had changed; but it wasn't until Judith Melki and Suzie Lefebvre cloned the gene that we understood. But even then we weren't sure that the SMN, Spinal whatever it is, Survival Motor Neuron disease gene was the gene, because Alex Mackenzie still thought that the NAIP gene was involved as it also varied in its copy number. And so these probes looked very different in all of the families; and we could also see change from generation to generation. So I guess that was the first clue. And so when Louise did her pulse field electrophoresis you

could see the copy number change. But we didn't realise then that it was SMN1 and SMN2 with this splice sequence so that you were out of exon 7 if you had only SMN2 genes.

I Right. What other diseases that you've been working on do you sort of feel a special involvement with?

D Fragile X syndrome, I guess. And that's when we were working with Marcus Pembrey and Robin [Winter]. And you know Robin was so, well they both were, thinking about ideas as to why you should have male transmission in that disease; and I was really interested in that sort of genetics, so again we did a lot of pulse field electrophoresis of that, showing that there weren't any major rearrangements. But in the end of course it was Grant Sutherland that cloned the gene and showed that it was a triplet repeat disease. And then I felt I had too much to with the DMD, the utrophin, that I dropped the fragile X syndrome, and concentrated on DMD and SMA.

I I'm interested you say that because, in a very modest way, we found the same; that while it was all based on DNA you could run several things in tandem. But the moment it got into the actual functional side, everything went in every direction; and you had to decide, I mean at least we had to decide -

D No, so did I; yes.

I You know, but you can't do the lot. And that was the point where we decided we wouldn't pursue the function for myotonic dystrophy but we would for Huntington's, and I suppose really, most people who had grown up through the DNA polymorphisms were in the same position, weren't they?

D They were. And you had a different set of collaborators and then you started to go to different sorts of meetings in order to be able to understand what your gene did. So we started going to muscle meetings rather than genetics meetings.

I Again, I think that's been universal because with Huntington's the emphasis was still with the neuroscience. Tell me, now that you've got this gene function unit, it is Wellcome funded, is it?

D The building is Wellcome funded but it has an MRC Unit in it.

I When did that start to become a real possibility? Was it after you'd taken the chair in genetics?

D Yes, it was. Because then I think I decided, because there wasn't a proper chair in genetics, not that that mattered, but there needed to be a closer affiliation between genetics and physiology; and Clive Ellory and Fran Ashcroft realised that too. So we came together and decided that we'd try to raise some money for this building. Peter Donnelly, on his population genetics, joined us later.

I Right. And remind me then, this building has been open now since -

D 2000. Ten years already.

I That's truly amazing. As a little bit of aside, I've always, despite having always been an undergraduate here and sort of keeping in touch with geneticists in Oxford, I have never quite understood, I never quite understood why Oxford never developed what you might call a proper genetics department before. I mean, have you got any insights or don't you understand it either?

D Not really, because I mean obviously we had very leading people; with David Weatherall very focused on that thalassemias and John Edwards doing an awful lot on the clinical genetics side. But I guess there really weren't the basic sciences that engaged with it except on the thalassemia side where you had really bright people like Doug Higgs. So that may well have

been the problem. Of course now it's very strong in genetics. And John Bell introduced Complex Disease Genetics, and set up the Wellcome Trust Centre for Human Genetics, so you know. What you're saying is at the very beginning we weren't very strong in the single gene disorders, except in thalassemia, and I think that's true. And then later then Andrew Wilkie and co set up, a dysmorphology clinic. With, I've forgotten his name now, who's the other person, … I'll remember his name, Richard Gibbons ; he worked with Doug Higgs on the ATRX gene.

I I mean do you think geographical separation and -

D I think it doesn't help, because the genetic clinic was actually on the Churchill site; the basic science was down here. So John Edwards had his basic science lab down here, David Weatherall was on the John Radcliffe site; I think that does make a difference.

I When was it that the university kind of merged the department and you found yourself in charge of the lot?

D Of anatomy, physiology and genetics -That must be 5 years ago now.

I Do they still function moderately separately, or -

D Not as separately as you might think, but there are difficulties: you've still got the anatomy building and the physiology building, the Sherrington Building. Until you can unify them and bring staff into one building, it's rather difficult.

I I can imagine.

D So as we get new university lecturers appointed, we try and muddle it up. So people working on Parkinson's disease, whether they're physiologists or molecular geneticists, are over in the Le Gros Clark building; although having said that Steph Cragg's over in this building. But it's quite difficult to run a large department, second largest department in the division, in two buildings. It's okay for me because I grew up with it and I know everybody. Whoever inherits the role of Head of Department from me will have more difficulty if they don't know everybody.

I I can imagine that. Can I ask you about one other kind of, what I might call, interlude, and that's your spell at the Hammersmith. Where did that slot into what you might call the rest of the time, which is being in Oxford?

D That's because my MRC fellowship was coming to an end and I didn't have tenure in the IMM, so I went to see Dai Rees, who was then head of MRC, and asked him about my future career. And he said, "Well, I've got the job just for you which is the head of the Hammersmith." [laughs] He offered me a lot of resources to make it as easy a transition as he could to go to the Hammersmith, so I was very lucky in that regard, and he supported me very well when I got there. And I really enjoyed the job for 2 years until the government decided to have this option appraisal between Charing Cross and Hammersmith as part of the reorganisation of London medicine, as you know. And then people didn't know whether Hammersmith was going to continue to exist, or if Charing Cross was continuing to exist, so we had planning blight and I started to spend all of my time sitting at dinners and arguing things with either other clinicians or politicians. And I felt age 40 I didn't want to die as a scientist. I could either become a political animal, or I could go back to the science. And I was very lucky that David Weatherall could see it happening and therefore never gave my space away. So for a time I had a group in Oxford and a group at Hammersmith, and then eventually I came back to Oxford.

I Yes, that was fortunate because a lot of people must have got really dislocated by all those changes involving the Hammersmith.

D They did. And of course then they had interim directors after I left. I mean, it's working very

well now of course under Mandy Fisher, but you know, it took a long time to find its feet because of the uncertainty. And it was such a pity because that was such a great opportunity: there were lots of academic clinicians you could collaborate with; and also it was all working, it's just that, you know, we couldn't recruit people to the unit; and you can't set something up without good people.

I No.

One thing, I've interviewed a good few women, but mainly in the older generation. And one of the things that has come over very strongly is what a terribly difficult time women in science had in the 1950s, 60s and a bit into the 70s. And that was an amazing generation of people and some remarkable women; but they had a tough time mostly.

D Yes, they did.

I Do you think this is something which is largely over and done with? And, I mean, how much did you find you were held back yourself?

D I don't think I was held back. Well, actually [laughs], no I don't think I was held back because I didn't get lectureships in Oxford but I probably wouldn't have done in any case, and that did me a favour because I could do my research before I had to do teaching as well as research; and I had a very good mentor, David Weatherall, encouraging me all the time. A very good spouse who threw me back in and said, "Keep going" as well. And that helped a lot. And I think the barriers are disappearing but they're not disappearing completely; mostly because men don't think about women. There's an article in Nature this week I noticed about the number of prizes that women get is significantly lower than the number of prizes that men get; and it's even lower than the number of professorships or senior positions that women occupy. And it's not you know, men being sexist, it's just because they don't think; they never think of those women. And I think if women have children they attend fewer meetings. I didn't go to many meetings, particularly when my son was between the ages of 11 and when he left home; I never went for a meeting for more than a week, and most of the time I would only go away for 3 or 4 days. And so that means your exposure is much less, and your networking potential is much less than that of a male. So when they're putting committees together, your name never comes up; they're not trying to exclude you, they just can't remember to include you.

I [laughs]

D [laughs] And that's inevitable.

I Do you think it's improving?

D I do; a lot. A lot.

I Do you think we will get to a critical point where women are so represented that this sort of amnesia can't happen any longer?

D Exactly; but I think it's going to take some time before we get there.

I Yes. I talked with Bernadette Modell, and she was comparing her experience with her daughter's and her mother's and she thought it took three generations, really.

D I think it might; I think it will take a least a couple of generations, because you've got to have the role models there. And there is still a problem with women not having enough confidence and feeling guilty about taking time off to have a family. And I think that guilt will never go away, but I think you have to encourage women that they can make it in spite of that, because generally women can be very organised individuals; not that men never are, but of necessity they can be, and so, you know, there are women who work in my group that can come back after 6 months maternity, but they still want to spend time with their families

when their children are young, and you can be understanding of that. So I think there's a much more family oriented environment now than there used to be, and that's the only thing that will make it shift.

I Yes. Going right back a bit: can I ask you, what was it like working with Bob in those early years?

D Manic.

I And you'll have an opportunity to edit anything out, but I mean, I was what you might call an amazed bystander then, so being right in the thick of things -

D It was manic because he had so much energy. I mean he'd start at 6 o'clock in the morning and just keep going. But the good thing was that you could walk into his office and say, "I need a new lambda phage" or whatever it was to do the experiment, and by the afternoon he'd found someone who'd got it. And it might be in Cambridge; it might be in Edinburgh, but he was so well connected he could find a collaborator to do anything; so it was very enabling. He had lots of energy. And for Bob, everything was going to work; he was the eternal optimist.

I I've always been amazed at, not just Bob's enthusiasm, but also at the number of really outstanding people who worked for a while with him, and whom he kind of launched off into their own careers, and have done fantastic things in their own right.

D It's an outstanding number, actually, but that's because once he lets you go, he doesn't ever let you go completely: he's ringing you up all the time, telling you what you should be doing next. [laughter] And it's not just because I'm female; he does it to everybody. He does it with Pete Scambler and Brandon Wainwright, you know, and Brandon's in Australia, and Peter, as you know, is in GOS now. So he does it with everybody.

I Yes.

D That's called extensive mentoring and it's incredibly useful. And he is forever saying… he never says you shouldn't do something, but he's always saying, "Yes, you can do this. Try for this." So, yes, I remember him telling Sally Davies what she could do; she'd go far; and she did. [laughter]

I I've been asking everyone I see, Kay, a couple of things, and the first is: thinking in terms of major influences on your career, is there any particular person or people that really stand out in terms of having been a really specially important influence on how things went?

D Jo Peach in Somerville, getting me in with biological chemistry; and actually Dorothy Hodgkin was still around then in Somerville and used to come to some of the lectures. So I found that… it was a good role model for women and also very encouraging. And then I guess really Bob Williamson and David Weatherall, who accepted my enthusiasm and channelled it in the right direction; and helped me focus it properly. And I think, you know, Bob liked to work on lots of diseases. I think what I learnt from working in the Unit with David is if you concentrate on a problem that you're really passionate about, like DMD, you can do a lot, and you can make a really consistent contribution. And that was good advice very early on, and I've enjoyed it so much because of that.

I The other thing I've been asking everyone: is there one particular piece of work that you identify yourself with more than anything else? So almost like a desert island thing: if you just had to take one of them with you; which would you feel is, not necessarily the most important, but the one you feel most for in terms of -

D I think it was the discovery of the utrophin gene. It was identifying it with Don that sequence and looking at the hybridisation blot and knowing that it was something different. It changed the whole landscape then for me because there was another gene. It not only told us a lot about dystrophin and the evolution of the genes but also about potential treatment. Well, it's

not only the importance but the excitement of that. And it opened new avenues.

I Kay, there's large areas which deserve to be gone over, but I've always tried not to make these discussions too long; but are there any particular areas you feel, you know, you want to include that we haven't really touched on at all?

D Well just that I was very fortunate to work closely with people like yourself; so being involved with those early days of advisory groups on genetic testing, and thinking about the ethical implications of the research, you know; I really enjoyed the opportunity to do that. Do you remember all those -

I I do.

D - I've forgotten the chairman's name now, the guy from Cambridge.

I Yes; mathematician clergyman guy. [John Polkinghorne]

D Yeah, anyway it will come to me as well.

I That will come back as well. I think I have covered most of my main notes, but anything else that you want to put on record Kay?

D No, just the, oh and I think the human genome mapping meetings. We mustn't forget those: they were incredibly exciting.

I [laughs] They were.

D And you know, do you remember in those very early ones, even the Helsinki meeting when we didn't have word processors and what we were doing was sticking bits of paper together and cutting chromosomes up to get the order of the markers right. I'll never forget the spirit of those meetings and how much we achieved collectively; internationally and collectively.

I I was terribly sad when, after that London meeting, they discontinued them, because it never felt the same again.

D I totally agree. And so, no, that was a very special time.

I We've been extraordinarily lucky to be around, I feel, at this time.

D Yes.

I Kay, I'll finish it there. Thank you very much.