David Harnden

Personal Details

Name	David Harnden
Dates	
Place of Birth	UK (London)
Main work places	Edinburgh, Birmingham, Manchester
Principal field of work	Cancer genetics
Short biography	See below

Interview

Recorded interview made	Yes
Interviewer	Peter Harper
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Personal Scientific Records

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

Biography

David Harnden was born in London but bought up in Edinburgh, studying zoology at Edinburgh University. He did a PhD in cell biology and genetics at Edinburgh before moving in 1957 to the Medical Research Council, Harwell, to study mammalian chromosomes with Charles Ford, being also involved with the early findings of human chromosome disorders.

In 1959 he returned to Edinburgh as part of the MRC Clinical Effects of Radiation unit, under Michael Court Brown and being involved with the 1960 Denver Conference on human cytogenetic nomenclature. In 1969 he moved to Birmingham as Professor of Cancer Studies, developing cytogenetic and molecular studies of ataxia telangiectasia, and later became head of the Paterson Institute for Cancer Research in 1983.

INTERVIEW WITH PROFESSOR DAVID HARNDEN, 18th MARCH, 2004

PSH. David, if I can just record one or two preliminaries first. Just to say I am interviewing Professor David Harnden at his home near Stockport on 18 March 2004. David, can we start at the beginning? Can I ask where were you born and brought up?

DH. I was actually born in London, but my father died when I was very young, only 3 years old, and my mother went back to Edinburgh. And I grew up in Edinburgh, went to George Heriot's school in Edinburgh and did a degree in the University of Edinburgh, my first degree was in zoology and my PhD was in really cell biology, not cytogenetics but genetics in general under the guidance of Murdoch Mitchison and Michael Swann.

PSH. So what was it that made you interested in zoology, science generally? Is there anything that caught your imagination in those early years, or did you just go into it.

DH. No I was always interested in outdoor things, collecting plant leaves and going walking in the hills near Edinburgh and I suppose if the truth be told, as a Boy Scout that took me out and got me interested in nature. And at school, I mean I just very much enjoyed the botany and zoology because at that time they were not combined into biology. They were two separate subjects and I took a Scottish Higher in zoology and a Scottish Higher in botany before I went to University.

PSH. Did you, when you did your undergraduate degree, was there any special emphasis on genetics or contacts with genetics there, or was it when you came to do your PhD?

DH. No there was a lot of contact with geneticists. When I started my first degree the Professor was James Ritchie, an old fashioned natural historian, but halfway through my undergraduate career, Michael Swann came in from Cambridge at a very young age and transformed the place and there was, in Edinburgh, a very strong department of genetics, Institute of Genetics with Waddington as the Professor and of course Charlotte Auerbach and we had not only lectures from Charlotte but undergraduate practicals with Charlotte, Drosophila mating and all that sort of stuff, so I had a good grounding at undergraduate level in genetics.

PSH. She must have been a really interesting person and I've read some of her books. I mean was she the kind of person that really inspired somebody to work in the field?

DH. Oh yes. Absolutely. Very much so and I very nearly switched over from zoology which was my original intent to genetics because of Charlotte.

PSH. Then you got your degree and then you did a PhD. How did you manage to get to do a PhD, because there weren't so many of them then?

DH. I was very close to being conscripted into the Army because everybody was doing National Service at that time.

PSH. What year are we now?

DH. We are now in 1954.

PSH. OK

DH. But at the last minute, I can't remember where the idea came from. The idea emerged of applying for an MRC studentship and so I got a MRC studentship which enabled me to do my PhD.

PSH. And then who were your supervisors for the PhD?

DH. Murdoch Mitchison was my particular supervisor He was a great expert in the kinetics of cell division, he and Michael Swann together published a lot of papers. But he was working at that time on an interesting yeast called *Schizosaccharomyces pombe* which became extremely popular.

PSH. Absolutely.

DH. So part of the work that I was doing, was trying to do was, Murdoch was doing work on single cells, but they wanted to switch over to doing work on mass cultures but they had to synchronise, so part of my study was on attempts to synchronise yeast cells, so that they could do mass biochemistry on them. But I also was studying the natural occurrence of synchronised cell division in things like sea urchin eggs. It was great fun.

PSH. Am I right that it was when you were working for your PhD that the human chromosome number was discovered?

DH. Yes. Yes, that is absolutely right. It was 1956, and what really triggered my interest in this was a lecture by Charles Ford in the Zoology Department. One of the regular seminar series and I was absolutely astonished to find that we had been taught that there was 48 chromosomes and here was Charles coming on saying "No, you are wrong, it's 46". And by that time not only had Tjio and Levan's paper been published but Charles had got information from meiotic chromosomes with John Hamerton, that the correct number was 46 and the reason for the incorrect decision was that the XY bivalent quite often split to give the wrong haploid number.

PSH. Yes

DH. And then you multiply it up and you get 48 instead of 46.

PSH. So you got your PhD and am I right that you went on to the staff of the MRC more or less right away?

DH. Yes that's right. As a result of this lecture by Charles Ford, I talked with him after the lecture and I was nearing the end of my PhD at that time and very soon he said, "Would you like to come and work with me", but before I actually went to join him in Harwell, I worked for 3 months in Cambridge at the Strangeways laboratory. He sent me there, Charles sent me there to learn

tissue culture under wonderful Honor Fell who was just the most wonderful person I think I have ever met. She was absolutely brilliant and as I said in the little bit that I wrote, she was generous with her time but frugal with materials. Her sort of thing was sterilising Petri dishes in dried milk tins and things like that.

PSH. So you really learnt hands-on . . .

DH. She sat down beside me and went through absolutely everything. She taught me how to grow cells in culture and one of the things that really sort of amazed me was, after I had left her, she wrote me a letter giving me a photograph of one of the cultures that had been set up while I was there, and she asked my permission to use it in a publication. I thought, what a lady this is to write to somebody as insignificant as me to ask my permission to use the picture. That was brilliant. She was terrific and I learnt a lot from her.

PSH. So you went then on to Harwell.

DH. Then I went to Harwell.

PSH. And what were you meant to be doing?

DH. What I was meant to be doing was studying the chromosomes of mouse tumours and that really went reasonably well. I think, again I mentioned that when I went there I was shown into a really, not very satisfactory laboratory which was occupied by a cage of rats which belonged to the Director, John Loutit, and with the arrogance of youth, I went along and told the Director to move his rats from my tissue culture room. But I was sharing that room at that time, it was the ante room to the dark room as a matter of fact, in addition to having the rats, so there was constant traffic through the room, to the dark room, and the other person in the room was Pat Jacobs.

PSH. Had you met her before?

DH. No. That was the first meeting with Pat Jacobs and that was brilliant. She was working on the bone marrow culture technique, because Lazlo Lajtha who was in Oxford at that time, he and Charles Ford and Pat worked up this way of looking at human chromosomes using bone marrow, which was really very good and a very, very important step forward..

PSH. I am always amazed by how many things come back to Charles Ford. It's an awful shame that he is not still here to be interviewed, but everyone seems to have found him a pivotal person.

DH. Charlie was very important. The sort of thing that was most important about him was that you had to be meticulous in what you did and you had to believe your own observations, because you shouldn't anticipate what you expect to see. You describe what you see and with great accuracy. And he was a stickler for detail and I think very, very important in this whole field.

PSH. Your project then was mouse chromosomes, and several people have told me that Charles really was primarily a mouse person and had to be kind of persuaded to look at anything human?

DH. I think that's right. The reason that Pat was, you probably got this from Pat herself, the reason that Pat was there was, she had been recruited to the MRC Unit in Edinburgh, which was then the group for studying the general effects of radiation which was run by Michael Court Brown, and Michael again thought it would be a good idea to study chromosomes. He had (the letter I showed you from Tjio) he had learnt about chromosomes from going to international meetings and he wanted to develop this, Michael was an amazing man, because he was a radiotherapist, an epidemiologist and developed an interest in genetics so that some people thought he was a geneticist. He was remarkable. But he had sent Pat to Harwell to develop the bone marrow technique.

PSH. How long did you spend then at Harwell?

DH. I was at Harwell for just two years but you see, Pat kept feeding me information about her work on chromosomes and I suppose I deviated from the straight and narrow by taking an interest in human chromosomes instead of mouse chromosomes and using the techniques that I had learnt from Honor Fell, I got David Barnes, one of the scientists there, to take a little bit of skin off my arm. I set it up in culture and I was able to look at my own chromosomes, which was just amazing. So that started it all off. And once I had got the system set up, people started sending me bits of skin from all over the world. It was truly amazing and Pat told me of her work with John Strong where they identified 47 chromosomes in Klinefelter's syndrome, so I knew of that before I really got stuck in.

PSH. And your fibroblast work, the paper you published I think was '58 wasn't it?

DH. No, no. It was 1960 actually.

PSH. It was 1960.

DH. 1960 before it actually got into print.

PSH. Because another focal point of that I have come across, everything seemed to happen about 1959.

DH. Yes that's right.

PSH. This mass of discoveries and it is very interesting how everybody communicated so rapidly with each other.

DH. That is absolutely true. We were in touch, I mean I was in touch with people in London, Lionel Penrose for example the Galton Professor, and Lionel was sending me bits and pieces. John Edwards was in Oxford at that time and he was sending me stuff. I was getting stuff down from Edinburgh and from all over the place because until the development of the blood culture

technique by Paul Moorhead, people were really using the bone marrow technique, and you can't really go to any person and take a bone marrow biopsy, but you could go to anybody at all and take a tiny snippet of skin. And so this, for quite a short period of time, was the preferred method of making chromosome preparations.

PSH. I feel tempted to ask whether you'd have been a volunteer for your own chromosomes if it had been bone marrow rather than a skin biopsy.

DH. I think I would not! I would not, and it was really quite interesting that when people got to know that this was possible, the material just came flooding in and for example, I had this idea about Mongolism. Again, Down's syndrome, partly because I had a cousin with Down's syndrome, and I was in the library one day reading about Down's syndrome and 50% of the offspring of female Down's patients also had Down's syndrome and I thought what's going on, and I knew about Pat's discovery on Klinefelter's and I thought my God, Down's syndrome is a chromosome abnormality. And I got in touch with Penrose and he got a biopsy off of a patient with Down's syndrome, sent it to me and I had it in my incubator growing up when I heard both Lejeune and Jacobs had discovered the 47 chromosomes in Down's syndrome. But that was very interesting because it turned out to be a patient who had 48 chromosomes. He was both a Klinefelter and a Down's. It was the first double aneuploidy and the other interesting thing about that, when we got this worked up, it was Penrose who wrote it. I did the work and when we wrote the paper up it turned out that the authorship was Harnden, Miller and Penrose and I said to Lionel, you know really you're the boss. You should be first author. He said "no, all my papers are in alphabetical order" so Harnden, Miller and Penrose, and that was O. J. Miller from Columbia University.

PSH. He was visiting Penrose at the time.

DH. He was visiting Penrose at the time and he was a clinician who was looking after a patient whose name I still remember very strange thing, called [?]. So that was my contribution to Down's syndrome. A bit too late to get the glory.

PSH. You must have had a lot of contact with other folk at Harwell. Who were the other key people who were in the genetic side when you were there?

DH. Yes, well I guess Ken Jones was very important. He was also in Charles' group. John Evans was there at the same time but John was actually in a different group. He wasn't in the genetics group but doing sort of genetic things - I don't remember - experimental radiation biology or something. Also there was Mary Lyon of course.

PSH. Mary was there already?

DH. Oh Mary had been there long before I got there and of course her interest was in mouse genetics, and she was a central figure you know, and one of the leading world authorities on mouse genetics and the activity which she set up still goes on at Harwell.

PSH. It seems to have been an amazing place and yet one of things which other people have said it was almost impossible to get to at that time.

DH. It was a bit isolated, yes, but it was no distance at all from Oxford on the bus, I suppose 20 minutes on the bus into Oxford but very little contact with Oxford. Although Charles later on, did actually move into Oxford and worked in the Dunn School of Pathology, but I guess that maybe why I left, was the sort of scientific isolation. The way in which it came about was really rather extraordinary, because before we left Edinburgh my wife and I had rented a flat in a large house in the Polwarth district of Edinburgh and I went back to visit the couple who rented us this flat and they said would you mind we've got another visitor this afternoon. There were two children in the house, this is the boys' Uncle Michael and they said he is a very strange man. A very strange man. He doesn't really talk when he comes in. He just sits. So when Uncle Michael came in, who should it be but Michael Court Brown. And we talked and talked the whole afternoon, much to the astonishment of my former landlord and I guess that triggered it because I realised then that the MRC Unit in Edinburgh was really the place to be. To go and work with Pat Jacobs and Michael Court Brown was something special and I don't think Charles Ford was awfully keen when I decided I was going away, but I was absolutely sure it was the right thing to do.

PSH. When was it you went back to Edinburgh?

DH. 1959

PSH. 1959 and there was Michael Court Brown, I suppose Michael Court Brown and Pat Jacobs really were the two in the unit.

DH. No there were more than that. Michael, as I said was a radiotherapist turned epidemiologist because he was interested in the epidemiology of cancer and so on and had worked closely with Richard Doll of course, but he felt that just doing epidemiology wasn't sufficient; he had the concept that you should have clinicians, epidemiologists and scientists working close together and that's what he set up in the unit in Edinburgh. It really was quite remarkable, the two clinicians, Albert Baikie, Jack MacBride and there was a third person, Albert's wife. But then in the cytogenetics lab there was Pat Jacobs, Karen Buckton and Ishbel Tough and they all contributed. Karen and Ishbel were very good scientists too in their own right and you will see if you look at the publications, their names are quite often first author of the papers.

PSH. And you have published in that phase, a lot with Pat. Can I ask, the Trisomy 18 work? Was that started while you were still at Harwell or was it just something which came, so to speak?

DH. That was done at Harwell, because at that time John Edwards, who was sending in material from lots of children with 'funny faces' basically, and this little girl he said, now this really is a strange little girl. I think you are going to find something here and when I looked down the microscope I found 47 chromosomes. It was really quite astonishing. I wasn't very sure whether it was chromosome 17 or chromosome 18 to be honest and that was written up and published, and it was back-to-back in the Lancet with a paper by Klaus

Patau on Trisomy 13. The two papers appeared side-by-side in the same edition of the Lancet. It was quite astonishing.

PSH. Was that based on skin fibroblasts?

DH. That was skin fibroblasts.

PSH. Because again it must have made it a lot easier to get the samples from that type of patient.

DH. Oh absolutely. You could never really justify it. This was a little girl who was terribly sick and the thought of taking a bone marrow just wasn't on. But of course when Paul Moorhead developed the blood culture technique this all became much simpler. But there was still a role for the fibroblast work, because the possibility for mosaicism was always there and when, for example, in Edinburgh we were looking at the Philadelphia chromosome, this was after Nowell and Hungerford produced their paper, it had already been spotted in the bone marrow of leukaemic patients, but then was it a mosaicim? And I can remember Michael and Pat sort of standing behind my chair, as I looked at the skin fibroblast chromosomes and of course they were perfectly normal, which confirmed it was confined to the bone marrow, because in CML the Philadelphia chromosome is in the majority of cases in 100% of the cells, so there was a possibility of a constitutional abnormality but it wasn't.

PSH. Just thinking a bit more about that Trisomy 18 case, I've never quite worked out and I haven't spoken in detail with John Edwards about it, but who were the different people involved? I mean you did all the cytogenetics.

DH. I did the cytogenetics. The authors were Edwards, Harnden, Cameron, Cross and Wolfe.

PSH. Yes, now Otto Wolfe was Professor at Great Ormond Street.

DH. Yes, I guess the case probably originally came from him. Hugh Cameron was a pathologist and I don't know who Cross was.

PSH. And was John Edwards – where was he working then?

DH. Well to be honest I'm not absolutely certain, but he was in Oxford and I guess associated with the Radcliffe.

PSH. Right, yes. And were you expecting to find something on that patient or was it just one of a series which came in and lo and behold there was an abnormality?

DH. John was particularly excited about that because he said, you know if you think of the galaxy of abnormalities in Down's syndrome, this is a similar but different galaxy of abnormalities. I looked at things like anencephaly and so on. I actually published a paper of all the negatives and that's in the archives somewhere and there were a whole lot of things, but that one was

indicated to be special because John thought from a clinical point of view, there were similarity with Down's syndrome.

PSH. What was your reaction when you found there was an extra chromosome?

DH. I guess I was astonished, because I'd looked at quite a lot of negatives up until then. Not only anencephaly, but hydatidiform moles, epidermolysis bullosa and all sort of things. But that was very, very exciting.

PSH. Coming back to Edinburgh, what was your remit for, when you got back to join Michael Court-Brown? Because again on the publications, looking at the author list it seems that the group worked very, very closely and it isn't easy to say, one person did this and another person did that, because it seems as if the group functioned very much in an integrated way.

DH. Yes, it really was very close and we all got on remarkably well together. It was really good. Michael, I think maybe Pat has said, could be awkward at times, but he was frank to the point of being rude at times, and he just said what he thought but I got on amazingly well with him because, he could be a bit awkward at times but if you were absolutely frank with him then you could establish a wonderful relationship and I felt I had a terrific relationship with him. But my remit, coming back to your question, really was to look at the chromosomes of anything that happened to come along I guess, but also to sort of cover the possibilities of mosaicism and so on. I got a bit, I suppose, felt that I was not really expanding myself widely enough and I guess it was the study on, it was the Philadelphia chromosome cases that really triggered my interest in a slightly different direction. It is interesting to talk about the name Philadelphia chromosome. Maybe Pat has told you about this?

PSH. Not really, no.

DH. Because I wasn't involved with the bone-marrow work obviously. But it's clear that Nowell and Hungerford had discovered this. Michael Court Brown was writing up the paper which Pat and I were authors of, together with I think Albert Baikie. Michael was writing down the phrase, 'there was an unusually small, small acrocentric chromosome' and it came up again and again 'a small, small acrocentric chromosome', and Pat and I got together and we said, this doesn't sound right. Then we remembered that at Denver there was a convention which was that you should use something which indicated the name of the city where the discovery was made and give it a superscript so that this was the first abnormal chromosome from Philadelphia, the Ph^1. And so it was in that paper that the Philadelphia chromosome got its name in honour of Nowell and Hungerford in Philadelphia.

PSH. Am I right that, again, that the leukaemia work that was going on in Edinburgh, essentially made the same discoveries around the same time?

DH. Yes, they had seen the unusually small, small acrocentric chromosome, but hadn't twigged that it was specifically associated with CML and of course as soon as the Nowell/Hungerford paper was published, they went back and

re-examined it, and realised that they had seen the same thing and not realised the significance.

PSH. And that was 1960 was it?

DH. It was about1960 yes.

PSH. And am I right that it was 1960 was the Denver conference?

DH. That's right

PSH. Just to come back again to that Denver conference, because it seems to have been a really interesting occasion. Who were the, what you might call the proper cytogeneticists who were there, the people who had actually done the work themselves?

DH. I'm not sure if I can remember them all, but T C Hsu, Ernie Chu, Jerome Lejeune, John Hamerton, Charles Ford, Pat Jacobs and myself, I'm sure there were others there.

PSH. Tjio?

DH. Makino was there, Makino from Japan. Tjio yes. By that time Tjio of course was actually working in Denver. He had been invited to go to Denver to work with Ted Puck and the conference was set up by Ted Puck and Arthur Robinson, really around Tjio.

PSH. Because, am I right that Puck was more a cell culture person rather than a cytogeneticist?

DH. Yes, and the cytogeneticist in Denver was Tjio. Puck's work, he did some very nice work on the cloning of establishing skin fibroblast cultures, I used some of his ideas using my technique I have to confess. His technique wasn't so reliable. He was seeding cells directly into a Petri dish, which was a bit hit and miss. I was growing with plasma clots and that was the secret. They just grew like wildfire in plasma clots. But yes, Puck was very important in stimulating things and making things happen

PSH. How did people manage to get an agreed system of naming sorted out? Because the people I have spoken to all say it was really difficult.

DH It was very difficult. I think it was because people already had begun to develop their own naming systems. Lejeune for example had already got the beginnings of a naming system and his stuff was very good and I guess the Edinburgh group had begun to get things together, and it got really quite difficult. We were almost at an impass when Ernie Chu proposed a Chinese method of naming chromosomes and that really sorted things out. People then said we don't really want to go in that direction without a final agreement and that's how it came out. There is one curious thing which I'm not really quite sure of, how we came to have 'p' and 'q' arms and I think it may well have been a typographical error because I think it was meant to be *petit* and *grand*, a concession to the French system. Somehow it got to 'p' and 'q'. I

can't say that that is exactly what happened, but I'm pretty sure the 'p' and the 'q' were a sop to Jerome Lejeune.

PSH. What I heard, but it was a long time ago and not recently, was that the 'p' was definitely *petit* and the person who told it to me, and I think it may have been John Edwards, was that they couldn't decide what the long arm, and then they decided that 'p' plus 'q' equals one, and that was how it was, but I don't know. I must ask other people.

DH. Well that's my version of it. But it was an extraordinarily interesting meeting. The personalities there were friendly in a way but very determined because each one had gone their own way for quite a long time and developed quite a lot of, a way of thinking. I think there was one person was missed out, Klaus Patau. He was not there.

PSH. Was he a cytogeneticist or was it . . .?

DH. It was his wife Eeva Therman.

PSH. I didn't realise they were a couple.

DH. Yes, Eeva Therman, but Klaus was I think, a more general medical geneticist. But Eeva Therman was with the cytogeneticists. They were working in Madison, Wisconsin. Interestingly, when I spent a while in 1963/64 working in Madison I didn't work closely with Patau and Therman but used to meet up with them regularly and I found him to be a charming and delightful person. He got this reputation of being rather difficult and yes, he his fought for his own corner quite strongly, especially somewhat later than the Denver conference, but he was absolutely delightful.

PSH. The other thing which I've heard a little bit about was there were difficulties in trying to decide which was 21 and which was 22 and Lejeune being very insistent that Down's was 21, even though it was the smallest.

DH. That's right. He had already said it was 21. I mean that kind of thing has happened a number of times. People make a statement in the literature, it happened over banding for example, and they are very reluctant to back down from an opinion or a view which has appeared in print. Quite understandably, but I think people agreed in the long run it was sensible. It had been said to be 21 so lets leave it 21.

PSH. What year was it you left Edinburgh?

DH. Yes, well I left, I hinted earlier that I was getting a little fed up with looking at just bits and pieces and finding this and finding that and I had got interested in the possibility that viruses might make specific chromosome aberrations or might break things. I had in the back of my mind the bacteriophage model where the phage integrated into the chromosome and I was curious about a case of Klinefelter's syndrome with CML where the Ph^1 chromosome was present in both the XY and XXY lineage because this man was a mosaic and I just couldn't quite figure out how

that happened. So I started looking at viruses to see whether they would break chromosomes and curiously I vaccinated a whole lot of people round the lab. I got them vaccinated with yellow fever vaccine, which probably wouldn't be allowed now, but indeed yes I found a lot of shattered chromosomes in the blood of these virus infected people. And then we also did some work on adenovirus, and adenovirus causes specific chromosome abnormalities in chromosome 17. But then I thought I had better go and get myself more familiar and that's when I went to Wisconsin and I worked with Howard Temin, nothing to do with chromosomes at all, but just learning about viruses, and then I went back to Edinburgh.

PSH. What year are we at now?

DH. That was 63/64.

PSH. And you were in Edinburgh until . . .?

DH. Then I came back to Edinburgh until 69. By that time Michael was developing all his huge population studies. Human population cytogenetics. The name of the unit was changed to the Human Population Cytogenetics Unit and it was becoming – I thought it had become awfully routine.

PSH. So did you leave Edinburgh before Michael Court Brown died?

DH. Well, he had a heart attack and then seemed to be recovering, and then the awful phone call came to say that he died. That was about three months before I was due to leave Edinburgh, and so Pat became the acting Director of the Unit and I moved off to Birmingham.

PSH. That must have been a pretty shattering experience for everybody.

DH. It was dreadful. It was dreadful because he was 50 years of age I think, and he was just such an amazing man, I mean a terrific spectrum because he'd got probably one of the most powerful intellects I have ever come across. He just was an amazing guy and the energy. I have referred also to the fact that he could be fairly awkward but that stood him in good stead when he was trying to make things happen. He would go in and his determination, for example setting up the automation of chromosome analysis, where he set that underway and brought in Denis Rutovitz. That is historical I think.

PSH. John Evans told me that.

DH. It might be worth talking to Denis, who is a very interesting character.

PSH. My list of people to talk to gets . . .

DH. Getting longer and longer.

PSH. Well that's the nice thing.

DH. But you see, without somebody with the dynamism of Michael the automation of human chromosome analysis would not have taken off as quickly as it did. It was interesting.

PSH. So you left Edinburgh in '69/70?

DH. '69 yes and went to Birmingham.

PSH. And what was the post? Was it a chair in Birmingham?

DH. Yes, it was the Chair of Cancer Studies in Birmingham and there had been a Cancer Research Laboratory there for a long time which had really, had really decayed quite considerably and my remit was to try and bring this laboratory back up to scratch, and we eventually created a proper Department of Cancer Studies in the Division of Pathology and that was very interesting because I was able to indulge both my interest in viruses, my interest in cytogenetics, and developing interest in chemical carcinogenesis. These were the three themes. We continued the work on adenoviruses and I brought with me a man called Jim MacDougal from Edinburgh, who was a virologist; we also recruited Phil Gallimore, who became one of the CRC's Gibb Fellows and Professor in his own right, but he continued the work on chromosome damage by adenovirus and that developed into a more general study of adenovirus transformation of cells, which was very interesting. But the cytogenetic bit in Birmingham really came through contacts with John Edwards, because John was by that time working in a Genetics Unit in the Maternity Hospital in Birmingham, and once again as I said, he was always drawing my attention to interesting things that were happening. And one of the things he was interested in was ataxia telangiectasia and we looked at the chromosomes of patients with AT, but by this time Fred Hecht had already found some interesting things about the chromosomes, but we confirmed these findings that there were very specific chromosome rearrangements in patients with ataxia telangiectasia and that led to a joint publication between Malcolm Taylor and myself and Fred Hecht in PNAS.

PSH. That was the beginning of the '70s?

DH. That's right.

PSH. Interestingly, I have a recollection of that time because soon after I came to Cardiff in the early '70s, I visited John Edwards mainly to see myotonic dystrophy families, and he took me around in his car and he stopped off because he had to see this family with ataxia telangiectasia and I remember the family.

DH. [ ]

PSH. I believe that was the case yes.

DH. I've been in their house too. The thing that astonished me about that was that I had previously seen these two girls, at a special school and they were in wheelchairs and they were terribly disabled. Seeing them in their own house was a complete revelation because they knew the geography of their

own house precisely and although they had difficulty getting around, they could move around really remarkably well. The other thing that astonished me there was, the way their mother spoke to them. You know I thought she would treat them with kid gloves. My goodness no. If they were getting up to mischief, just like any other parent would. It was just an absolutely wonderful relationship.

PSH. So Malcolm Taylor started working with you in Birmingham.

DH. Yes. He was a PhD student of mine and that was another interesting thing that happened then, was how we got into this sort of thing away from the cytogenetics. Suddenly there was one of these few blinding flashes that you have. I knew about xeroderma pigmentosum being an unusual sensitivity towards UV light, gosh forgotten his name.

PSH . Cleaver?

DH. Cleaver. Jim Cleaver. Yes that's right. And that was well established. It was Jill Mann's patient who was called [ ] and [ ] had a tumour, a lymphoma, and he was treated with radiotherapy after the tumour was excised and he responded extremely badly to this and that was just extraordinary, and Jill Mann, I think met up with Robert Miller, an epidemiologist from NIH in the States, and he knew another case where there had been a bad response to clinical radiotherapy and I just thought, my God it's going to be sensitive to radiation in the same way that Jim Cleaver had shown XP cells. So we had at that time cells from [B J] in the freezer and I was at a meeting of the Genetical Society in London, met up with
Bryn Bridges who was Director then of the MRC Cell Mutation Unit. We were in a pub just off Gower Street, because the meeting was in University College, and I told him about this idea of radiation sensitivity of the AT cells, but we didn't have the technology to do the studies, but he did, so we arranged for Malcolm Taylor to go to Sussex and he did the necessary experiments using the cells from this young boy [B.J] who by that time already had died. And Malcolm came back showed me the sensitivity curve and it was just astonishing. It was absolutely clear as crystal, from the very first set of results Malcolm got at Sussex, and it just took off from there and it held up every way round and that led directly on to the studies which led later to the identification of the ATM gene. And Malcolm has continued his interest in this ever since and that happened to make a big contribution.

PSH. It's quite a long saga isn't. It took a long time.

DH. It took a long time to get there yes. We had several meetings. There was a meeting in Sussex where we discussed this, but then sometime later there was a meeting in Birmingham when the gene was really virtually on the table and very soon after that Yossi Shiloh in Israel, he put the whole thing together but he had had help from lots of people including Malcolm Taylor. The data was all fed in.

PSH. Did you have any contact in the early days of ataxia telangiectasia with Freidrich Vogel's group, because I seem to remember they were looking at the chromosomes or at sister chromatid exchanges or something of that kind.

DH. No I really didn't have any contact with him, no.

PSH. How long were you in Birmingham altogether?

DH. I was in Birmingham I guess fourteen years and we went through whole a lot of, we were fairly diverse I suppose. There were interesting things going on. The virus work went very well with Phil Gallimore and Jim McDougal. Jim went off to, first of all Cold Spring Harbour and then off to Seattle and continued the work there. So we spawned a lot of interesting people from there. The other interesting thing we've done is growing epithelial cells, you know fibroblasts are easy to grow. And Ken Parkinson working with Margaret Stanley who was from Cambridge who was a visitor in our lab. They developed a system for growing human epithelial cells which was really very remarkable. So there were lots of things like that going on.

PSH. I think I saw in your publication list, there were some studies on skin tumours and maybe they were cultured epithelial cells from there?

DH. Yes, we didn't really do an awful lot with skin tumours. I mean I looked at pretty well everything that was going around. I guess I'm not that systematic

PSH. What year was it then you moved to the Paterson?

DH. 1983.

PSH. How did that come about? I know some of these things come about in strange ways.

DH. Well, I was very happy in Birmingham and I'd got a great group there – Phil Gallimore, Malcolm Taylor, Tessa Webb and Ken Parkinson and Chris Paraskeva. It was a terrific place and we had a really good going operation, but I guess one of the things that triggered it was that my predecessor in Birmingham had been the Director of the Cancer Research Laboratory for 30 years and I had a dread of ending up in the
way that he had. He did some super work in his early years but the last 15 years I guess were really quite sad. And I had seen the advertisement for the job in Manchester. I hadn't paid any attention and then I had a phone call from Alistair Currie, who was at that time Chairman of the CRC Scientific Committee, and he said "Are you interested" and I said "Maybe" and he said "Laddie. You will be 100 miles nearer to civilisation", and I guess that did it. 100 miles nearer to civilisation, because I had been thinking of a move and in fact had a couple of quite tempting offers to go into industry but that's really not my scene at all. I enjoy the freedom of the academic life and able to do something you are interested in, not working for somebody else. It's a kind of arrogant attitude but I just want to be able to do the things I was interested in doing.

And I went up and I was interviewed and I was offered the job. It was really very exciting. It was amazing because it was very, very much bigger than the nice little group we had in Birmingham and of course was very much more

diverse. There was good genetics there. David Scott was there doing some nice work. There was also all the work on carcinogenesis which I was quite familiar with, because I had done some work on chemical carcinogenesis myself, looking at chromosomes of people exposed to benzene, and things like that. And then there was all the biophysical chemistry and all that sort of stuff which wasn't my bag at all but it was a huge challenge and huge stimulation. I think I would recommend it to anybody to make a move from time-to-time. Not flipping from one thing to another, but the stimulation I got from going to Paterson was enormous. It was amazing.

PSH. How did you manage to make links with the more clinical side because really, as you were saying earlier, Manchester was one of the very first groups to develop cancer genetics as a clinical specialty?

DH. That's right. But it's curious, having been a biologist, I guess I had worked with clinicians throughout my entire career, except possibly at Harwell, but then there were people like David Barnes for example in the unit there. He was a clinician but no longer doing clinical work. But when I went to Edinburgh, I mean the links with the clinicians were absolutely crucial and there was Tom MacGregor the gynaecologist, John Strong who was the Professor of Medicine and Neil MacLean. I did some nice work with Neil MacLean on Klinefelter's syndrome. He was a pathologist and so that worked there and then when I went to Birmingham, again I was able to link in with the clinicians there, particularly with Bill Hoffenberg, Professor of Medicine.

PSH. Yes

DH. And great stimulation from him and of course Tony Howell worked with Bill Hoffenberg and Tony said he couldn't find anywhere to do his work and I said come and work in my lab and so Tony came and worked in my lab in Birmingham for a little while before he became a Consultant and came up to Manchester. And then coming here to Manchester what I found was that the work that had been going on in the laboratories was really not very connected into the work of the hospital and so I
deliberately set about trying to work up links with the hospital. And that worked very well. And of course Derek Crowther being there, that was an enormous help in medical oncology, and I went out of my way to build bridges with the radiotherapists and the surgeons and so on and I think that worked quite well. So I mean it needs an effort on both sides – it's not something that happens naturally I think– and you as a clinician will see it from a slightly different perspective.

PSH. Yes that's right

DH. I think it needs fairly determined scientists and willing clinicians but I have always felt that a combination of working very close to patients is a huge stimulation.

PSH. Tell me again a bit about how you managed to get the clinical cancer genetics off the ground.

DH. Well Tony Howell had got the Family History Clinic going long before I ever went there and that continued. We were doing work on groups of patients with breast cancer. David Scott was doing work on radiation sensitivity of cells from breast cancer patients and so on and we were doing a lot of work on a variety of inherited syndromes and we suddenly realised that we were not really looking after the families very well, and so I talked with Tony but also particularly with Rodney Harris, and we agreed that we really needed a clinician specialist looking after the cancer families. Tony was great in looking after breast cancer patients and he had a heavy clinical load and although he was interested in that, he wasn't a specialist in this area and so we actually advertised for somebody to come along, and the deal was, if I could find money for a couple of years, Rodney would find ways of getting the Regional Health Authority to create a position for a Consultant Cancer Geneticist . One of the applicants was Gareth Evans and he turned out to be a huge success. He was great. Took off very very quickly and committed himself to looking after the patients. Not just the breast cancer families but the Li Fraumeni; families; we were doing a lot of work with Jill Birch on the Li Fraumeni families. And Rodney came back a couple of years later and said if you can get another couple of years, I've got this promise of a consultant post at the end of it. And that's how Gareth got into his present position, now a Professor in his own right. Terrific. Great guy.

PSH. Over the years, who would you say, can you pick out a single person who you would say they were the person who really most inspired you?

DH. Oh well, certainly Charles Ford started it off. That was absolutely clear. Had it not been for Charles, I don't think I would have ever got into this field. And I think I said before, he had this amazing ability to be very, very strictly scientific and made you believe what you saw and so on. The other major influence was Michael Court Brown. Michael I just thought was terrific and we could argue with him and Pat and
Michael as you know, got on very well too and we, I think we were a pretty good team. But Michael was the driving force, there's just no question about that. But I suppose a lot of people stimulated me. I could go back further than Charles, because Murdoch Mitchison and Michael Swann really switched me on to cell biology as opposed to zoology per se, whole animals.

And the other person who made a big difference to the way I looked at things was Howard Temin when I went to work with him, when I tried to learn about viruses. He had a very sort of casual attitude which was really quite interesting. He too said if you see something you believe it and you stick to your guns no matter what people say. But he also was less meticulous than Charles Ford, but what he was after was big differences and he said "you know. All this statistical nonsense. If you show that something is significant to a particular level, it may or may not mean something. What you want is the really big things". And when we were for example counting foci of transformed, virus transformed, cells in petri dishes, I was counting them 1, 2, 3, 4 ,5 and Howard would lift up a petri dish and say "Mmm 50", "Mmm 200". I said "but that's not very accurate". He said "it's accurate enough because if the differences are the kind of differences I am looking for, that will show you". But then also, when he discovered the reverse transcriptase or the possibility that the RNA virus has a DNA intermediate, he got some very nice

experiments which showed that he could inhibit Rous sarcoma virus with actinomycin D, and actinomycin D normally works on a RNA polymerase from DNA, and he said therefore there must be a DNA step in here somewhere and he got all sorts of abuse when he talked at meetings and he said "I've got my experiments. I know they are right". When I was working with him he was regarded as 'off-the-wall', that he was a crank but he was proved right and he had the good fortune not only did he have the idea that there was a DNA intermediate, he actually discovered reverse transcriptase and I remember meeting him at a cancer meeting in Houston in Texas and he came rushing up and he said "David. David. I've found it" and one of his rivals, Saul Spiegelman, left the conference immediately and went home to try and replicate Howard's work. But of course Howard got a Nobel Prize for it. So he was a big influence.

PSH. Last question really, David. Can you pick out any one piece of work or one area of work which you feel most proud of?

DH. That's very difficult. It sounds crazy but I think the development of the skin fibroblast culture technique, because although it had a relatively short life, as the way of looking at lots of people with, looking at their chromosomes, the ability to culture fibroblasts from any individual has had a major impact in sort of biochemical genetics as well as cytogenetics and I remember being asked by John Paul, who was Director of the Beatson in Glasgow, he was running a conference, I can't remember exactly what it was about. He said can you think of somebody who could talk about you know, the sort of history of the culture of fibroblasts? I was giving him all sorts of names and he said "No. I mean you". And so I was not very old at that time and to be told that I was this historical figure was strange. I have recently had contacts with plastic surgeons for example. A man called Gus McGrowther, who is one of the top plastic surgeons in UK when I was working in Wythenshawe Hospital, and Gus is using almost the identical techniques to seed out fibroblasts into superficial wounds. He's using techniques not very different from ones I devised, although it was interesting that to begin with all the papers said fibroblasts were cultured, method of Harnden 1960. Gradually it was fibroblasts were cultured by standard techniques. And although that paper was quoted in the Current Contents as a citation classic, but it if had actually continued to be quoted 'Harnden' it would have been a super citation classic. So I guess that's probably the one thing, though I really still feel that the ataxia stuff, that was a bit of inspiration which led on to much more important scientific discoveries than the technical stuff of the fibroblast cultures.

PSH. I think you are allowed two favourites

DH. Like desert island discs.

PSH. A bit

DH. Like what can you take with you.

PSH. A bit yes. Well many thanks David. I'm going to finish there and turn the machine off.

End of tape