Bob Williamson

Personal Details	
Name	Bob Williamson
Dates	
Place of Birth	USA (Cleveland, Ohio)
Main work places	Glasgow, London, Melbourne
Principal field of work	Human molecular genetics
Short biography	See below

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Biography

Robert (Bob) Williamson was born in America to Scottish parents but lived in London from the age of 16, studying chemistry at University College London. Following his PhD he moved to Glasgow in 1963 to work in molecular biology particularly on the molecular basis of human haemoglobin and its disorders. In 1976 he moved to St Mary’s School of Medicine, London and was responsible for the development and use of DNA polymorphisms in gene mapping, especially for cystic fibrosis and Duchenne muscular dystrophy. In 1995 he moved to Melbourne, Australia, as head of research at the Murdoch Institute, and is now Secretary of Science Policy to the Australian Academy of Science.

Interview with Bob Williamson, 9th August, 2006

PSH. It's the 9th August 2006 and I am talking with Bob Williamson in Brisbane. Bob I would like, if I may, to start at the beginning and just ask where were you actually born?

RW. I was born in Cleveland Ohio, brought up in Cleveland, New York and then London.

PSH. When did you go to London?

RW. 1955

PSH. So you'd have been . . .?

RW. When I was sixteen.

PSH. Sixteen, OK. So you had enough time in America to be very much influenced or at least be familiar with America.

RW. Oh yes. Absolutely. In my high school years I was in New York, living in Manhattan, and I went to Bronx Science which was a very selective science-orientated secondary school which in those days, at least, was very very good.

SH. Was there any kind of science background in your family that influenced you to go into that?

RW. None at all. My father was a shipyard worker turned trade unionist and political organiser. My mother was a typist. No science background on either side. My father left school at fourteen, my mother left school at sixteen and I am the first person in my family who ever went near a university.

PSH. Do you think that your father's work was a factor in radicalising you at an early stage or at least in making you aware of problems outside science and academia?

RW. My family was very active in left politics and of course that does radicalise you, particularly during the McCarthy years in America. I think the other thing though, which we have talked about before, is that it is very hard to convince young people today, in 2006, the extent to which everyone in the 1950s, at least in Britain, was interested in politics. There was Campaign for Nuclear Disarmament, there was Hungary, there was Suez. It was also quite different at University. Only 3% of the population went to university and the critical thing in those days was whether you went to university or not. Once you went to university you didn't worry about getting a job afterwards. Also, many of us, including myself, won full scholarships, so I didn't have to work. I had to work in the summer, but I didn't have to work during term. So the result was

that there much more in the way of collegiate life, much more in the way of time to think about things apart from studies. A very different world.

PSH. Yes and one didn't really have to worry too much. There was no fixed curriculum or anything was there, or nothing very laid down.

RW. You were examined after three years. You might do the occasional exam at the end of one year but there was no continuous assessment whatever. In fact a proportion of the people who read chemistry with me at University College London, didn't turn up for months on end and they still sat the exams. Most people passed the exams; after all if you were in the top 3% of the population who made it to university, your were probably fairly bright and were able to pass exams, and it was quite different. There was no continuous assessment at all.

You see the other thing was that in the 1950s there were still a proportion of students who had been through the war, they were older students. There was a much more varied mix of students in many ways and therefore the staff and students were closer together. I was London student secretary of Campaign for Nuclear Disarmament for a time so I would mix with John Maynard Smith and Pat Clarke, and J B S Haldane and Peter Meadawar and we would all do things together all the time, and it wasn't just me. There were other people who have now become very prominent in biomedical research, like Robin Weiss and Patsy Healey who was Town Planning guru in Newcastle. And a large number of people, all of whom were on this interface between a total commitment to science and at the same time doing a lot of other things that brought them into contact with other people.

PSH. I guess University College was a pretty good place in terms of being in the centre of things in that way. Who were the people who really, you interacted most with on the staff at UC?

RW. Well when I was an undergraduate, I interacted a lot with Sir Christopher Ingold. who was Head of chemistry, and Alan MacColl, who was my tutor. I read chemistry, but got to know Franz Heymann who was Professor of Physics and had been working on the bomb at Los Alamos, and also Sir Harry Massey, who was Professor of Physics. I knew J B S Haldane. I knew Haldane more through politics, although the boundary between politics and science was also blurred, because all of the scientists were taking a position, most of them in opposition to nuclear testing and the development of the hydrogen bomb. So you had the Pugwash Conference when I was a postgraduate in London, which I helped on the administrative side of. You meet all of these fantastic people, and I suppose the main thing that I learned when I was at University College London came from watching the scientists. There were others: Pat Clarke in biochemistry, a woman who actually

discovered permeases back in the fifties was an influence, and Dame Katie Lonsdale, a famous X-ray crystallographer, was an influence and Eric Crook, Professor of Biochemistry. The Head of the Biochemistry Department when I switched into biochemistry and genetics was a man called Ernest Baldwin, who wrote a famous book called Dynamic Aspects of Biochemistry.

PSH. Yes I remember him.

RW. Ernest Baldwin was by this time not terribly well and didn't have as much influence on me perhaps as the others, but he also was a person who tried very hard to protect and build biochemistry as a separate discipline. You see that's the other thing, the nature of the undergraduate courses in those days. The vast majority of people went up as an undergraduate to read either botany, zoology, chemistry or physics. I don't believe there was an undergraduate course in genetics at all, even at University College, which after all was where Galton and Pearson and Haldane and Grüneberg and most of the . . .

PSH. Fisher.

RW. Fisher. Most of the famous people who set the foundations in the UK for genetics were from University College London, and yet I don't believe there was an undergraduate course in genetics at that time. That only started really in the late 60s. So there was also the fact that we were all just broader in many ways in the number of things we looked at; the courses were broad and took a wider view of science.

PSH. At that point, thinking of now, the late fifties, had molecular biology entered chemistry or biochemistry, or was it still regarded as something a bit weird and separate?

RW. Molecular biology did not really exist until the sixties. In the fifties, you have to remember Crick and Watson's paper only came out in '53. It was not accepted until roughly 1960. I remember a debate between Francis Crick and Lionel Penrose where Lionel Penrose argued against the double helix in favour of a self replicating form of protein, and against DNA being the basis of information. I remember J B S Haldane was there so it must have been '57 or '58. Crick was not accepted. Of course Crick was a physicist, and we didn't actually accept the idea, or at least some of my colleagues didn't, that a physicist could have a part to play in relation to biology. When I went to Glasgow in '63, J Norman Davidson would comment (J Norman Davidson was at this time probably one of the two or three most prominent biochemists, of course not as prominent as Hans Krebs, but a very powerful figure of the biochemistry establishment) and he would always refer to molecular biology as biochemistry practiced without a licence. And he was not saying this in jest. His intention was to force people without a licence off the road, I can assure you. And a lot of the

traditional biochemical establishment didn't accept that there was anything to learn from molecular biology. What they didn't really accept, was that molecular biology was any different from biochemistry. That was the key thing. They said, well why call it molecular biology? It was biochemistry, but molecular biology actually was a different way of looking at things.
It is also worth noting that Britain was the home of the study of intermediary metabolism. [interruption]

PSH. If I can come in just at that point Bob, and say, would it be fair to say that London, in terms of acceptance or lack of acceptance of molecular biology was really not much different from Cambridge, where Max Perutz never got really accepted into the Department of Biochemistry and had to plough his own furrow?

RW. Absolutely, and biochemistry was the place that it was hardest to get acceptance. Max was more accepted in chemistry and physics than he was in biochemistry. University College wasn't quite as stuffy as Cambridge. It actually was quite a radical place and of course Haldane was there until '58. John Maynard Smith was there. Peter Medawar became head of Zoology. J Z Young who was Professor of Anatomy was a wonderful iconoclastic force for good. And there were people, like CAB Smith who remained in genetics and always, although he was never a particularly good and dynamic populist of anything, CAB Smith was basically a very esoteric mathematician, with a wonderful understanding of statistical genetics. Nonetheless he was always accepting of radical change. The biochemists were the ones who were difficult. I started research as an MSc student in '59 and switched to a PhD in '60 and Ernest Baldwin wanted me to work on the enzymology of elasmobranch fish. He told me 'Williamson, nothing will come of that DNA stuff'. That was the general attitude and he wasn't being contemptuous or unhelpful. He thought that he was doing me a favour by getting me into the field that mattered, intermediary metabolism, but the point I was making was actually an interesting one, because now I live in Australia I see another aspect of it. One of the reasons why the biochemistry departments resisted molecular biology, was because they had been so prominent in, and good at, intermediary metabolism. So there was a wonderful tradition of winning Nobel Prizes, Hans Krebs, people like that, winning prizes for just that sort of intermediary metabolism. Why change? And here in Australia it was immunology that had that history, with Gus Nossal and Don Metcalfe and so on.

PSH. So what was it made you go to Glasgow?

RW. Well, I did my PhD in London. My family are from Glasgow originally so I'm sort of Scottish American but I always loved Scotland. I always found Scotland interesting. At a meeting, I met a man called John Paul, who was a cell biologist of really superb personal and academic qualities. I liked Glasgow as a city. I still love Glasgow as a city, it's a great city to live in. I am very much a

city boy. I don't like the country very much, and John Paul offered me a post. Now I have to tell you the other people who were there at the time, it was J Norman Davidson's department. J Norman Davidson, although he was not a very nice person, he actually was a towering intellect and he was a very good friend to Chargaff for instance and he knew all about the Chargaff rules. He knew about nucleic acids and he also knew a great deal about RNA polymerase, as did Martin Smellie. Hamish Munro, a very very charming and erudite character was there at the time, and John Paul. It was terrific.

And so Glasgow was a city I wanted to live in, I wanted to go to Scotland. Although I was brought up at least to some extent as Scottish, I had never lived in Scotland. I finished my PhD, and of course that's another thing. I finished my PhD in 3 years. Everyone did. You just finished your PhD in 3 years and I got out a couple of good papers in the Journal of Molecular Biology, which at that time was the top journal in the field, which was nice. My research was on what we could now call messenger RNA. Now you see, that's the other thing. When I started no one knew messenger RNA existed in mammalian cells. In fact some people like Henry Harris argued for ten or fifteen years that messenger RNA did not exist in mammalian cells. It was all a lot of nonsense and we would never find it. The work that I did for my PhD was on polysomes, an interesting experience. I worked on rabbit reticulocytes because at that time you thought you had to know the protein in order to do any genetics at all. So it wasn't a bad choice and I worked with a terrific guy. You have talked about mentors. Hugh Huxley did electron microscopy with me, was one of my mentors, and we had these wonderful polysomes that we thought were aggregates. So we spent all of our time trying to work out ways to dis-aggregate these aggregates of ribosomes that of course were really polysomes. Hugh Huxley was the most superb technologist with electron microscopy, I didn't realise until some years later that it wasn't actually easy to do electron microscopy because he made it looked so easy. He would just take the grid and throw a couple of drops of osmium tetroxide on it, wave it over some fumes and then get these beautiful, beautiful pictures. We published the work but we got it wrong. I mean basically John Warner in the States, in roughly Christmas 1961 it must have been, published the first paper showing that the aggregates of ribosomes were not aggregates at all. They were polysomes held together by messenger RNA. I then did some work on isolating messenger RNA using zonal ultracentrifuges. This was before messenger was known to have poly A and so you couldn't isolate it biochemically. You had to isolate it by spinning it out on these monstrous machines that had a capacity of over a litre of solution. They were quite unbelievable.

PSH. Was it human RNA?

RW. No this was mouse at that time.

PSH. And was it any, I mean what kind? Had you yet gone into the globin area?

RW. Oh yes, I started work on globin in 1959 and I started work on globin because even then I realised that at that time it was the only way to look, I believed in messenger RNA in ‘59/’60, and I realised that the only way to isolate a messenger RNA and work out what coding might mean. Remember the genetic code wasn’t worked out until 1961 by Matthaei and Nirenberg, who did the poly U translation experiment getting polyphenylanaline?

PSH. Yes.

RW. I was at the International Congress of Biochemistry in Moscow in summer ’61 when that was announced. Until then no one had any idea what coding meant, what messenger RNA meant, so the one thing I did recognise was that in order to do this you had to start with the cell which only made one or two proteins. So we made rabbits anaemic, with phenylhydrazine. We isolated large numbers of reticulocytes and these reticulocytes only made alpha and beta globin and the messenger RNA runs at a characteristic size 9S and the ribosomal RNA is 28, 18 and 5S. So if you spun it out on a gradient, you could isolate the messenger RNA and we worked out a number of ways of doing that. As I said this was before messenger RNA was known to have Poly A so there wasn’t any other way to do it. And doing this we also showed that very low amounts of ribonuclease would actually break the polysomes into monosomes. So when I went to Glasgow I continued to work on this but of course John Paul was a wonderful tissue culture person. I should say another person who was there at the time, Robin Cole who tragically committed suicide some years later, was a wonderful person to be with, and Bob Edwards who did the first IVF work.

PSH. I didn’t realise Bob Edwards was there.

RW. Bob Edwards was there with John Paul and myself. We overlapped by about 6 months and it was enormous fun to be with some of these people. They were wonderful mentors. They knew so much.

PSH. At what point then did your work take, what you might call a human molecular turn?

RW. Well, John Paul was a medic and so he was always interested in the implications for humans. But right from the start I wanted to work on medical applications. I got a grant for my PhD work from the British Empire Cancer Campaign in 1959 or 1960 and right there I was already talking about sickle cell anaemia and so on, and that may have been influenced by J B S Haldane who was in India at that time but who had influenced me a bit on that a couple of years before.

PSH. Were you familiar then with Haldane's kind of almost throw-away idea that there might be heterozygote advantage?

RW. I don't remember being aware of it, but Haldane was hard work to follow, because he constantly threw out new ideas. A very, very rich person in ideas. So the real question was always how can you do this with humans, and for the next three or four years I actually didn't publish much. I did a bit of work on erythropoietin and how erythropoietin stimulated erythropoiesis. I did quite a bit of work on sequencing messenger RNA. I sequenced human 5 SRNA with George Brownlee at Fred Sanger's lab. I went to Cambridge to do that and then I met two people in about 1972 who had an enormous influence on me.

The first was David Weatherall, who at that time was Senior Lecturer or might have just been made Professor of Haematology in Liverpool. He didn't go to Oxford until roughly '77 I think. The second was Bernadette Modell, who was the clinician delivering care for thalassaemia to the Cypriot community in North London, and was a very, very good embryologist and developmental biologist long before she was a medic. She only trained as a medic in her thirties. I also knew Anne McLaren very well at that time; I had spent a lot of time with Anne, who was still in Edinburgh at that time, not in London yet. I also intereacted a lot with other Edinburgh staff, people like Bill Hayes and Martin Pollack who were bacterial geneticists with an interest in human genetics. But David and Bernadette were the first to point out to me that if you wanted messenger RNA from humans, the place you could get it from was exchange transfusions for babies. If they were suffering from haemolytic disease, Rhesus haemolytic disease you could get both alpha and beta message, but if you wanted just alpha message, what you could do was to get blood or bone marrow from a child with beta thalassaemia. And if you wanted beta globin message, you could take the placenta from a child with alpha thalassaemia; these children die at birth with homozygous alpha thalassaemia. David had very good contacts in Thailand and we actually got the blood from a hydrops foetalis baby sent to us by a doctor in Thailand called Pootrakul. and it was wonderful to put all this together.

The other thing that happened was that Sergio Ottolenghi, who was a medic from Milan, joined me for 2 or 3 years as a post doc, and Sergio was just wonderful. He understood the medicine, he understood the science and he has something that I don't have. He has patience, so was able to actually stay in the lab and do the work and make sure it really worked. Whereas I have ideas but I don't have that much patience.

PSH. Were you in contact at all with Y-W Kan and his group at that point?

RW. We weren't in touch with Y-W Kan until a bit later. I know Y W very well now. In 1974 or 75 we started doing an experiment. This

was before PCR, before cloning. So what we did was to make globin cDNA using reverse transcriptase. We made globin cDNA from blood from an exchange transfusion from a Rhesus haemolytic case. So that would have both alpha and beta and gamma globin mRNA. Then we hybridised that against an alpha thalassaemia hydrops mRNA, which would have beta and gamma globin but no alpha. The only cDNA that would not hybridise was the alpha globin cDNA. We isolated, I think it must have been about two thousand counts in all. Two thousand tritium counts, and this took Sergio about 9 months and we then hybridised it against DNA from a normal individual and from someone with alpha thalassaemia and we showed that in alpha thalassaemia the genes were deleted. We then heard a rumour that Y-W had done exactly the same experiment so I phoned his colleague Harold Varmus. I rang them up and said look these are our results and they said well we've got these results too. So I said let's co-ordinate and submit the papers together and they said 'sure'. Because in those days you did that sort of thing and so the papers were published back-to-back in Nature.

RW. And I actually spoke to Harold Varmus, I don't know if he will remember. It must have been '74, it might have been '75, and the papers were published back to back in Nature. That was the first demonstration of that kind of molecular analysis and it's still an experiment of which I am really very proud. This was an incredibly hard experiment to do in those days.

PSH. Was that really the first time when you realised you could actually do something in human molecular genetics that was going to be of major medical significance?

RW. No. That experiment was actually an obvious experiment, so I had no doubt that the approach would work. Because remember, the thing about sickle cell anaemia and thalassaemia was we knew the protein that was involved, and because we knew the protein it was obvious, By then Sanger was sequencing RNAs, not DNA yet but RNAs. By then the biochemical geneticists had identified enzymes that were defective. Some of these were being localised using a whole range of cell genetic and cytogenetic technologies. Although it was lovely to participate in that experiment, everything up to that point was just obvious and built on what went before. The thing that changed that was cloning, totally. Gene cloning.

PSH. Yes, but then, I'm thinking a little bit of the chronology. Am I right it was '76 when you moved to London.

RW. Yes, I moved to London in '76, yes.

PSH. But at that point, my kind of impression is that you were still centred on haemoglobins.

RW. Completely.

PSH. With RNA and cDNA,

RW. Completely.

PSH. And what used to be called reverse genetics, but then became positional cloning, hadn't really entered the scene.

RW. It wasn't there. It wasn't there at all. For positional cloning, it came at a distinct moment in time, and the man does not get enough credit for it. The key event was the Kan and Dozy paper and the letter that appeared from Walter Bodmer and Ellen Solomon in Lancet, I seem to remember, which suddenly brought molecular genetics and traditional genetics into conjunction. And I was there when Kan first reported those data. We have to go back. In '76 we came down to London. I was a member of GMAG, Genetic Manipulation Advisory Group, and one of the things we were very keen to do was to clone the human globin genes. My group, Peter Little, Mike Courtenay, Emma Whitelaw, people working partly with Charles Weissmann in Switzerland, set out to clone alpha, beta and gamma globin genes and we did. We did it in '76/'77. The minute you have cloned, you have unlimited material and using nick translation as the labelling technique, you are suddenly not chasing two thousand tritium counts, you are looking at a million P32 counts and you can do a whole lot of Southern blots. You can do everything. So we were able to define the organisational structure of the genes, and by this time Poly A had been defined as a component of message. Therefore oligo DT could be used to get mRNA out.

We isolated the cDNA clones for alpha, beta and gamma globin, human, of course. We were able to use these to define the gamma gamma delta beta organisation of the gene and I organised a meeting in Crete in 1978, I think, which Y-W Kan came to. In those days this was a 12 day meeting and everyone came and stayed for 12 days. We actually paid everyone's fare. No one paid their own fare. We paid for all expenses and everybody came to the meeting. There were 100 people at the meeting including the whole of the Italian and Greek community of physicians who later became all the leaders of the field. And Y-W was talking on day 4 or day 5 and he didn't say a word until day 4 or 5 and then he described the critical linkage experiment, showing the polymorphism that's in linkage disequilibrium with haemoglobin S. And it was stunning and everyone realised the minute he said it exactly what it meant. There is a certain revisionism of history around this. A number of us including David Weatherall and myself went up to Y W and just congratulated him. It was seriously, probably the most important thing I have heard in the whole of my scientific career. The Kan and Dozy paper explained it beautifully. Solomon and Bodmer realised, were the first to realise, the extent to which this allowed the super-imposition of a genetic map and a physical map. And so called reverse genetics, positional cloning, is really about the super-positioning of a genetic and a physical map on each other. And so

all of a sudden, because of cloning, we had a very large number of positionally located sequences of which we could prepare large amounts and which we could distribute to one another and at the same time, we also had, we were beginning to develop the family resources, and the DNA resources to look at it. So Kan and Dozy really were the people who suddenly made the whole of genetics accessible to molecular technology through that one advance.

PSH. Now the Solomon and Bodmer letter, was that late 1979?

RW. I thought it was '78. It was well before Botstein and White.

PSH. Yes that was 1980 I think, wasn't it, or thereabouts.

RW. Incidentally, it is also a lovely letter because it is only 3 paragraphs long, as I remember, and has everything in those three paragraphs.

PSH. Apart from being an insight, was that the sort of thing that started your re-orientation of your own department's work would you say?

RW. Absolutely, until then, I was totally on haemoglobin and working on thalassaemia. I should mention that one of my personal characteristics is that I do get bored very easily with what I am doing and so I tend to jump from one thing to another. I also have a principle that if I have a first rate PhD student or post doc, I let them take the project with them. I don't keep projects. So in 1979 and 1980, several people moved, Peter Little was moving, Mike Courtenay was moving. Ray Dalgleish was moving. Since these people wanted to take projects with them, I let them and that meant I had to find new things to do. I realised that we could now do linkage with anonymous probes, one chromosome at that time. I wanted to work on cystic fibrosis, literally from about '78/'79.

PSH. I was going to ask you about that because, I was going to ask you later but since you've got to it, I will ask it now. What was your particular motivation for CF, which is something you have stuck with for many years?

RW. Well, in the first place, there was a man called Ron Tucker who ran the Cystic Fibrosis Research Trust in the UK, who came to me and said "I hear you are pretty good at molecular genetics." I don't even know if he called it that. It might have been molecular biology at that time. We've got this disease, cystic fibrosis. We understand there are about a couple of million carriers in the UK. Why don't you work on it? We will give you money (something that helps, because you need money to tackle hard problems). The second thing is that although in some ways I'm an internationalist, and I like working on diseases that affect large populations, like Italy and Greece and Cyprus and South East Asia, I do think that research should be relevant, after all I have received backing from the MRC and the

British Empire Cancer Campaign, virtually from Day 1 and I thought it would be nice to be able to do something on a disease that was the most common severe inherited disorder in Britain.

So I was interested in it but of course you couldn't just start working on CF. The reason was there were only about thirty DNA sequences that had been located to chromosomes and indeed in Oslo (when was the Oslo Human Genome Meeting, number 6? It would have been about 1981 or something like that). I remember at that time there were only about thirty or forty sequences localised and the only chromosome, as you know, that was mapped at all well was the X. At least the X had about twelve of these sequences up and down. At that time, I had a sabbatical in Paris with Francois Gros and Margy Buckingham, which was a terrific time. I met Kay and Steve Davies and Kay agreed to come back and work in our lab. At that time Julian Crampton and Derek Woods were also working in the lab on chromosome mapping for CF. Julian is now Vice Chancellor of the University of Brighton and Derek is head of some big biotech company in America. And we started by making libraries, gene libraries from CF cells and normal controls and then we tried to compare the libraries. It was actually an incredibly bold thing to do that had no chance whatever of working. We didn't know anything, we really didn't. With hindsight, I shudder to think how naive the experiment was.

PSH. Well it was a very good thing. If you had taken people's advice about what was impossible, a lot of those things would never have happened.

RW. Yes. So at that time, Kay and I decided to focus on muscular dystrophy and you come into the story here at some extent. But once again the revisionism of history is very interesting. Very few people remember that at that time Becker was localised towards the end of long arm of the X chromosome and Duchenne to the short arm.

PSH. Indeed.

RW. And there were all kinds of things like that and there was no agreed location. There were one or two translocation cases which we didn't give enough weight to, I must say, with hindsight. We should have given more weight to them. But it is also worth remembering that karyotyping wasn't that great in 1978 or '79 either, and all you saw a lot of the time were blobs, you know, grey blobs superimposed on black blobs and so we decided to start by trying to localise Duchenne muscular dystrophy using molecular techniques, and met you and you had wonderful, wonderful clinical resources which you could access and understood the disease and we had a lot of chance to progress. The other interesting thing at the time was that we were told in absolutely no uncertain terms by John Edwards, who was Professor of Genetics at Oxford, that this was not only impossible, but foolish, career wrecking and so on.

PSH. I remember that. I remember we were both in the same muscular dystrophy symposium when he said that, but I can't quite remember whether it was before, I think, we had already got results by then and so we just kind of kept quiet. The other thing which I have always reckoned on as being very critical, I remember the excitement at the time, was the chromosome sorting and the production of an X specific library, because that was really something that nobody else had done at all.

RW. Yes, we sorted human chromosomes and we started as I remember with a 3X cell line and then Brian Young, who was a physicist, who at that time was still in Glasgow, and Rob Krumlauf who eventually became Director of the Stowers Institute in Kansas. Brian Young is Professor of Cancer Physics at Barts. They were both involved in this and with Kay and myself. And yes, we made an X specific library in that way. The thing we did the next year was to use chromosome cutting, we made a gene library from a band of the chromosome and Steve Brown and Gill Bates were involved in that work. Yes.

PSH. Those were very fascinating times. At what point did you feel it was time to go back to CF, that it was feasible now to do it? Was it when the linkage came up?

RW. No, the CF linkage?

PSH. Yes.

RW. No, we found the CF linkage.

PSH. I wasn't thinking of the DNA linkage. I was thinking of the protein.

RW. No. The paraoxonase linkage. No that actually, you know you are testing my memory a bit on exactly what order those things happened in.

PSH. Not to worry.

RW. No, the Duchenne problem changed. A whole number of things happened around then. Kay decided to move to Oxford and set up her own lab and to work at that time with David Weatherall. Kay wanted to take Duchenne with her and that was fine. So Kay took Duchenne, and Derek Woods and Julian Crampton moved on, but Brandon Wainwright arrived at that time. Brandon wanted to work on CF and this must have been 1983. '83 it would have been and Pete Scambler, who is a paediatrician, arrived from UC. And so we had Brandon and Pete and a sort of changing of the guard. It was a good time to try it. By this time, by '83, there must have been about a hundred and twenty, a hundred and thirty gene probes around the genome. The very first chromosome we tried as I

remember was 19. If you look at my CV you will find there's a paper there on exclusion mapping and I think it was 19 we used because I think we used C3 as part of that map.

PSH. I think it was. That was one of the early probes that Kay was involved with.

RW. So we showed that it wasn't on 19 and then we began to do the total map. Now Eiberg, was it Hans?

PSH. Hans Eiberg

RW Hans Eiberg found the paraoxonase linkage studying a protein polymorphism. But Hans was very silent, seldom spoke at meetings, indeed seldom spoke at all. And so we only became aware of the significance of the paraoxonase linkage when paraoxonase proved to be linked to one of the DNA markers, and by that time we had already looked at several. We had found the linkage, and had two markers that were closely linked both to CF and to paraoxonase. Ray White also had one or two, as did Lap-Chee Tsui. The whole issue became confused because Helen Donis-Keller, who had provided markers to Lap-Chee, announced that she had patented the human genome and this idiot from some biotech company which is now deceased, thank goodness, said 'we own chromosome 7' and that created a political furore at the time. The three papers again, for probably the last time ever, were published back-to-back. in Nature one after another. Brandon (Wainwright) and Pete (Scambler) were very much involved in that work.

PSH. One thing at this point, if I can revert to again, your links with Bernadette Modell. I hadn't realised they had started so early, but in terms of what you might call practical application, these were very critical coming in again in chorion villus sampling.

RW. I was involved in the very early chorionic villus sampling experiments too and in fact we had a paper, I think it was in the New England Journal, that showed that chorionic villi could give a completely clean fetal DNA analysis. There was no serious problem with maternal contamination in the chorionic villi. Also Charles Coutelle and I did some single cell DNA analysis. But I remember before chorionic villus sampling was available, before it was first done, in 1977, Bernadette and I held a meeting to which we invited Anne McLaren, and the original suggestion to try CVS actually came from Anne, and was also based on some work published in a Chinese medical journal. Anne McLaren said to look at these beautiful little villi. Why don't you get one out? And we had an obstetrician there from UCH, whose name escapes me now, not Charles Rodeck who became the academic one.

PSH. That wasn't Humphrey Ward?

RW. Yes. Humphrey Ward. He was doing needling and trying to get chorion out, just doing it by touch, and he was just the most superb operator I have ever seen.

PSH. Bob, we have got limited time and we could go on to a lot of other things, but before I just ask you a little bit about Australia, there's one thing I think is so important that I would just like to bring up and that is, if you look at the people who have worked and trained with you, they are the most extraordinary roll call, able people who have gone on to things in a tremendous range of fields and places and that's in my view a tremendous legacy to leave. Can you think of, perhaps difficult to ask you, I should ask them, but can you think of any reasons why you were able to attract and enthuse such a very large series of outstanding folk?

RW. I'm very proud of the people who trained with me and where they have gone. It's a terrific bunch and they have done incredibly well. I think I am an enthusiast myself and if you are an enthusiast you attract enthusiasts. I love working with bright people and I'm reasonably good at spotting bright people. I commented already that I think that anyone who is a leader in this kind of area and in advancing scientific field, has to combine this with generosity and the generosity in my case meant that many of these people actually took their projects with them. And as you know, with myotonic dystrophy which was the other thing you and I worked on together, I gave Keith Johnson myotonic to take away with him when he moved.

PSH. Absolutely.

RW. . . . and work on himself, and Steve Humphries took cardiovascular genetics and Kay, Duchenne and they've mostly continued to work on those subjects, while I've worked on everything under the sun. I think that the other thing is, you have to mentor people and teach people to be brave and try to do very difficult projects. I suppose the fifth thing would be, you have to teach people to respect other's skills. I'm a chemist. I'm not a medic. If I judge my medical friends by the standards that Sir Christopher Ingold and Sir Harry Massey taught me in Chemistry and Physics, they wouldn't measure up. But they measure up so much higher in other skills, in different things, and it's a matter of having respect for what people are excellent at and accepting that sometimes it's different, qualitatively different from what you are excellent at. So I hope that a fair number of the people who trained with me picked up some of these things. When I now spend a certain amount of time trying to teach senior people how to mentor other people, it's amazing how many senior people have not learnt to be generous. How many senior people are actually mean and try to control everything. They are fine with junior people as long as they are junior and as long as they are working *for* them, but there's no generosity there. Those are the sorts of things I do.

PSH. They are good reasons. The other thing I wanted to touch on. You moved to Australia, what was the year ’92?

RW. ’95.

PSH. It must have been a really big jump, change and I mean in terms of your years here at the Murdoch, can you sort of single out what you feel really most proud of?

RW. In Australia?

PSH. Yes.

RW. Oh I’m proud that I was able to make the Murdoch a very much broader genetics and Child Health Institute with 600 staff, where people who are interested in genetics mix with people who are interested in cardiac surgery and mix with people who are interested in the psychological determinants of accidents and all the rest of that. I really believe that all of the advances in 2006 are happening in between silos and in interdisciplinary areas. When I was a kid, when I was a university student the advances were happening inside silos. They really were. If you look at the history of immunology and the history of biochemistry, immunology was run by immunologists and the advances were made by immunologists. Same for biochemistry in the 1950s and 1960s. But now the advances are all made by genuinely interactive multidisciplinary teams, between disciplines, so I am very proud I was able to introduce that. Very proud I was able to start an ethics unit. Julian Savalescu, who is now at Oxford, was our first professor of ethics and to actually have an ethics unit embedded in a major medical unit was great. You might ask, why is it that LMB in Cambridge, why is it that NIMR in Mill Hill do not have an ethics unit and this goes back to where I was brought up. There was at University College London in the fifties, Freddy Ayer used to come, he was professor of philosophy at that time in UC before he moved to Oxford, used to come and talk to us and talk to us as an equal about the interface between philosophy and ethics and what was happening at that time, mostly in nuclear physics, mostly around the bomb, mostly around testing, all of those things. But nonetheless it was natural that you did that. So I suppose I’m proud of those things. I’m very proud of getting things like a life membership, sort of emeritus membership. Emeritus sounds incredibly old. I don’t feel quite that old, but I am proud of getting my AO, the equivalent of a knighthood here, because it is nice to be a new Australian and have so many friends.

PSH. A couple of things I have been asking everybody, just to finish. One I have half asked but if we go back to your early work before Australia, is there anything you feel you particularly identify with, as what you might call your favourite contribution in the pre-Australian years?

RW. Oh, definitely participating in and being a figure in the transition from using molecular techniques to advance conventional genetics, which was what we were doing with thalassaemia, where it was all predictable; we were just using better tools. The molecular tools were better tools but it was all the sort of thing one would have done. Being involved in the transition from that through to whole genome mapping, association studies, the coronary heart disease studies, which I didn't talk about very much, but which Steve Humphries and I started at Mary's. It was terrific to be able to find a complex disease and to put together the interactions of several genes. All of this was new. This was not classical genetics at all. This was the new genetics. That's what we used to call it, wasn't it? The new genetics. And so participating in that from roughly 1978/79 until roughly 1989 and seeing the start of the real movement into the big genome projects.

You see once '87, '88,'89, came, although I have nothing against big projects, God knows, the whole way in which the project is done changed. What we have heard about at this meeting is that if you don't have five thousand bucks a night to do a run, forget it, and it does make it difficult for the little people and funnily enough, in a way your lab and my lab always were little people in a sense. And it's hard now to do that, but there was that wonderful period from roughly '78 to roughly '87 when people like you and me and the others in the field, and Kay and Steve, we actually changed the way in which the field looked and I'm terribly proud to have participated in that.

PSH. Last question, because you've got to go. Can you identify any one particular person who you feel was an especially important influence on your early development of your career and work, or does it share out between a number?

RW. It shares out enormously. John Paul was very important to me. He was Professor of Cell Biology and Biochemistry back in Glasgow. I worked very closely with him for about 10 years. And John was important because he tried to teach me patience. He never succeeded but he tried to teach me patience, but he did teach me generosity. He really did teach me generosity. So John was very important. And John also didn't agree with all of my outside views so it was nice to actually have a mentor who didn't agree with everything, didn't go on the same marches that I went on In the early days there were people, some of whom were actually very influential without realising it. I mean Haldane, Maynard Smith, Pat Clarke, Ingold, Massey, Hayman. And the reason they were influences was because they taught me a little bit about what it means to be an intellectual, just the way you think intellectually, the way you do things intellectually.

I suppose the other person who had enormous influence on me was Don Brown, D D Brown at the Carnegie Institution in Baltimore. I spent a year with Don Brown on sabbatical. Don Brown is the only

person I have met, actually to be fair, Fred Sanger did it too, but Don Brown did it better than anyone else I know. Don would sit around doing nothing for a week, absolutely nothing. His sole interventions in the lab were "Come on Bob, let's go for an ice cream sundae." We would go over the road, have a sundae at the drug store, go back in the Baltimore sun, and then we would just sit around and talk; and then Don would do an experiment, one experiment every two weeks or so, but the experiment was perfect. It actually gave him a figure for a paper. It gave him an answer, every experiment he did was beautifully designed to give him an answer and I have never achieved that. It's just so wonderful to work with someone who could do it. And the reason was that although he was sitting there doing nothing, he was doing mind experiments all the time, and working out what is the most economical and precise and rigorous way in which I can prove that 5S RNA is used in this way and in a Xenopus oocyte or something like that, and for a paper that he would publish in PNAS that had five figures in it, he would do no more than six experiments. Every one of them worked, and that had an enormous influence on me, although I am still embarrassed I can't do it at all.

PSH. Bob before I finish, I've had to be very selective, but are there any major things that you feel you want to be asked that I have completely missed out?

RW. No.

PSH. There's room for lots of people to do different interviews but I have deliberately concentrated on the earlier years. So Bob, many thanks and now you've got to catch your flight.

End of recording.