Walter Bodmer

Personal Details	
Name	Walter Bodmer
Dates	Born 10/01/1936
Place of Birth	Germany (Frankfurt)
Main work places	Stanford (USA), Oxford, London
Principal field of work	Population genetics, cancer genetics
Short biography	See below

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Biography

Walter Bodmer studied mathematics at Cambridge University where, having become fascinated with genetics through courses taught by R A Fisher as part of the final year mathematics programme, he did his PhD with Fisher in population genetics. He then went as a Post Doctoral fellow in 1961 to work with Joshua Lederberg at Stanford University and to learn molecular biology. While there, eventually as a member of the Faculty for eight years, he initiated the work with his wife, Julia Bodmer, and with Rose Payne, which contributed to the discovery of the HLA system, and also his long standing involvement with somatic cell genetics. In 1970 Walter Bodmer returned to the UK to take up the chair of genetics at Oxford. In 1979 he left Oxford to become Director of Research at the Imperial Cancer Research Fund Laboratories in London and was appointed the first Director-General of the Fund in 1991. On retirement from the ICRF in 1996, he returned to Oxford University as Principal of Hertford College until 2005, and as head of the ICRF, now CRUK, Cancer and Immunogenetics laboratory at the Weatherall Institute of Molecular Medicine where he continues his research. Walter Bodmer was one of the first to suggest the idea of the Human Genome Project and was first a Vice- President, and then the second President of HUGO. He has made major contributions to human population genetics, somatic cell genetics, the development of the HLA system and more recently to cancer genetics, especially as applied to colorectal cancer. Walter Bodmer was elected FRS in 1974, Knighted in 1986 for his contributions to science, is a Foreign Associate of the US National Academy of sciences and is the recipient of more than 30 honorary degrees and memberships and fellowships of scientific and medical societies.

INTERVIEW WITH SIR WALTER BODMER, 12TH JUNE, 2007

PSH. It's Tuesday 12 June 2007 and I'm talking with Sir Walter Bodmer at the Weatherall Institute of Molecular Medicine, Oxford. Walter, I try in these talks to start at the beginning, even though briefly. Where were you actually born?

WB. I was born in Frankfurt in Germany. My father was Jewish and my mother was not, and we had to leave because of Hitler. We left very late, in mid 1938. I was only two and half but I had two older brothers who were four and six years old. So we came here then. It had to be a subterfuge. My mother brought three young kids and my father went to Switzerland on holiday or something.

PSH. Did you all manage to get out, your immediate family, OK?

WB. Oh yes we did. There were sisters, at least one sister of my father that didn't. Some other members of the family left early, on his side, went to what was then Palestine so now I have cousins there. And you know as a kid it all seemed perfectly normal, but in fact it was a very difficult time. They couldn't take any money out and my father, who knew no English really, had to take his medical exams. They had a quickie course for people like that in Edinburgh. So he was able to take an LRCP and S as it was then, in a couple of years, and they were very helpful. And then of course when the war came, although he was interned, fortunately for only 6 weeks, my assumption is that all the British doctors were called up so there was space for the refugee doctors, so he was able to settle down quite quickly at that time. We remained stateless with him, because you couldn't get, and it's an interesting comment on sex bias in the wrong way, because although my mother was formally British born and was given back her British passport, she never lived in England. She had an English father who was part Swiss and was registered with the British Consulate in Germany. The British gave her passport back immediately we came here, but we were not allowed to take her citizenship. We had to follow my father's, which was of course to be a stateless alien and it was only after the end of the war when we were allowed to be naturalised. And then Bodmer was actually my mother's name. My father's name was Billigheimer, after a small town in south Germany, which must have been connected with the family. He was born in Würzburg. And Bodmer is my mother's name and is quite a well known Swiss name. We have some moderately distinguished Swiss ancestors on her side.

PSH. Which city were you in?

WB. We went to Manchester. For reasons that are not entirely clear, the government only allowed settlement in a selected way, so presumably, although the natural place for him to settle would have been London, he was sent to Manchester because they felt that that was where there was more need, and they wanted to spread people about. Which actually for us was quite fortunate, may have made it easier for him. Quite surprisingly my older brother, who was nine when we came over, went to Manchester Grammar

School. My father was quickly aware where you had to go to get a good education so in fact all three of us went there and that's where I met my wife and all that. So actually Manchester was not a bad choice.

PSH. Were there any special factors that took you into science and medicine?

WB. Well I didn't go into medicine, to my father's great regret. He was a doctor. He would have loved an academic.....

PSH. I'm thinking of what you might call medical science.

WB. Well, I understand. I mention that specifically because he was thwarted in wanting an academic career because he was Jewish even in the 1920s, and he always wanted one of his sons to study medicine and I was the last hope and went and studied mathematics in Cambridge. In those days you could do the Maths tripos, part two of it, you didn't have to do part one if you'd got a scholarship, which I was fortunate enough to get. There's another story there too. I did part two in two years and then part three was what you would probably think of as a graduate course now. I think it's largely done now as a graduate course, in which you could choose topics and I'd become stimulated by an interest in statistics because David Cox , who you no doubt know about . . . It was his last year I think there giving lectures of a survey in statistics, which was excellent and that's what stimulated my interest. And I took this statistics course with numerical analysis; then there was this guy Fisher who gave these courses in genetics that I thought were interesting, and I'd heard of him obviously. So I decided to take those courses the summer before by a guy called George Owen, who was in his department. He actually ended up by formally being my supervisor, though not in practice. I was told to read a few books on genetics. So there was Srb and Owen and then there was Fisher's Genetic Theory of Natural Selection, there was Design and Experiment and Statistical Methods for Research Workers. As I always say, just a little light reading list for the summer. But in fact it was a whole new world for me, especially just the basic genetics, and I was immediately fascinated. So within the first term of my third year when I'd already started taking Fisher's courses, I went to him before the end of the term and I said, would you consider taking me on as a graduate. Well he was very positive and very encouraging and the interesting thing is, although he was such an outstanding scientist, I think one of the greatest scientists of the 20th century and a mathematician, he'd hardly ever had any maths students come and work with him. So I had already got a first in part two and so he supported me very strongly for getting an Agricultural Research Council Studentship.

PSH. Am I right, you must have been one of the last students that Fisher had?

WB. Yes I was. There was a small group of us, Peter Parsons was another one, a guy called Jeff Gale who you may know of.

PSH. I've heard of him.

WB. And we were contemporaries and Anthony Edwards was a year behind me and he parcelled it out a bit and we were amongst his last students.

PSH. Sam Berry?

WB. I don't think, Sam Berry didn't do his PhD as George Fraser did. They did part two Genetics. George I think was actually possibly the sole person to do part two genetics in Cambridge in the first year it was given, and the Department was very thin on the ground. And Fisher retired a year or two after I came and he was still around. And so George Owen, he did a lot of lecturing at one time and then didn't do that much, so in the end a lot of the genetic teaching was done by Peter Parsons and myself and that's how I learned microbial genetics and then I went Sidney Brenner's lectures. So although in some ways formally you know it would be considered not terribly acceptable it was a tremendous experience because it forced you to learn things.

PSH. What was your thesis project?

WB. It was a mixture of things. Fisher had suggested I look into the problem of homostyly in primroses, so a lot of it was actually that and he had collected data on the incidence of homostyles, particularly in Somerset and I later went there again with David Hopwood, which is another interesting little story. So it was to do with in the end, the population genetics of homostyly in primroses, how it could increase in frequency. How it didn't overwhelm the population, and what kept it in balance. I did some experimental work showing that in fact you didn't always get self fertilisation, because you got a disparity between pollen maturation and stigma maturation and when the anthus dehisced, and Jack Crosby, who probably had told Fisher where the homostyles were, had a totally different idea what maintained them, which I totally disagreed with. He was quite antagonistic, but it was very good for me because first of all, I was then, I think, at the same time as Jack Crosby, and there was a guy called Fraser in Australia a little before, really the first person to do complex computer simulation of genetic models as they were quite complicated equations and wanted to introduce nonlinearity and stochastic elements and that was a large part of my thesis, so I used Edsac II the computer that LMB were using for all protein structure work. That was extremely useful and also it led me to the idea merely based on what Fisher had done on perturbation analysis near equilibrium which is, you know, what John Maynard Smith later called evolutionary stable strategy. I mean all of that was merely artificial. What I did was, all it is linearising the equations near the points of equilibrium and you can get a lot of information about the initial rates of change and so on. So that was a major part of my thesis.

And then there was a mixture of other things. I did some mouse genetics linkage between pallid and fidget. I was doing some work on polydactyly and did some general things which Fisher suggested, actually one problem in numerical analysis, distribution of prime numbers and things like that.

PSH. Did you have much contact with what was happening in Oxford with E B Ford and the insect work?

WB. A certain amount, because Fisher and Ford were good friends. And it was always said that Fisher liked to have pretty young girls looking after the mice and had Ford succeeded him there would have been pretty young boys around the place. And so Ford and he, I have to go back a minute, he certainly knew of my work on Primula before I went to the States and in fact when I came back in 1970 to the Chair of genetics he said I was one of the world's outstanding Primula geneticists, which wasn't very difficult. There were probably only about half a dozen of them anywhere in the world. So yes, and of course I then later got to know Ford reasonably well when I was in Oxford.

PSH. Did you meet Luca Cavalli-Sforza at that point, or was that later when you went to America?

WB. Luca and I have the distinction of having been mentored both by R A Fisher and Joshua Lederberg, a unique distinction, so I knew about Luca's work quite well at a very early stage. He of course spent some time in Cambridge and in fact, later when I took up some experimental work on Neurospora, I opened a fridge that hadn't been used since he left, which had some of his plastic in. So I actually met Luca first in Cambridge in 1957 because I had been interested in some ideas of quantitative genetics and he visited. Then we met again at the first scientific meeting I ever went to, was the International Statistics Institute Meeting in Stockholm. In the summer of '57 I had been a graduate student for one year and Fisher said why don't you come and he was President that year. I'm pretty sure Luca was there. And then, I'm not entirely sure if this was a coincidence, to this day I don't know exactly what happened but I have a feeling Luca must have said something to Joshua Lederberg that eventually enabled me to go there. Luca had worked a lot with Josh, jumping ahead a bit, he'd given a course in statistical genetics and Josh had asked him to give another one and he didn't want to do it on his own so he said to me would I partake with him and that was the origin of our work together

PSH. So did you go direct from Cambridge to Stanford?

WB. Yes, I finished my PhD in '59, done all the computing and stuff and I was fortunate to get a research fellowship, college research fellowship at Clare College which was where I had been an undergraduate and a postgraduate. In fact I was promised a job later that would have been a tenured job but I actually, somewhat at Thoday's instigation you know, Go West Young Man, and obviously I got to know Francis Crick through Fisher and I had been to Sidney Brenner's lectures so I knew, first heard from Fisher about the structure of DNA and how it works, but you couldn't not be involved in that and just occasionally go along to the LMB. In fact I first applied to go to the States to work with Max Delbruck at probably Francis Crick's suggestion who spoke to Delbruck when he was on a visit there. I applied for a Harkness Fellowship, which I didn't get because they didn't want young people with families, which I then had. That's what Eric Ashby told me who was master of the college, and that was fortunate because then I took things into my own hands and wrote to Lederberg and said I wanted to go and work with him. He said at first he wanted me to and he suggested he couldn't take me on and why didn't I go to Caltech with Horowitz and so on, and I wrote back and I said

I want work with you. I don't mind waiting. And he wrote back and I've still got the letters somewhere and he started off in his own handwriting to this young guy who was applying, "your persistence is very flattering". Which is a lesson that I have also learnt in another context because I got to know Pontecorvo quite well at an early stage and actually persisting with people is quite important. So he took me on and in fact he first said he couldn't take me until a year later; and after Julia and I decided to have our third child, which is why our youngest was a few weeks old when we went, he said I can take you next year, and I never knew and I know Josh extremely well and I never asked him why, but I suspect it had something to do with Luca and he'd asked Luca and he needed someone to do as it worked out, genetics lectures, wanted a bit of population genetics, so he just thought I would fit in. So then Gus Nossall who essentially I replaced was going back to be MacFarlane Burnett's Deputy at the Hall Institute so I think he sort of thought well maybe this fits in.

PSH. So what was your remit when you went to Stanford? Was it mainly in the area of bacterial genetics or was it . . .

WB. Oh it was entirely. My aim was to become a molecular biologist. I always remember Jeff Gale saying you'd got to do that and of course he never did it himself, and we went with our very young family thinking it would only be one year on sabbatical and then before the end of the first year Josh had offered me a job as Assistant Professor and so I asked for a second year and Thoday was very generous, but I never went back of course to Cambridge. I went to learn molecular biology and become experienced in molecular genetics through working on DNA transformation, as it turned out to be, in Bacillus subtilis and that was my initial work and for several years, published on that. Worked very closely with A T Ganesan whose widow is now my partner. They were both PhD students of Josh's and that was a great experience. Josh had suggested, very wisely, that I take the phage course at Cold Spring Harbor on my way over so I went a month ahead of Julia with three kids via New York, it was not that easy in those days. One crawling on the floor and a two year old and a four year old, and the four year old having to wait outside while she took the others in and breast fed the baby at the airport in New York. I'm always a bit, not terribly sympathetic to the people who complain about these things nowadays when there's so much more help. They don't realise actually what it can be like. Anyway that worked out very well. And I had chosen Josh and he was obviously outstanding as a scientist but I also had the feeling, which turned out to be correct, that he would have more of a sympathy to a mixture of the classical genetics and the molecular biology which was very true and we got on extremely well together. He was second only to Fisher in my judgement, intellectually an amazing man. So in the end I stayed. I got to know Pontecorvo for the reason that I had started some experimental work with Neurospora with help from David Hopwood and Robin Holliday and somehow got interested in the idea that one can do quantitative genetics properly on biochemical characters and actually select for modifiers of mutants that needed certain nutrients and then maybe analyse what they were, and had learnt about Pontecorvo's work with Aspergillus, so I wrote to him and said, actually it would have been my supervisor, but I wrote the letter basically and said, look I had these interests and can I come and see him and he wrote back an absolutely furious letter saying 'first of all you can't learn anything if you just come for a few days and secondly it is quite the

wrong thing to do with Aspergillus. You've got to do good basic biochemical and molecular genetics without all the quantitative stuff. So I took in a deep breath and a few weeks later I said I'm coming up. Can I just come and see you anyway for a few days.

PSH. Where was he based then?

WB. He was in Glasgow. Initially, again because he was Jewish he studied agriculture I think, went to Edinburgh at the time Muller was there and then went I think, originally, as an assistant lecturer and built up the genetics department in Glasgow which was a very fine department, did a lot of pioneering work, and ever since I persisted with him, we

became really very good friends and colleagues which is another example of persistence in that way. Shortly after finishing my PhD, Julia and I went up there and spent a few months in the Autumn of 59 working in his department.

PSH. So this was before you had gone to Stanford?

WB. Oh yes, two years before. And at that time Ponte had made very interesting suggestions about how one might do somatic cell genetics with chromosome segregation and actually he had a guy, Gene Bell, it wasn't John Bell, working on that and his idea was to make hybrids and see chromosome loss a bit like, not like the interspecific hybrids, more like what happened with intra-specific. I was very stimulated by that interest and then I realised that in Josh's department, Len Herzenberg, who I got to know very well, was doing a bit of work like that so I had always had a feeling that that might be an area to take up, so that was why I later took up somatic cell genetics in Stanford. And then the other thing that took me away from bacterial genetics was fairly early on Josh had introduced me to Rose Payne and said she had a lot of data to analyse and he told her that this young statistical guy might be able to help. And in fact I got to know Rose, I got her to give a lecture in the genetics course, which I really gave the first proper genetics course to medical students in Stanford. I thought it had been going for ever and a day but in fact Josh had given about two lectures the previous year.

PSH. Yes.

WB. And at that time I think Stanford was possibly the first actual genetics department in a medical centre. It was one of the first anyway.

PSH. Jim Crow told me it was Lederberg who specifically wanted the Madison department to be called 'medical genetics' and then he had moved to Stanford before it had actually been created.

WB. Jim would be right. I later got to know Jim Crow very well and he was very close to Josh and I think they influenced each other a lot, and of course Josh started as a medical student and was very stimulated by the medically interesting problems. But I am not sure that that Department was actually in the medical school or not. I mean Jim was later Dean of the school of

medicine there, probably uniquely, at that time, a non medic in charge of a medical school.

PSH. What was it then that took you over to population genetics? Was it the statistics?

WB. I'd been in population genetics from the start.

PSH. I suppose what I am meaning is more general population genetics as opposed to the more microbiological aspects.

WB. Oh no my thesis was penned in population genetics and I went into genetics because of statistics and I took all those courses in population genetics, so I started from day one as a PhD student with an interest in population genetics and although the work that I did on linkage and selection, which as you know came immediately alongside Sewall Wright's work and Lewontin, and Kojima and Kimura, I did probably the first proper analysis of the way selection works with two loci. That was done sort of during the time I was finishing my PhD. It wasn't actually a part of my PhD. So I wrote that review with Peter Parsons. I finished that off before I went to Stanford. So in fact my main work was in population genetics and I thought I would give that up when I went to Stanford, but it was actually Josh's thinking that basically that's a silly idea and I never did, because then I brought out the book with Luca which had a lot of original stuff that you did, and of course through the interaction with Rose Payne, I had been very stimulated by Fisher's interpretation of the Rhesus blood groups. I sort of had the intuitive feeling, which was correct of course, that here was something that was as interesting if not more so. So that whole thing kept me in population genetics and moreover took me into the experimental side because although initially it was Julia, actually, I was still busy with bacteria, Julia was looking for something to do to get her out of the house and had this somewhat statistical background doing PPE in Oxford and then initially worked in Rose Payne's lab as a sort of collaborative thing. But she was supported through an NIH grant which I shared with someone called Sam Karlin. I don't know whether you know Sam Karlin is an outstanding mathematician who took a major interest in population statistics.

PSH. Sam . . ?

WB. K.A.R.L.I.N. He's probably not in areas you are familiar with. He did a lot more work in theoretical work and more recently he's done a huge amount of work on analysis of DNA sequences. He was part originator for the blast protocols which was comparing DNA sequencing. Again it was an introduction from Josh, which is a reflection of the breadth of his interests. And Sam had started doing some work with a colleague, Jim McGregor, on stochastic processes and population genetics and was interested in having someone who actually knew some genetics alongside. So all the time I was at Stanford we had a joint programme grant from the NIH. I always tell Sam that the most important thing he did was supporting Julia's work on HLA. I always thought, because I go back to Stanford a lot, I'm still in close contact with him.

PSH. What year was it you wrote the book with Luca?

WB. We started work on the book , in fact the idea grew out of the course we gave in the summer of '62 and we thought well, having done that work, we will just put together a book. It took 9 years or something, but then the following summer I was able to spend a few weeks with Luca in Pavia and then we began more detailed planning and then over a period of time, I was able to go back in '65. Then in '66 we spent the whole summer as a family in Italy and we actually kept writing and then the culmination of the writing was actually when Luca spent a sabbatical year at Stanford, '68, '69, which was basically, I don't know whether you have read his, he's got a very nice autobiography in Italian which is published and there's also quite a nice biography . . .

PSH. I've read that. It's very nice.,

WB. I gave a bit of advice to the people who wrote that and they did a good job. So it was actually a testing period for him to decide whether to come to Stanford. So the basics of the book were finished by '69 but then it took two years to actually get it out, copy editing, dealing with diagrams and stuff and I put a lot of effort in because Luca's

English is not native English. There was a lot of re-writing but there was a genuine collaboration and we each took different parts and wrote them and then checked each other's parts and filled in. It was a very stimulating thing. It was a huge effort of course, but that was done during a time when I was taking on the HLA somatic cell genetics as well.

PSH. So how did you get led into the HLA work then?

WB. Oh it was through Rose Payne. Do you know who Rose Payne is?

PSH. I do but I have to say not as much as I should.

WB. Well there were two or three early pioneers in HLA. Jean Dausset, who was lucky enough to get the Nobel prize for what he did, who realised early on you could tell something about the genetics and things that were on leucocytes using serum from transfused patients. And it was quite confusing and it was Cepellini actually who suggested to him why don't you get some reproducibility by seeing whether identical twins have the same patterns. And he claimed from that to have identified an antigen which was called MAC. It's a bit iffy in my view. And then simultaneously Rose Payne had done somewhat analogous work. She was a haematologist, as was Jon Van Rood and they both independently at the same time realised and discovered that you could use sera from fetal-maternal stimulation and of course that gave you a much more limited range of differences and so those were the sera that really established the fact that you could do serology, that led to the identification of the HLA blood groups, and that was in '58. Jon Van Rood then took this somewhat further systematically, and he was the first to do a bit of computer analysis and showed that by 2 by 2 association you could begin to define antigens. Rose had accumulated a lot of data but didn't have a clue

how to analyse it and what's his name, Ernie Hackle. She got together with a human geneticist and published a very confusing paper. She told me she locked him in the bathroom or something until he'd finished writing. Anyway she had this data and didn't really know what to do with it. Josh got to know about it, and again it was his insight to say well maybe this is something you could be interested in. So Rose gave me, in a sense, access to her data and gave me Jon Van Rood's thesis and I immediately realised what you could do with it. In fact Julia wrote the first simple programmes doing lots of 2 by 2 analysis. So we confirmed Van Rood's what he called
4a and 4b and then we discovered the new antigens what we called LA1 and LA2 which is the origin of HLA and what later became to be known as the A locus and suggested the idea that they were allelic series. Initially we made the mistake, because the technology was very crude, agglutination tests with pre-war pipettes as Julia used to say -very unreproduceable. So it wasn't clear that the two sets of alleles were actually closely linked. That came out later simultaneously from a few different people.

PSH. Was that before the HLA workshops had started up?

WB. The HLA by the time, yes the first HLA workshop was in 1964. It was the only one I haven't been to and that was because that was when I gave the paper at Cold Spring Harbor. That was the first Cold Spring Harbor symposium on human genetics and actually if you look at the second one in '86, when I talked about the genome project and

all that, there's a picture of the four people who were at both; Victor McKusick, myself, Arno Motulsky and an unidentified I think it was Mark Fellous by chance, was the fourth one because I knew him and he had been in my lab. Anyway that was the origin of our first paper. At that time it was not yet clear that there was just one system but it very quickly transpired within the next year or two that they all had to be linked. And that developed because of better technology. The technology that came to be standard was introduced by Paul Terasaki which was to do cytotoxicity assays and eventually on the micro scale. So around, I guess it must have been '65/'66, I took the experimental work into my own lab and I started applying the cytotoxicity assay and we developed the use of fluorochromasia which made it a lot simpler which was the basis for automation. That was another fortunate thing for Josh's interests. He'd had a guy called Boris Rothman in the lab who'd discovered this principle where fluorochromasia, which goes back to something Josh did. Fluorogenic assays like beta galactosidase was really his innovation so he had an enzymatic reaction which turned a non coloured into a coloured reagent. And I don't know who had the idea initially with beta galactosidase. It was probably Boris. You could do the same with fluorescent compounds, so you could make a compound that had say, acetate groups or some groups that prevented it from being fluorescent, but then when the groups were cleaned you got the fluorescence and that was done with the beta galactosidase but the fluoridation assay was based on the fluorescence diacetates. So the acetate groups prevent the fluorescence that enter cells fairly easily and then it's cleared by esterases in the cells. The fluorescence in the cells which doesn't escape . It's the cell membrane and Boris and a guy called Ben Papernas tried to develop a slightly cumbersome assay using this principle for cytotoxicity essentially, and we adapted it in a simpler way and it

worked like a dream. That was the basis of what we did for many years and it was just a much more accurate assay. There were a lot more ways of working out the relationship between serum reactions because they were all mixed antibodies, so you had to use statistics to sort out its clustering. I mean what everybody does now is what we were doing then with serum reactions. How you do expression and everything else, but it was just the same principle. So you cluster serum reactions and a cluster that worked together to define an antigen. And that's how they would define them until the molecular biology came along and there was a lot more data on linkage disequilibrium. We did some of the first population studies. We went with Luca to collect some samples from the pigmies in '68. So that led to a whole range of work in . . .

PSH. At what point then with all this did you come back to Britain?

WB. We came back in 1970. We had always thought that maybe it would be nice to come back to the right sort of job in the UK. We were not unhappy at Stanford at all. We had a wonderful time there and I had been offered all sorts of jobs elsewhere in the States including the successor to Dobzhansky at Rockefeller and Tracey Sonneborn in Indiana. Good jobs Even before I was a tenured professor at Stanford they asked me whether I wanted to be head of genetics at Berkeley and I fortunately said no because you didn't do things like that at that age.

PSH. You must have been pretty young?

WB. I was 29 but they'd tried to get Josh and I was the second person they nearly tried to get. But it would have killed my academic career and I was doing so many things that depended on being active. Boris Rothman who was a good friend said you are daft to turn that down. You'll never get another good job like that. I mean you've got to think carefully about these things. They are sort of lessons in, how maybe if you are fortunate. Anyway it turned out that Oxford in 1969 had made the decision that they wanted to establish a chair in genetics and that was when E B Ford was retiring. He had a personal chair. Cyril Darlington was the professor of Botany and there wasn't much genetics anyway. There was absolutely nothing at the medical school and it was obviously before David Weatherall came.

PSH. Yes I remember because I was a student in the fifties in Oxford and there was a remarkable lack . . .

WB. Yes but in those days there wasn't much genetics anywhere was there?. If you look back in those days after all there was Charles Ford and other people just down the road doing cytogenetics

PSH. True. Yes.

WB And there was Stevenson's unit in Oxford, probably had more genetics in that way than other places did but it didn't get anywhere near the students. As far as I know. I don't think Stevenson's unit contributed anything.

PSH. Nothing.

WB. So Julia and I had thought of, and I had written for the particulars on applying but then out of the blue Joel Mandelstam who was the Professor of Microbiology at the time who probably knew of my work on Bacillus subtilis wrote and said would you be interested in putting your hat into the ring. So I said yes. It seemed if you didn't take something like that you never think of going back. Peter Medawar whom I got to know a bit through the HLA work was also an elector, so was influential. So after a couple of visits they offered me the chair and we decided to take the plunge and go. I mean it was a complete unknown in a way. I mean salary would go down probably by a factor of two or three. It wasn't clear what research and support you got there, but actually people were very good. David Phillips was marvellous. Rodney Porter was terrific because, I've just been reading a history of biochemistry by Marjorie Ord Lloyd Stocken and she doesn't get it quite right. The formal situation was that Pringle and I think Porter, between them, had agreed that they wanted a geneticist. Pringle had always thought that it would be a successor to E B Ford and an ecological geneticist, maybe Philip Sheppard who at that time was at Liverpool. Other people thought may be it should be a molecular biologist. So there was some statement that if there was a lectureship associated with it, a Professor of Molecular genetics, the lecturer should be population genetics and vice versa. And then they found space in what was the old biochemistry which later became, many years later, the Walter Bodmer building, which is now destroyed, the old physiology building. But there was still left open formally the choice, whether the professor would want his sub-department to be allied with biochemistry, botany or zoology. To me it was just obvious it had to be with biochemistry, which I think is what a lot of people . . . John Pringle I got on with very well actually and he was never bitter about that decision. It was the obvious decision and I said you know, to heck with all this business about who else should be appointed. If you want population genetics I'll teach it. I'll appoint whoever you want. David Roberts was the first. I don't know whether you know David Roberts who has recently retired as a lecturer.

PSH. No.

WB. And then Ian Craig who I'm sure you do know, came first as a post doc and then as a demonstrator so they were critical. And I got very good advice. I mean Porter was, everybody was actually tremendously helpful and friendly. I was just a young kid from California didn't know really what was like and the registrar at the time was a guy called Sir Folliot Sandford, a traditional ex civil servant with a little black notebook that he wrote stuff. And everybody thought that he would not be very . . . and he was tremendously helpful actually. I got what for the time, to me seemed quite a good deal on renovating the department, getting equipment and he helped when we had trouble getting our youngest son into the Dragon school where we thought we'd get in. They first said you can't get him in unless you put his name down at birth, so I said how on earth could I have known I was going to be here then. And then when I said I was coming back to a chair in Oxford then they said we can't do anything unless you are going to be permanently in Oxford. So I said to hell with that. I mean they were actually quite rude. So he helped us get Charles into New College School. And that worked out really quite nicely and then Jim Gowans must have been on the MRC at the time. He was very

helpful with advice. I went to see him, put in for a programme, didn't get a unit but I had a programme grant going for 10 years and that was based on the HLA and somatic cell genetics which developed very well really .

PSH. So was it ten years you were in Oxford?

WB. Came in '70 and left in '79.

PSH. And how did your move to ICRF come about?

WB. Oh how did it come about? I can tell you exactly. Well I knew about the ICRF. I mean this is just a little side story and I had been asked to review, because I had known Michael Stoker from the time he was the medical tutor at Clare College and I had known him, although I wasn't medical at that time and when I was in Glasgow we got to know each other a bit more and he was very friendly. So when he was Director he got together a visiting group to review the molecular biology programme, which as far as I can recall was Sydney Brenner, Paul Berg maybe, and that must have been in '73/'75, I forget, maybe '76 even. I remember then, the then secretary, Nobby Clarke saying you're not spending enough money. You ought to tell them to build another institute. Little did he realise how prophetic those words would become. Anyway what happened is, Richard Doll came to me early in 1977 and said Scowan, Eric Scowan wants to see you. I said Scowan who is he? By the way Richard Doll had been extremely helpful to me. You know I had rescued Martin Bobrow from Stevenson's unit, for which he never forgave me. He thought that was terrible. But Richard Doll engineered it so that Martin could have a half NHS post, the other half supported by my programme grant and he then was part of my unit.

PSH. Was Richard Doll Regius professor?

WB. He was then Regius Professor and just was extremely helpful and it must have been actually the first medical contact going back a bit then, do you know who Peggy Pickles was?

PSH. No.

WB. Peggy Pickles was one of the pioneers in the red cell blood grouping, knew Rob Race and Ruth Sanger pretty well, of course, and she had set up some HLA typing here. She was in charge of the haematology and all the HLA problems and things and when we came people said you might find it a bit difficult with her, but she was marvellous actually, because we were coming in to a non-medical department that needed the contact with the medical school, we needed a way of getting sera, we needed to have some in into the medical scene and she and her husband Alistair Robb Smith who was the Nuffield reader in pathology, were enormously helpful in making those contacts. In fact it was easier in some ways to make those contacts when we came to Oxford than it had been doing similar things in the medical school at Stanford. Partly personalities I guess. So it's almost certainly through that, that I gave seminars and got to know Richard Doll and asked his advice. Anyway he came and he said Scowan. And I said who is Scowan? He said he is in charge of the ICRF so I sort of had a clue then that maybe they were

looking for a successor to Michael Stoker, but there was a specific date. As far as I knew it was March 31st, he is going to come and see you. So he came on that day into my office, which was there until recently as the professor's office, and basically offered me the job. It was clear later that he had no mandate to do that at all. They had set up a committee under Walker, Peter Walker, who was very helpful, from Edinburgh, and they were looking at candidates and thought that John Cairns was the obvious person. Obviously other people didn't and then I didn't quite know what to do and then actually there was a hiatus until I wrote back and said, because I thought were they going to come and approach me more, but it turned out they were waiting for me to say whether I would be interested or not. So after a bit of negotiation they offered me the job, I suppose sometime in the summer that year or maybe it was even the Autumn.

It was eighteen months before I finally went, which was a long inter-regnum, not ideal. I mean Michael Stoker was extremely good and I got to know some of the people there. I even gave talks to various teams before I was taken on, but it was not necessarily the easiest way to do things. But it was a tremendous stimulus to my own research. I should say, going back to Julia's position, in fact each time we moved it improved her position, because she had been basically a research assistant at Stanford because she had no formal qualifications in the field. When we came to Oxford she was given a proper scientific position on the programme grant, and by the time we were going to London, she had established herself with an international reputation and just about that time got a DSc from Oxford because she had never taken a DPhil, so she then got a professorial position and was in charge of a lab. All of that was a bit delicate in negotiation. Not everybody thought I was the right person and they didn't know what I was going to be like, and was I going to do genetics and nothing else all the time, but it worked out fine and it gave an opportunity to develop the molecular genetics and really get into competent DNA work which just hadn't got going in Oxford. Strange, I mean Rodney Porter was a terrific guy. We got on extremely well. We used to talk a lot about that and we tried to get George Brownlea to come, who later did come in order to get some DNA work going. But you know we had no control over these committees and so I tried to get some DNA work going in my own lab before I left, but it was difficult. There was nobody else doing any recombinant DNA work in Oxford. That was in '78/'79. When we went to ICRF and there was one Wang desktop computer in the whole building and nothing else. So things were rather different. I was the first person to use a preparative ultra-centrifuge and do scintillation counting in Kornberg's department. We were in genetics but there was a collaboration. Anyway it did work out very well and they had got the recombinant DNA work going at the ICRF. They had some very good people working on the molecular side so that was how we were able to get into cloning reasonably early. We had of course started the work with monoclonal antibodies before I left Oxford and I basically brought that technology to the ICRF, which was very helpful. So that meant a whole new direction of molecular genetics, cloning HLA products.

PSH. Had you started or had you developed an interest in the colorectal cancer field by then or was that after you went to the ICRF?

WB. No. I mean when I went to the ICRF, I had obviously had a general interest in cancers as any geneticist has, and already clearly had the notion you know, at the cellular level cancer is a genetic disease. It seemed the rationale for going. But of course we really didn't know anything about cancer at all and the minute you are appointed to a job like that as a scientist and I was already an FRS, you know people assume you are an expert. And I remember going to Ken Bagshawe and saying Ken you've got to help me. I don't know anything about cancer. How do I learn about it, and actually he had written quite a nice little textbook which I found very useful. I didn't know what a clinical trial was, phase 1, phase 2, things like that. So there was a lot to learn and I read a book on cancer immunology which was awful. I thought my God what's this? You know I knew some immunology and cell immunology, but all my involvement in HLA and other things and I had learnt immunology quite well at Stanford associating with Len Hertzenberg and other people. So actually when we got to the ICRF I decided well, I've got to do something that's cancer related. I've forgotten exactly how it worked out but knew about familial polyposis and there was these ---- St Marks, Duke there, what's his name? --- The successor to Dukes who ran the polyposis clinic.

PSH. Not Bussey?

WB. Yes. And so from a very early time we just said, well let's look at the genetics of FAP and we had the idea that you could do mapping by that. I think that was the first COH to suggest that with Ellen Solomon. So it came just at the right time. And so we started working on the families at St Marks and the first thing we did was HLA actually, because somebody had said there was an association, there was nothing in that. And then Vicky Murday came as a fellow, I mean there was an ad hoc programme set up through the College of Physicians and I think it was she probably that noticed the publication by Ferreira et al that showed a small deletion and then we were lucky, we got a probe in 5q from Bob Williamson and the linkage fell out very quickly and then spent a huge amount of time trying to find the gene because we had a deletion that came from what's her name Deborah, is it? No Donnai in Manchester?

PSH. Oh Di Donnai.

WB. Di Donnai. The picture I always showed of the deletion that was like the one that Ferreira had was actually from Di Donnai. It was a girl. It was an interesting story that. At the time it wasn't clear that she had polyposis but and in fact, probably our determining the fact that it clearly didn't have by genetic mapping, that it was a deletion, a formal deletion of the gene was probably the first diagnosis at the molecular level of polyposis. And it helped. We used that. We got that into a cell line but it was about 10 megabytes, so it was a big region to try and encompass and so we had a whole group of people that worked together to try and cover it with cosmids. We would have discovered the gene within a very short time if other people hadn't but you know the guys in the states they just happened to have a 200 - 300 KB deletion which made it a bit easier. Just the luck of the draw and even then Nakamura always told me, I don't know who to believe, Vogelstein said Nakamura didn't realise it was a deletion. I don't believe that. I think Nakamura did. He should really give him credit for having moved in there.

And then there was this business of mutated in colon cancer which was a totally irrelevant gene, but we knew it was near there and by that time we could use that to find the gene ourselves. But I had and through that contact with Bussey and the surgeons and that kind of thing, that led to the idea of setting up a research unit at St Marks and then, I'm so terrible on names. The woman who was there, she set up the family clinic, Joan Slack.

PSH. Joan Slack yes.

WB. So that all worked out reasonably well. I think that was the first proper cancer genetics.

PSH. Yes. When did you start the Family Cancer Study Group?

WB. That was an interesting story. I couldn't exactly date it. David Harnden had started something a bit like that, that flagged. And then I thought that we should try and do something like that again so I resuscitated it jointly with David. We used to have meetings that alternated between the Patterson

PSH. I remember.

WB. and ICRF and it was very stimulating in those days and it was that that led to the formalities of who really should set up proper cancer family clinics. They should have a clinical geneticist. They should have a good link with the oncologists and that was really the basis for it which led, I've forgotten who spearheaded that. Were you involved in that?

PSH. I was involved but . . .

WB. Because there was a point at which we sort of went . . .

PSH. It may have been John Burn or perhaps before that.

WB. No it was before John.

PSH. Derek Roberts also.

WB. No.

PSH. But it was one of the very few initiatives that linked in the basic scientists with the clinicians.

WB. Yes, and we went to the Department of Health and said that should set something like that up. It wasn't - John Burn came quite a lot later. John Burn, we had, ICRF had traditionally supported only its own people, either in Lincoln's Inn Fields or in units which they set up and I generalised that a bit. I said if anybody had from one of our units, first of all we expanded the units like St Marks. Edinburgh had got going. There were others of course who had set up a developmental biology unit and set up the unit here and so on, and I said if anybody who was an ICRF person had an active collaboration with someone else who was non ICRF then we would fund that to some extent. Put money into that.

PSH. Might it have been Tim Bishop in Leeds?

WB. Tim Bishop? No. He was a clinician.

PSH. Never mind, it will come.

WB. Anyway I was also conscious of the fact that the more we could say we had support from different parts of the country, the better it was for the fund raising. So that's how we set up, we funded people to help the cancer family clinics. There was one in Cardiff and then there was one in Newcastle and that was before John Burn came. And then when John Burn came that was enlarged and that was after I left. He was sort of put more in charge of that. I wonder whether it was John Burn then.

PSH. Never mind Walter.

WB. It could have been John Burn. But the idea that developed that started before that, I haven't been so active in it subsequently, partly Ian Tomlinson took over the family interests which were harder for me to sustain when I left ICRF and it sort of broadened out into a more of a regular society. I had thought of it as more like the HLA field. You know, that it should be active collaboration to collect material, to develop procedures and so on and not just a scientific meeting.

PSH. I suppose these things grow don't they?

WB. Yes, and then it became too much of a society.

PSH. Walter, to finish up with, because we are running out of time, can I just ask you a bit about your 'People of Britain', or, I don't know what the formal title of it is.

WB. It's People of the British Isles. I'd had an interest obviously, with Julia for many years in population studies and when the biobank project was initially being proposed, Julia and I, I certainly took an active part in the communication of that, but actually before that we had the idea of putting in an application to the Millennium Commission.

PSH. I remember that.

WB. Which we thought was the human seedbank as opposed to the seedbank at Kew. It was a unique opportunity to collect information on the British population as it stood then and be preserved for ever more. We put together a very carefully constructed proposal which already had this idea that you had to sample rurally and use all four grandparents from the same area in order to minimise ad-mixture and we fought hard on that and it got to a sort of preliminary stage and I think it was killed by a mixture of ignorance and political prejudice. I think it was a shame in some ways. I mean we asked for quite a lot of money but it was carefully constructed and it had to emphasise the cultural side. We were really finding out who the British people were and we said well, the medical side which has had its applications we will get from

other sources including the Wellcome Trust because they didn't want to support money you could get from the medical research supporting agencies.

So as a result of that I sent that round to quite a lot and it went to the Wellcome Trust and it was after that that the biobank started and I said you ought to put aside at least a small proportion,10% or less, to do a decent control population and nothing happened there. Then Peter Doyle from the European cell bank by that time had gone to the Wellcome Trust and we talked to him and said well what do you think? And he actually said you had better put in a proposal for this because it's never going to happen through biobank. So we put in a preliminary proposal and the Wellcome Trust people had already known a bit about what we were doing and it was a long haul, I mean from the preliminary application to a proper application to a complete review by all the scientific members of the Wellcome Trust and outside I think. And eventually they gave us most of what we asked for and I have to say have been terrific to work with. There were two things we were encouraged to include; genotyping of the 1958 birth cohort. Well David Strachan wasn't the easiest person to deal on that and then and we were also encouraged for political reasons to say we would do something on minority groups. We also wanted lymphoblastoid cell lines. Those three things were not allowed. The 58 birth cohort. I was glad to leave that. I never agreed with the idea that we'd do the minority groups, but we did think it was silly not to fund the lymphoblastoid lines and actually we are now putting together a proposal to be considered to Peter Doyle, an application to grow the lymphoblastoid cell lines. So that started in 2004. It was a five year programme, quite generously funded with Lon Cardon who has gone to Seattle, Peter Donnelly as joint investigators who were very helpful in putting the application together, to provide the ethical analysis and it's gone well, more slowly than one might have hoped but probably better than we should have thought. In other words, you always do these things, you say them, with the sort of conviction without having any idea of what the problems would really be, and of course it's actually not that easy to get people to satisfy those criteria. We said we would get three and a half thousand. We're at two thousand one hundred, which isn't bad. We'll reach the total, but it's effort. We have been very lucky, we've got a research nurse who used to be the matron at the R.I. in town who helping us, who has got contacts everywhere in the world. It's terrific actually and we've got of course collaboration throughout the country who have been very helpful. Some more helpful than others. We have had to prod them a little and some that came up that we weren't aware of who have been extremely helpful, the Historical Society, Genealogical Society, The Women's Institute, we do a lot through agricultural shows, things like that and set up a stand and do everything to get local publicity, which is why we did that Channel 4 series which was ideal, may have helped somewhat.

PSH. Do you think that the huge changes in technology in terms of the abundance of variation and things, does that mean you can be a lot more definitive doing it now than it would have if you had started it 10 years earlier.

WB. Yes, not only that, it is more for the future. So partly because of the sorts of things that I have said and others have said, the European Framework Seven programme had a call for a proposal to do this in Europe. Now we have put in, I have put together, I think a very good consortium, it was

a heck of a lot of work at short notice to do the same throughout Europe and we have got very good people. We've got the cancer centre in IARC, we've got in Spain and Mark Stoneking, a whole lot of people who have bought into this idea of doing it this way. Now I know there's at least one other and they said they wanted genotyping doing. Well when you take twelve million euros, you divide it by twelve people, you can do hardly anything with it so we said the absolutely essential thing is to collect the samples from them. We are not going to spend huge amounts of money on doing the genotyping based on predictions because in 5 years the technology may be totally different and you can do a heck of a lot more. So we've said get the samples, preserve the samples and then you've got them for the future. And that's what we've put in for. Whether we'll get it, I think I just hope that the right people will review it and realise that's what we ought to do. So that's a part answer to what you are saying. The more you wait the more you will be able to do.

So my view on this, is get the samples and secure them, and then you've got them there then in the future, you may be able to do a complete genome sequence on everybody, but at least you've got the samples and you can accumulate the information and if you don't get them now it's going to be more and more difficult. Nobody, I don't think anybody is ever going to do the same thing now as we have done in the UK, and of course we've continued those with the Europeans. European would be thirty thousand samples collected through Europe which I think would be fascinating. And of course the range of markers gives you huge strength in what you are looking at although you have to be careful, these 500 K chips of Affymetrix, probably 95% of the markers are useless for population studies, too uniform distribution, so I'm very keen that we include markers that we think are functionally interesting, so we have to have a mixture. That makes things sometimes more expensive, but I think the range of information would be enormous.

The argument is of course is to have decent controls for case control studies. There's this huge plethora of studies. All of that comes from work we did on HLA and the suggestion of linkage disequilibrium, but we had relative risks if they were four or five they were low. I've got to give a keynote talk to the Sanger Centre Meeting, Nature Genetics 15th anniversary. I'm giving the first keynote talk and I'm thinking about it quite a bit because I've been very much in favour and I still am of the idea of rare variants as the major source but I want to plot the relative risks that people are finding. They are 1.1, 1.12, 1.15. Well I've no doubt they are probably significant if they are reproducible in two different populations, you've got more reassurance. At that level I think there's a serious risk of population structure influencing what you find in at least some cases, but you've also got to ask what does that mean? I mean if you are finding things with a relative risk of 1.15 or 1.2 that influence type 2 diabetes, there must be practically half the genome could have some influence on that, and what does that actually mean. What can you do with it? I'm trying to think through that. I mean even simple questions which I'm going to have to sit down and do a little theory. I like to do theory in simple ways. The relationship between a relative risk, the penetrance of a gene and the contribution, the relative contribution to the genetics of a trait. I don't think it's clearly worked out.

So we talk about 25% you know, the inherited contribution to colorectal cancer. What does it actually mean? What does it mean in terms of hundreds of genes that have 1.1 relative risk and a small number of genes that have 2 or 3 and then a few familiar ones?

PSH. It's hugely more complex than most of the people starting in the field a decade ago realised.

WB. I think that's true, but also the whole question of interactions. I'm not a great believer in what has come to be known as polygenic inheritance, a term which I dislike because 'polygenes' was a term that Mather and Jinks coined, for a type of genetic variation they thought was different from everything.

PSH. Can I ask you one final question which I have been asking everybody. Is there any one particular person that stands out as having been a special influence in your career?

WB. Well there are two, R A Fisher and Joshua Lederberg. I mean I was extremely fortunate. One was and one still is absolutely outstanding scientists. I think they were some of the great scientists of the twentieth century and they had an enormous influence on me. In a smaller and different way, David Cox stimulated my interest in statistics, but it was Fisher and Lederberg who dominated in many ways my academic development. No one else to my mind that I have interacted with can compare with those.

PSH. Walter I am going to stop the machine here. Thank you very much indeed.

End of recording.