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Sir Walter Bodmer FRS in interview with Max Blythe Oxford, February 1988
Interview II

MB Sir Walter, at the end of our first interview, you were just about to return to Oxford from Stanford to take charge of a new sub-department of genetics within the department of biochemistry in Oxford..

WB Yes.

MB What brief were you set?

WB Well, E B Ford[1] - the late E B Ford, who just died recently - a noted ecologist, ecological geneticist, who actually coined the term 'genetic polymorphism', had had a personal chair in ecological genetics, having been originally a lecturer, and the University, in its wisdom, decided it was time that genetics was put on a permanent basis. So the departments... I think it was of botany, zoology, and biochemistry, clubbed together to turn the lectureship that it would have reverted to, into an established chair, assigned one or two other posts, and create, therefore, a new sub-department of genetics. And that was what the new chair was. And it was advertised that they wanted, as a professor, someone who was either a population or ecological geneticist, or a molecular (biologist. And then the one lecturer post, if the professor was a population geneticist, he should be the other way round. And... another one. So I applied, and I... no, I didn't apply. I was really asked if I would take it, and came. And it was left to me, as the new person appointed, to decide which department I would be associated with. And it was clear that the real intention was, in many of the University, that it should go with biochemistry, although John Pringle, the professor of zoology, had hoped that it would go there and be a continuation of Ford's work. So it ended up as a sub-department in the biochemistry department, where it was going to be located physically, anyway, in the old physiology building.

MB And you had good links with Porter[2] anyway, and that was at the right place.

WB Yes. I had only met Rod Porter, first through being approached to take the chair. And I've often wondered, at the time what he thought about this sort of young whippersnapper coming over from California, that he was going to have to deal with very closely. And it was a delightful relationship. I mean, he was enormously helpful in every way.

MB That was right from the start, wasn't it?

[1] Edmund Brisco Ford (1901-1988) Professor of Ecological Genetics, 1963-69, and Director of Genetics Laboratory, Zoology Department, 1952-69, University of Oxford..
[2] Rodney Robert Porter (1917-1985) Whitley Professor of Biochemistry, 1967-85, University of Oxford. Awarded Nobel Prize in 1972 for Physiology or Medicine.

WB Right from the start. And we became very good friends, and I learnt a lot from him as I moved in some ways more into certain types of biochemical work. And I, in the University, took the responsibility for teaching genetics, and I said, 'Well, I can teach the population genetics, so I'm not going to be bound by what my lecturer is.' The lecturer, David Roberts, who's still there, was a Drosophila biochemical geneticist, and we built up a small lively department, with interests in biochemical genetics in one way or another, and human genetics.

MB Did you bring the work that had been at Stanford, your central work, with you?

WB Yes. At the time, in order to get going, we had to get Medical Research Council support, and I had to put in a programme plan, which supported our work most of the time we were there. And there were two major strands through the work that I wanted to do and continue. One was the work on the HLA [human leucocyte antigen] system, which I'd been doing with my wife, which we brought to Oxford, and the other was to continue the work that we'd just started two or three years earlier, on the somatic cell genetics, where just before leaving Stanford, we had done some of the earliest work, really, on assigning genes to human chromosomes, making human mouse hybrids. And as we came to Oxford, and during the first years that work really flowered. So that was during those first years that the first international meetings on human gene mapping took place, which is now a major field. And a lot of the whole early excitement of putting genes on to human chromosomes developed, and we, of course, were centrally involved in that.

MB And did you have good links at that time with Henry Harris? Was he into that field as well, at that time?

WB Well, Henry Harris, of course, had with John Watkins, used Sendai virus to show that you could fuse the cells, particularly of different species, and that emphasised the possibility of making human mouse hybrid cells. But he, himself, had not really, at that time, pursued the genetics. And we were very close, and we talked a lot about the work, but our interests, on the whole, really, were rather different. He was emphasising the applications in the cancer field, which I was not yet involved in at that time. So the areas that we emphasised were just the excitement of being able to map the genes - simple questions that one could, all of a sudden, begin to answer. It was known that in bacteria genes involved in different steps in biochemical pathways, tended to be closely linked. There was evidence, of course, that this wasn't going to be true in higher organisms and in mammals, and now we could get at that problem by the somatic cell hybridisation, and show that the enzymes, for instance, in the glycolytic pathways, that we could analyse them that way, were all on different chromosomes. And we could look at, for instance, the enzymes of mitochondria and compare the mitochondrial with the cytoplasmic enzymes, and show that they were not linked either, on different chromosomes. And we could begin to do similar work on the genetics of mitochondria, which has its own DNA, in contrast to the nuclear DNA, and do the sorts of ... almost like the classic experiments that one was able to do in yeast, and show when there was separate inheritance of the mitochondrial activity. So all of these things, as developments of formal genetics, were really quite exciting and were part of the initial work that we really got going, and with the inter-relationship with the HLA work, went in two different directions. One is we were very keen, and had been already at Stanford, to do the genetics of HLA in tissue culture, because with the reagents that we had to detect the HLA determinants on cells, we could look at those in our hybrids. And we had a bit of bad luck, we were not the first to show that the HLA region was on chromosome 6,

and it was because none of the hybrids we had at the time had chromosome 6 in them. So that was a bit of bad luck, in a way, and just the way it worked out. And it was only then when a Dutch group showed that, of course, we were able to confirm that. And then we were able to study the associated molecule, a molecule called beta-2-microglobulin, which many people might have thought would have been genetically in the same region and we were able to show it was on a different chromosome. These sorts of...

MB Where was that?

WB This was in Oxford.

MB That chromosome?

WB On chromosome 15.

MB That was on 15.

WB Yes. So, and the sub-units of different enzymes, lactate dehydrogenase, where classically the A and B sub-units, and we could show that they were on a different chromosome. So those sort of beginnings of formal genetics were really quite exciting. And then that developed in two different directions. One is the use of somatic cell hybrids to study other surface markers. We realised that, for instance, if you took a human mouse somatic cell hybrid that might have only one human chromosome in it, and then you immunise the mouse strain from which the mouse parent cell-line came, the only thing it should see was the genetic contribution of that single human chromosome. So you had a sort of genetic purification. And in those days, it was making anti-sera, so you could make anti-sera that were specific for things coded for by that chromosome, which was an interesting development, and then we could use those sera to manipulate the hybrid. For instance, we could then, having shown that we'd got an anti-serum that detected something on chromosome 11 and that was coded for on the surface of the cell, was made on the surface of the cell, we could then in other somatic cell hybrids see whether chromosome 11 was there with that, and actually select hybrids that had lost it. So it was a new development in the manipulation of hybrids, which was then later transferred into monoclonal antibody technology. And that was interesting, and again, opened up a way, perhaps, of studying the surfaces of cells, using somatic cell hybrids, which subsequently has been applied quite a lot. And then, of course, the other major development that came after [Georges] Köhler and César Milstein's[3] famous work on making monoclonal antibodies, was that, was the application of somatic cell hybrids to make monoclonal antibodies, which, as I think we may have discussed before, of course, had its origins in being able to make somatic cell hybrids with lymphocytes, as we had first done some years earlier, but to make them with the right sort of cells. Because if you cross a cell making antibody molecules with one that doesn't, then you get this phenomenon that Boris Ephrussi and his colleagues had shown, an extinction, that you switch off the differentiated expression. Whereas if you cross the cell with the antibody producing cell of a tumour, or a tumour myeloma, then you enable antibodies still to be made, and so you rescue the single lymphocyte into the hybrid. Well, within a year or so of that technology being discovered, perhaps a little more slowly than

[3] Georges Köhler and César Milstein. Awarded the Nobel Prize in 1984 for theories concerning the specificity in development and control of the immune system and the discovery of the principle for production of monoclonal antibodies

might have been expected, we took this up in the lab and got it going. And we also collaborated with César Milstein. He with Alan Williams who, at that time, and still is, in Oxford, had made some antibodies to... just human blood... a source of human blood, and they were wanting to characterise them. And the first work we did with them was to take these antibodies and show what they were. And one of the first ones we could show, using the somatic cell hybrids, the fact we knew that HLA was on chromosome 6, beta-2-microglobulin was on chromosome 15, we could show that it was against an HLA determinant. And it's an antibody, W632, which is actually still very widely used to characterise the presence of HLA molecules on different tissues. And then that, in the HLA field, became an absolutely major activity - to produce monoclonal antibodies to HLA determinants. And round about... just about, I suppose, '77, when it really got going, the last few years I was in Oxford, that was a major part of our activity. And, of course, made, in the end a significant contribution to unravelling other components of the HLA system.

MB That's right. I mean, when you look at what spun out from that period of six or seven years in Oxford, it was...

WB It was a very active time. We might have thought that coming from the wealthy California situation to Oxford that we'd be more constrained, we never really felt that. Obviously there were some things that were a little more primitive, and the wires on the wall got hot because they didn't quite have enough capacity for all the bits of equipment we had, and we were in this funny old building, the original department of physiology, but it worked well, and we had a good team spirit. And, on the whole, we had what we needed to move forward. And we had very good collaboration with people in the Medical School. We had, at an early stage, met Peggy Pickles, who was a pioneer of the red cell blood grouping field, that had taken up tissue typing in Oxford. And she and her husband, Alistair Robb-Smith were extremely helpful to us in making contacts that enabled us to set up the tissue typing and the HLA work, and get the materials there. And so we had a very happy time in Oxford that way, and a very stimulating environment with colleagues, with Rod Porter, with Henry Harris and David Phillips and others.

MB Did the link with Stanford and your American contacts, did that all help as well? Did you keep that...

WB Yes, we kept that going, and sometimes, you know, I wonder where I am, because a lot of the people that were with me in Oxford, went to be post-doctoral fellows in Stanford. One of our best young students who's now our Senior Scientist at the ICRF, Peter Goodfellow, who was involved in our early work on the biochemistry of HLA, and we'll have to talk about that a bit. When he finished his PhD, a DPhil with me in Oxford, he went to work with a close friend of mine, Hugh McDevitt at Stanford, and those contacts kept on, so he then became very friendly with Rose Payne[4] with whom we'd started the HLA work, and you create a sort of network of contacts that continues, of course, to this day. And the HLA work also went very well. It ... there were two major strands that developed there. On the one hand, we started work on the biochemistry eventually. Until we'd come to Oxford, it was a set of types, rather like at one time the blood groups were, and you thought of them in a way as types, and you didn't know what on earth they were chemically, they were just

[4] Rose Payne (1909-1999) Pioneer and expert in tissue typing and one of the researchers responsible for the HLA system

letters on a piece of paper. And obviously, one wanted to know, 'Well, what are the molecules?' And it was through Rod Porter that I met Mike Crumpton(?), who is a distinguished biochemist, who had an interest in isolating molecules on the cell surface. So that round about '72 or '73, within the first few years, we decided we'd set up a collaboration to get at the biochemistry of the molecules. We would provide the technology to identify them, he had the biochemical skills of purification, so that between us we could do the purification, because for that you need to know how to separate molecules, and membrane molecules, which have special problems because they're stuck into the lipid membrane. And then the assays, which is the key to knowing whether you've got the right molecule or not. And so we developed inhibition assays - inhibition of our standard way of detecting them. And within a year or two, we had begun to identify what the molecules were. And this followed on a little bit, and then extended work that others had done, and initiated the whole area of knowing actually what the molecules of the HLA system were. And we did some of the earliest work then on having a purified protein, providing a bit of sequence, and really knowing that here were things that were not just letters on a page, but the structure of the molecules. Then, of course, that later led into the explosion of work at the molecular level.

MB You were in the foothills, really, of describing the kind of topography of the cell surface. I mean...

WB That's right. It was the beginnings of identifying the various molecules of the cell surface, and the HLA, and, of course, the mouse counterparts, H-2, which have been studied by others, were important landmarks in that. And the other main thread was that until about the very early seventies, when we came to Oxford, HLA types are what we now call the class I, what I tend to call the histoglobulin type I, the classical HLA A, B, C antigens, which are present on most of the cells of the body. And at about the time we were leaving Stanford, a good friend and colleague, Hugh McDevitt, who's a pioneer of studying the genetics of immune response differences, had speculated that these were... he had shown that these were coded for by genes, in the H-2 region of mouse's equivalent of HLA, and we had worked together at Stanford in looking for HLA equivalents, by looking for associations, which is another importance, between HLA types and disease, because he had felt that if there were immune response differences controlled by H-2, then there may be similar things for HLA, and, therefore, there may be diseases where certain HLA types predispose towards them. And we had started working together on that, and he came and spent six months or so with us on sabbatical in Oxford. And at that time it became clear that perhaps those immune response genes were another category of HLA types, or H-2 types, on particular subsets of lymphocytes. And Jon van Rood, the pioneer of the HLA system, was probably first to show that clearly for the HLA system, and we, at about the same time, realised that we had some odd serological reactions with a type of lymphocyte that we used, the lymphoid cell line, that we could gel out from people using the Epstein Barr virus that was becoming widely used, which worked in B lymphocytes, the subset that produces immunoglobulin. And we realised that we had some sera that seemed to have extra reactions with those and not with other cells. And at the same time, other people realised they had sera that had extra reactions with leukaemias that were of that sort. And through that, one was able to define the second main category of cell surface molecules, which came to be called the D region, HLA D region, or class II molecules'. And that all transpired at roundabout, '74/'75, when that all came about, and there was this whole new range of HLA types. And then we became deeply involved, more than ever, in the international HLA workshops. As I described last time, the workshops were started by Bernard Amos in 1964. They were a very important stimulus to getting the HLA field going. They brought together the key workers in the field, exchanging reagents,

and really working together to define the determinants, because no one laboratory could really do all the work themselves. So over the period of time, '64, '67, '70, '72, '75, and then in Oxford in '77, these international workshops were taking place, each leading to a new step, in a way, in understanding of the HLA field. And we had become much involved, from the early days. And in 1970, and '72 and '75, especially with Julia, my wife, had taken a major role in the organisation and analysis of the data, and then took on the job of analysing the workshop ourselves in Oxford in 1977, which was a lot of fun but a lot of work. I took a sabbatical year and Julia devoted a large part of her time to organising it. But it was exciting, it was fun, because it was that workshop that really, properly, for the first time, defined the HLA D region types. But that was exciting, it was simple stuff in some ways, but it was a major... another major step forward in the HLA work.

MB But apart from just the massive intrinsic interest in the genetics itself, I mean, the medical implications were so far-reaching, it must have been quite a heady... I mean, it really had to be quite a heady time.

WB Yes. What was happening during that time, of course, was, first of all, the clarification of the role of HLA differences in matching for transplantation. And it was during those years in Oxford that Peter Morris, who is still the Professor of Surgery here, came and set up a major classifying programme, and also, of course, had an interest ... we'd known him before he came to do that, in the tissue typing field, and he was one of our close colleagues and friends during our time in Oxford -of course, still is. And it was he and others elsewhere, who really began to establish, very clearly, the importance of HLA matching, particularly for kidney transplantation, also, of course, for bone marrow matching. And then there was this other area which really exploded during the 1970s, of the role of HLA in disease association. We had done some early work with Hugh McDevitt, looking at autoimmune diseases, systemic lupus erythematosis was the one we chose. Well, we'd shown a significant association, which was difficult to work with later, because it involved a somewhat heterogeneous disease. And the first real winner in the stakes of HLA and disease associations was the association of a type called B27 ankylosing spondylitis, shown at the same time in this country and in the States. And that generated a huge industry of work on HLA associations, and we, of course, became involved in that. Julia, with some colleagues in Stoke Mandeville, was the first to show that the ankylosing spondylitis association was the same in women as in men, because it was a lesser disease in women. We were able, as others were, to show that one could detect, at a serological level, something which had been seen using a different approach to typing, the association of rheumatoid arthritis with one of the types, one of the new tvo DR4, as we call it, one of these second class of antigens. And then there was wo k [6] diabetes that had shown an association, and we got involved in that. And we also involved in approaches to the analysis of the HLA and disease associations beca with my statistical and population genetics training, it was an area where o'ne could make some simple points: how careful you have to be when you're looking at a lot of different types associated, to take into account that you weren't just looking at a statistical artefact. And we also became interested in the problems of what you could do with family data, not just looking at associations and populations. And with a post-doctoral fellow, Glenys Thompson, we got very much involved in approaches to analysing diseases in families that did not show a clear-cut pattern of inheritance the so-called sib-pair analysis, and how genetic markers could be studied just in the affected pairs of sibs, and use that as an approach to looking for linkage of a genetic marker with an abnormality, which becomes of rather importance now with the whole DNA technology for doing these things. So it was an exciting, an exciting time.

MB And how far had your observations and thinking gone towards the surface of the cancer cell and recognition of cancer?

WB Well, cancer, in a way, came up a bit later, perhaps before we can get to that, just to mention one or two other things. Another area, as a population geneticist, we got involved in, was population studies, because the HLA markers are so informative, they're nearly as good as fingerprints, not quite, as Alec Jeffreys' DNA probe. And they provided a tremendous range of new markers for doing population studies, and looking at their interrelationships. And we got involved in that. One of the international workshops that we were much involved in in 1972, organised by Jean Dausset - who was later one of the Nobel prizewinners for the HLA work - that workshop was an analysis of population differences. And in 1968, just before we came to Oxford, we'd done probably the first population study. We went to look at the pygmies in Africa, took all our equipment with us and did some typing there and brought the cells back. So that was another interesting area of that projection. And, of course, in Oxford, I also started getting more involved in the affairs of science, I suppose one could say. I was on MRC Boards, I had become involved in some of the discussions of the issues of biology and genetics and cloning.

MB And with the Royal Society.

WB Yes. And ... and the British Association. I was asked by John Maddox to be on a committee looking at biological concerns connected with advances. So... and, of course, it was while I was in Oxford that I was elected a Fellow of the Royal Society, and got involved in some of its activities. And, of course, those are things that had an important influence in my future career. And, perhaps, just to mention one local Oxford thing, David Phillips[5], who was a very good friend, and one of the first people I met when I came to Oxford, had become chairman of the Biology Faculty, and I became his vice-chairman, and then I took over as chairman, and between us we tried to modernise things a little bit in biology, and I'm afraid I don't think we quite succeeded in what we wanted to do - an integrated biology course. But we became very good friends, and had really worked together, and I think it must be as a result of that friendship that later when, much later, when he became chairman of the Advisory Board for the Research Councils in 1983, more than four years ago now, he invited me to be a member of that, and, of course, that's taken up a certain [amount] of my time and interest in later years.

MB It's nice also that later on at the Royal Institution Christmas Lectures, you were to follow David Phillips.

WB Yes.

MB It was a rather nice link, in fact.

WB Yes. And he had, of course, given them in the more structural aspects of molecular biology, and I did them on more of the genetic aspects and their applications.

MB Yes, just nice complementations yes.

WB Yes. And the interest... I had acted at school, and I've always thought that was a

[5] David Phillips, Lord Phillips of Ellesmere (1924-1999). Professor of Molecular Biophysics, University of Oxford, 1966-99.

good training for what we do here, for giving lectures, for describing what you do to the public, and I became interested in that. Also, during my time in Oxford, I'd been asked to give a Royal Institution Discourse, which was my first real contact with the Royal Institution. And that's something else I enjoyed subsequently and found valuable, and important in my present job.

MB Can I just put something in at this point? You talked, a moment or two ago, about the integrated biology course for undergraduates at Oxford, that it didn't possibly quite succeed.

WB Yes.

MB Where do you think the shortcomings were, there? Because there were some quite good decisions about that new course. Where did it go adrift?

WB Well, the collaboration in teaching of biology in Oxford was excellent, and I enjoyed that, because we were a sub-department of genetics in the biochemistry department. We had the responsibility for all genetics teaching at the undergraduate level: to medical students, to biochemists, to the biologists. We worked as closely in our teaching with the zoologists and the botanists as we did with the biochemists. All of that worked very well. But it was as a result of that, that we felt it was no longer sensible to have separate zoology and botany courses, and that, you know, one should at least try and have biology. And we taught the same genetics whether people did zoology or botany. We taught a common first year course in the prelim, and we taught a common course in the final honours. And so we tried to say, 'Well, you could somewhat unitise what was being done, and all right, you could still do botany or zoology according to your selection. But let's say that some people can do biology by choosing a set of subjects that cut across the botany and the zoology.' It seemed a simple and rather constructive suggestion, but it was not readily accepted by all our colleagues, because the zoologists said, 'You can't do without the whole of the animal kingdom,' you see. And we thought, 'Well, maybe you could take bits of it,' you know, 'a bit for the botanists'. It just didn't quite work. Now, I don't actually know what's happened since, but it does seem to me that one should teach biology in a more integrated way, and that that was what the students would have welcomed. At that time, also, and that's sort of shades of the present, if one can put it that way, there was a discussion about a new exam - I've forgotten what it was called, some sort of mixture between 'A' levels and 'O' levels. And I think David Phillips and I were the only people in the University who argued for that, because we thought it was a good thing to have a rather broader background. Maybe the details of it were ill-conceived, but the principle seemed absolutely right, that the education at the sixth form level was appallingly narrow. Even within science, you couldn't really do physics, chemistry, maths and biology, you had to make some choices, and let alone keep a certain breadth between the humanities and arts and the sciences. And, of course, that's another thing that I continued to feel strongly, and made a point of emphasising later, when I got involved in discussing questions of public understanding of science. So I think, as in one's career, it's... everything that happens, builds up, and it's an evolutionary process, and your experiences over a period of time, your contacts, influence your thinking in the future. I think it's interesting to trace back how those things develop.

MB Given Oxford, though, I think we initially had to overcome with that new course, would have taken a few, a couple of decades to do that.

WB Yes, well, I would say that Oxford, inside, was not what many people outside

thought of it. It was not Brideshead Revisited, at all. And I always used to get very cross, along with my colleagues, when people sort of gave the image of Oxford as the traditional arts place and all of that, and Cambridge was science. It was a load of nonsense. It was true then and it's true now, that Oxford draws more support for science than any other single university in the country, outside London, and it had excellent science and excellent collaboration between the different departments, and great strengths, and was forward-looking. And when they approached me to be a professor there, they were realistic in saying, 'Well, you know, even if it's a young whippersnapper from California, we can't expect him to go down on his bended knees, just because it's Oxford. We've got to negotiate reasonable conditions and support.' And I always felt that I was very well-treated in that respect, and that Oxford was much more forward-looking than many people thought the ancient University was. I think some of the views from the outside were quite wrong there.

MB Sir Walter, with that destination, can I take you over, given our time-scale today, I'd like to take you now towards your next step, because you moved to London, and a new research post...

WB Yes.

MB .. .after quite an exciting eight or nine years in Oxford.

WB Yes. Well, what happened there, I suppose you always wonder, coming at a young age, and seeing that your retirement was going to be in twenty thousand and something, two thousand and something, are you going to do the same until you retire? But you don't quite know what's going to happen. And so it really came as something of a bolt out of the blue when, in early 1977, Richard Doll came to me and 'Sir Eric Scowen wants to see you'. And I said, 'Who?' And then he auietl explained to me that Scowen was the chairman of the Council of the Imperial Cance Research Fund. Now, I'd had a bit of contact with them, I'd been on a site visit there because Michael Stoker, whom I'd got to know earlier - again an earlier contact - he had invited me as a site visitor there, and he was the director of research there and had turned it round to become one of the really flourishing institutes in biome'dical research. And he had decided he wanted to retire a little early, and I then realised although it was another two months before Scowen was going to come to see me that perhaps what they wanted was for me to succeed Michael Stoker. And that was the case. And Scowen more or less offered me the job on the spot, which I gather he shouldn't have done at all, because he hadn't really had the approval of the council! And after a few months, for one reason or another, I did decide to accept. It was a fairly obvious decision in many ways because it was such an opportunity to do something that was on a different scale, and with different opportunities, than I could ever have done in Oxford, and that's no criticism, in any way of Oxford, it's just a different scale of opportunities. We had never thought we'd really move to London, we'd never thought of changes like that. It affected my wife, of course, a scientist in the department, as much as it did me. So my appointment was confirmed in late 1977, but not for going until the summer of '79. So I had a long period of time to overlap with Michael Stoker, to find out about the ICRF and to learn something about cancer because I was not medical. Genetics, of course, is relevant to cancer, and I had understood that element, taken a general interest in the problems of cancer, because of that, and seen cancer at the cellular level as a genetic disease, but I didn't really know enough about it. And, of course, when you're appointed to a job like that, you are defined as an instant expert. And so I went along to colleagues, I remember going along to Ken Bagshawe, who's a noted oncologist, and said, you know, 'What should I read to learn a bit about cancer?' And he pointed me to a textbook, I think one he was the co-author of, actually! And I just had to learn. But it was

exciting and interesting. And when you take a job like that, you really don't quite know what it is you're taking on. You know, I remember saying to Sir Alex Scowen, 'Well, I presume I'll just be able to go on with my work like I'm doing now and just have a few of these extra responsibilities.' And, of course, that's very naive; it can't be like that. It's a charity, and that's an important influence. It has a mission to deal with cancer. You have to get totally immersed in that. And I have done, and I've welcomed it. And I think I've been fortunate in being able to take my science and use that, not only in the development of my own research interests, but in the development of what ought to be done in cancer research, with the tremendous resources and opportunities there, to have another very exciting period in my career.

MB Can I ask you a couple of questions about the Research Directorship? Are you responsible, apart from carrying out your own research and following a scientific interest that's personal, for catalysing and checking out and monitoring what's going on in research right through the British Isles?

WB Very much so. I mean, well... throughout the world. I mean, as the Director of Research, and more and more during the time I've been there, because we've had an enormous expansion – we've more than doubled in size – a lot of turnover, a lot of new things, of course, happen, you're necessarily responsible for promoting the new areas, for the new directions, for implementing new research policies, for catalyzing the way people get together, for bridging the laboratory in a clinical way. All of that is very much a part of my job there.

MB And it's fairly diffused? And by now, you have units widely dispersed?

WB Yes. The ICRF started as the earliest of the cancer charities in this country, in 1902, and one of the earliest in the world, always with the aim of supporting its own research laboratories. And as we grown that's continued to be the case. So, initially, it was a small and then a larger, and larger research laboratory in the centre of London, but then that was not with a clinical base. So then my predecessor, Michael Stoker, established clinical units, at first in London and then in Edinburgh, and now we've got one in Oxford, so gradually as it's expanded, we've expanded our activities in London and outside London, because we are responsible, overall, for about a third of all of the cancer research in the UK. And this expansion and new area of new developments has been very much a part of my job over the last... nearly nine years. And an exciting time because perhaps... to go back to, you know, why should you have a geneticist in charge of a cancer research institute? And why has it been such a particularly exciting time? Well, as I've already said, the reason for a geneticist is because cancer is, essentially, a genetic disease at the cellular level. That had been something that had been emphasised, interestingly, by the second Director of the IRCF, James Murray, in the early years of this century, but at a time when the technology was totally inadequate. Now that we can look at chromosomes and cells, and now, of course, use the fantastic tools of molecular biology, we see that that's true, and cancer is a series of genetic steps, taking cells from the normal to the abnormal. And that was, of course, beginning to be realised. And so that a geneticist, and a molecular geneticist, was an appropriate person to have in charge of the Cancer Institute. And then with my statistical background, and the importance of epidemiological approaches, that's also been a valuable tool which has enabled me, at least, to appreciate some of those areas which are so important. During the time in Oxford, of course, that was also the time when the recombinant DNA revolution started. And I was a member of the Ashby Working Party, which was the earliest, even before the Americans, earliest

discussion of the implications of recombinant DNA, and a very effective one. And again, it's personal contacts, it was probably knowing Michael Stoker, who was also a member of that, that got me on that. Well, during the last two or three years in Oxford, we decided to get recombinant DNA work going, and perhaps that was a time when one realised that the deficiencies of support... that the scale on which one could do things, and at that time there was no DNA biochemist in Oxford, which was an amazing deficiency, something that Rod Porter and I tried to remedy in appointments that we promoted, and didn't come off until later. And we had started as soon as I knew I was going to the ICRF in some contacts with there, because Michael Stoker, in bringing the virus approach to cancer, very much into the ICRF, also made it one of the first places in the country where molecular biology could be done, the recombinant DNA work, I should say, of course, could be done in a major way. And so, in going to the ICRF, I was able to give to my own work a tremendous boost to the applications of recombinant. DNA technology, which, of course, permeates the whole of our work now, and is just an amazing revolution. And in my own work, the immediate application was to the molecular biology of the HLA system, so that we were amongst the first to obtain DNA clones for the products of the class I HLA molecules, and were the first, in fact, to provide a clone for the class II products of either mouse or man, and then became much involved in the tremendous flowering of the understanding of the genetic organisation at the DNA level of the region and the definition of the products. I mean, a level of understanding that one couldn't have dreamed of, even at the time that I came to Oxford. And that was tremendously exciting, and all of that was really made possible by moving to the ICRF, by the resources that could be developed there, that one can bring together. And I think that's an important point. We have a lot of discussion now, which I support, and comes through being on the Advisory Board for the Research Councils with David Phillips, on the need for concentration of resources, and I think the ICRF is a supreme example of that. If you don't have that sort of concentration of resources, not only the support that people that work together in different areas, you cannot easily do research at the forefront, internationally. It's not that any one person has a huge machine, and that you have an impersonal large set-up. It's not like that. Our individual groups at the ICRF are quite small. No one has more than about ten or a dozen people working closely with them, but they work together with other groups, and the combined resources are tremendous. I mean, as one always says, the sum is... the whole of it is so much more than the sum of the individual parts. And I think that's a very important lesson which we've got to learn for the way that research is done now, throughout the country. So, in my own research, in going to the ICRF, I undoubtedly felt that I had to look at what the cancer implications should be. And I had no regrets in that at all. I think there's a lot of nonsense talked about pure and applied work, and... and a lot of inverted snobbery about having an applied problem, that I think is quite wrong. The applied problems can be a major challenge for the basic, and the other way around. So I was very happy to take on some of the challenges of getting involved in areas that I felt needed to be developed in the cancer field, where I thought, perhaps, my own activities could act as a bit of a catalyst for others. So, for example, in the work on the cell surface, we realised that with the monoclonal antibody technology, one had to generalise to making monoclonal antibodies to different cell types, to applying these to diagnosis, and to the potential for applying them in vivo, for making monoclonal antibodies that had radioactive label that allow you to pick up where the tumour is in an individual, and allow you to target the therapy on to it. So we developed, in my lab, and then in collaboration, and stimulated other work which has taken off in a major way, the applications of monoclonal antibodies in the cancer field. And I think, through that, we really were the first to do that in this country,

and amongst the first anywhere, having the background of knowledge and experience there. And I took on in my own laboratory clinical fellows, who was able to apply this work, and make the bridge with the clinical side, which I've found tremendously interesting and exciting, and it was another area in my own scientific work which then, in many ways, moved more into the cell biology associated with cancer, the applications of somatic cell genetics and recombinant DNA work to that, and the applications of that in the clinical areas, which has proved to be extremely exciting. And so now we do have, in the ICRF, a major programme in monoclonal antibody base work. I think we've helped to disseminate the applications of monoclonal antibodies in their applications in pathology, and we've got, I think, what is the beginnings of a very effective approach to some therapies in using monoclonal antibodies.

MB How far, when I talked with Sir Gustav Nossal, a friend of yours, up here, we actually philosophised about the main steps towards the conquest of cancer. Could I invite you to similarly kind of look ahead, to speculate a little?

WB Yes. And perhaps I can weave in some of my own interests in what goes on at the ICRF. You see the major challenges were, and are, to identify these individual steps in the cancer process, and at the fundamental level, that's the understanding what leads, and when you have that, then you must have the confidence you can apply it. So from the sort of work that Michael Stoker brought first of all, on the virus work, where there'd initially been great hope that viruses would be a major cause of human cancer, that didn't seem to be the case. Now we know it is an important cause of some cancers. But what came out of that work, not from the ICRF, but from others, was the discovery of oncogenes, the discovery of the genetic changes in the viruses. And that was made possible by the applications of molecular biology. And then that led to the identification of some very specific genetic changes in normal genes, knowing that the oncogenes are genes carried by viruses that they've picked up, they've hijacked from the normal cell. Now, then the question of the function goes, and there at the ICRF had been developed interest in growth control, which must be a major feature, and the growth factors that control the growth of cells and trigger them. And it was through that, that it was at the ICRF, and the stimulation of that work, that it was first shown that one of the oncogenes, was actually an abnormal growth factor, and another was an abnormal growth factor receptor. And it was through the bringing together of these different areas of work and the interdisciplinary approach, and through, I might say, having set up decent computer facilities, which Julia and I did while we were at the ICRF, all of that that made this possible, and that's, of course, been an absolutely major step forward in the fundamental understanding of the cancer process. Other aspects of the genetics came from work which Janet Rowley first pinpointed, of the role of chromosome translocations. Janet had been a visitor in my lab in Oxford, the first year I was there, at a time when chromosome banding techniques developed, she went back to Chicago, applied those, and identified what was known as the Philadelphia Chromosome, it's a specific translocational exchange of genetic material, pointing to the fact that there, where that exchange took place, must be the genes that were affected by it, that it somehow would be important for the cancer process. So that then became something one could study at the molecular level, and indeed, one of the aims that we set ourselves when I set my lab up in London, was could we identify the genes at those translocation points? Well, we didn't, directly. But indirectly, we were involved because we applied somatic cell genetics that are likely to do human genetics, to say, 'Where are these oncogenes that have been identified from the viruses?' Because we thought, perhaps if we knew where they were, that would give us a clue as to whether

they were involved in these genetic changes. So we did the first mapping of some of the oncogenes, one of which was called Abelson, and showed it was on chromosome 9, and that was the chromosome involved in the Philadelphia Chromosome translocation. So that, already, was a clue, a wild guess perhaps, but a clue that that gene might be at the translocation point. And then it was others who did beautiful work, partly in collaboration with us, that clearly showed that was the case. So these were major steps forward, in which we played some part, in understanding the genetic changes in tumours. And then, more recently, there's been another very important development that comes through studying inherited susceptibilities to tumours where, it's a bit of a long story, but basically, using restriction fragment polymorphism, using the genetic variation one can detect with DNA markers, it's been possible to show another category of genetic change in tumours, discovered through studying the role of inherited susceptibilities and the genes concerning those, at the cellular level in the tumours. That was first done by others with retinoblastoma, actually using, initially, a marker that we had placed on chromosome 13, which is the one that had been shown to be involved in retinoblastoma, and again emphasising the importance of just the formal genetics for somatic cells genetics. Then more recently, we've been able to apply that to an inherited form of bowel cancer, and showing the level of genes in that. I made that a slightly personal story, but, of course, it's a worldwide activity at the fundamental level. And it brings up all sorts of possibilities that come from the recombinant DNA side. The discovery, of course, of the interferons, and then the use of the recombinant DNA techniques to make them, to make all the growth factors, to manipulate them. The sort of understanding that comes from that is providing totally new approaches to dealing with cancer. And I was relevant, in a way, to understanding the needs for prevention, which is so important, as to treatment, because if you look for substances that are released early on in the development of a cancer, you're now going to use these techniques of molecular biology. If you study the deficiencies in DNA repair –which we have a first class group at the ICRF in – now you can study the genes, and see whether changes in those genes predispose people in those that are not yet quite well defined at that level.

MB In a way, you're looking down two roads. You're looking down to the microscopic, and the beginnings, the origins, the causality story, but also fitting very much with your concern about tribes and peoples. You're looking towards the epidemiological, you're looking towards the larger prevention scale...

WB Yes. You have to have a very balanced view of the overall picture, and you have to be convinced that the basic level, as I am, is as relevant as the very applied things. I mean, recently, we've established a programme at the ICRF of working, supporting work, using the general practitioner to get over the message of stopping smoking, and to go and get screened, and, in fact, working with Jonathan Fowler, who is one of the pioneers in this area, and supporting his work here in Oxford. The very practical questions of dealing with people, which are just as challenging in some ways scientifically, how to set up studies that can tell you what to do properly, are as important and are a concomitant of the basic work. If we discover a new substance that's released early by a bowel cancer, then that test will be the thing that, you know, the GP has to tell the patients to go and see. The gaps there are narrowing. And one of my main jobs in a challenging and existing job, is to see that whole range, and to (?) balance, and to make sure that we take advantage of all the different possibilities.

MB So you see the future as a combination of switching off the problems at a

genetic level, where possible...

WB Yes.

MB But also manipulating the public to reduce their...

WB Oh, absolutely. I mean, if we asked, 'What should we do about smoking?' which is the... still the major identifiable cause of cancer, smoking cigarettes. And Richard Doll, of course, the pioneer of discovering that with Bradford Hill, has been, and still is, on an acting basis, Head of our Unit here in Oxford, in Epidemiology. The answer is not more and more detailed studies of how smoking causes cancer, but how to stop it. How to stop people smoking cigarettes: it's partly a matter of public policy, persuading the Chancellor who, unfortunately, doesn't put the price of cigarettes up enough; persuading people that the economic arguments that are sometimes made against reducing smoking are a load of nonsense; persuading people how not to smoke; finding out about nicotine addiction. All of these are the practical issues that we've got to face, so again, you know, talk about nicotine addiction, it's a fascinating problem, but I see clearly genetic differences between those that are more easily and those that are less easily addicted, can be used. DNA clones full of nicotinic acid receptor to study genetic differences between people as a function of their addictability. So that's a thing that I hope we're going to be getting into. Which leads me to mention something else, a little off the cancer tack, which I think I ought to, that is the tremendous opportunities that have arisen from DNA technology to study differences between people. Ellen Solomon and I, nearly ten years ago now, pointed out that you could use polymorphisms, genetic differences, the genetic polymorphisms that my predecessor in Oxford, E B Ford, defined, that you can now study these with DNA clones, and you can, therefore, study an unimaginable range from what was known before, of differences. You can define differences between people at a level that simply wasn't possible before. And that allows you to apply quite classical ideas on establishing the genetic basis of differences between people – their face, their behaviour, and their disease – in ways that simply were not possible before, using a combination of the modern DNA technology, and classical population statistical genetics. And that, of course, together with the real possibility of finding out all the human genes, and where they are, that come from genetic mapping approaches, creates this... project, in a way, of the human genome, of which I've been much involved in promoting. I think I was amongst the first, really, to discuss it, in 1980 already, in a lecture I gave when I got an award from the American Society of Human Genetics, because of realising the tremendous power of the knowledge of where every gene is, and being able to associate a location on a chromosome, with a genetic difference.

MB And your challenge to map the human, the human chromosomes by the year 2000?

WB That's right.

MB This is a real hope?

WB I think it's a real hope, and it's, of course, become a very popular thing to discuss. I think it's become rather distorted in its discussion, by the technology and the sequencing, and moving away from the real challenge it is. I think it's the challenge of the century in human biology because it's going to give us a power that is enormous in the study of human disease. If we just take an example of having located, roughly, within a

million bases, within, perhaps, a one-thousandth of the human genome, where the gene for this inherited susceptibility, polyposis, to bowel cancer is, if we knew where all the human genes were – and I think we will before the year 2000 – we could just look up what's there, and we would know a bit about each of those genes. And just from looking up we'd make a fair guess at which was the gene that was involved, and quickly focus in on the one that it was, and then have knowledge about a major gene in the development of, you know, 25 or more per cent of all bowel cancers, and obviously have an immediate possibility of applying that knowledge. And now, of course, what we've got to do, which is part of the genome project, is to start from where we know we are, walk along the chromosome, and do a little bit of the large project. So I think that's a tremendously exciting and important development. I think, fortunately, that's beginning to be realised by the public, by the politicians. We understand the Prime Minister's really quite interested too. It will cost money, but I think the main thing is bringing people together. And, in fact, on Monday, we're having the second of a series of UK get-togethers – and, I hope, a very significant one – of all the people, in this country, interested in the human genome work, to really stimulate a collaborative effort, which is needed, so that those that have skills and knowledge and resources in one area, can match them with others. And again, scale of effort is going to be so important. And we're pretty good in this country in collaborating. So I see it as a collaboration that is a little analogous to what was done in the HLA field, only with much wider implications.

MB Sir Walter, we're coming to the end of our time today. You stand in the course of a great many developments relating to the molecular constellations of the genome. Perhaps, at a later date, we'll see how some of this has taken its course.

WB It seems a never ending story!

MB Thank you.

WB Thank you.