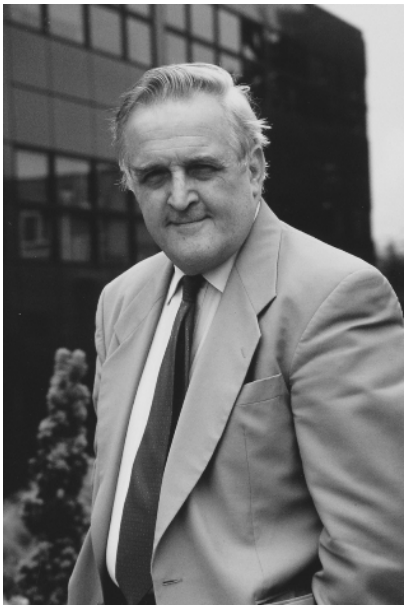
David Weatherall



Personal Details

Name	David Weatherall
Dates	Born 1933
Place of Birth	UK (Liverpool)
Main work places	Liverpool, Baltimore, Oxford
Principal field of work	Haemoglobin genetics
Short biography	See below

Interview

Recorded interview made	Yes
Interviewer	Peter Harper
Date of Interview	16/12/2004
Edited transcript available	See below

Personal Scientific Records

Significant Record set exists	Yes
Records catalogued	No
Permanent place of archive	
Summary of archive	

Biography

David Weatherall qualified in Medicine at Liverpool University in 1956 and, following research at Johns Hopkins Hospital, Baltimore, was Professor of Haematology at Liverpool University from 1971 to 1974, when he became Nuffield Professor of Medicine at Oxford University. He was appointed Regius Professor of Medicine at Oxford in 1992 and founded the Institute of Molecular Medicine (now Weatherall Institute of Molecular Medicine) in 1989. He is the recipient of numerous scientific and other honours.

His principal research contributions have been on the clinical, biochemical and molecular characteristics of the thalassaemias and related disorders, and the development of programmes for their prevention and management in developing countries.

INTERVIEW WITH DAVID WEATHERALL, 16th DECEMBER, 2004

PSH. It's Thursday 16 December 2004 and I am interviewing Sir David Weatherall at his office in the Institute of Molecular Medicine in Oxford. David, can I start at the beginning and just ask where were you actually born and brought up?

DW. I was born and brought up in my earliest years in Liverpool and then just outside Liverpool on the Wirral.

PSH. Which part of the Wirral?

DW. The Wirral, in a little place near Hoylake on the coast, where there used to be the main fishing industry.

PSH. And can I ask, did you come from any kind of scientific or medical family, or was there any kind of family influence that made you go towards medicine.

DW. My father was an industrial chemist in a company in Liverpool but he was also a very good musician, so he spent his life 50/50 between chemistry and music and I suppose there was some influence directed towards science, but there was certainly no medicine in the family, but for some bizarre reason I wanted to do medicine from about the age of 3.

PSH. Was it medicine you wanted to do or science?

DW. No, medicine, to be a doctor really. One just didn't associate those two worlds at that age, well probably not until one was at medical school, that there might be two parallel opportunities.

PSH. So did you, in your school days did you go for it in the sense of doing those things that would get you to medical school?

DW. Yes. We had things called the school certificate in those days and I really pushed very hard for the subjects that I knew would allow me to do science in the 6th form, which would qualify me to go to medical school. There was a bit of a row about this, because I happened to do particularly well in English and they wanted me to give up this idea, but I wouldn't, so I was very much focused on getting the appropriate qualifications for medical school.

PSH. And I mean, by medical school do we mean Liverpool, or did you think of going further abroad at that point?

DW. All I wanted to do was to get out of school and get into medical school and I applied to 3 universities I think. Oxford and Cambridge I don't think we had heard of them up there in those days, so I applied to Liverpool and Bristol, I can't remember the other one. The other two you had to have photographs and they never replied at all so I just got an interview at Liverpool.

PSH. What year was it you started in the Liverpool medical school?

DW. 1950.

PSH. And did you go straight from school, deferring the Army, or did you go into the Army first?

DW. No no, I had the interview quite early at Liverpool, at about 16, so I went straight from school into the medical school and then managed to defer, in fact I deferred the Army for two years after qualifying because they lost my address. That enabled me to do the MRCP exam, which meant I could do something more interesting in the Army.

PSH. Now Liverpool as an undergraduate, I knew Liverpool a bit later on as coming from the outside as a doctor and I never really got to understand Liverpool Medical School as an insider. What kind of place was it?

DW. Well it was a strange place, because we just, of course, in 1950 got the tail, real end, of the people who had come out of the Army at the end of the second World War, so quite understandably they were partly there to enjoy themselves and there was no rule about how many exams you could fail. So some of them had already been there a very long time. There wasn't an enormous intellectual atmosphere about the place but there were just a small core of exceedingly good people. I think in the pre-clinical years the person who really set me alight was Gregory the physiologist, the guy who discovered gastrin, but he just used to come out of his lab in a kind of filthy coat and teach physiology and you could tell that he was making physiology happen as he was teaching. He was very inspiring but the quality of teaching was very patchy and there was a kind of anti-intellectual atmosphere. I mean if you asked a question after a lecture you would be met by a lynching party outside and we were really in the hard-drinking womanising part of the year with a lot of older students who had been in the Army and so on. So it wasn't a very intellectual atmosphere I have to say.

PSH. Then when you got onto the clinical side, I mean even when I was there some years later there was a huge wealth of pathology in terms of real serious disease, much of which has disappeared now, so was it a very hands-on course, the clinical years?

DW. Yes it was. The pathology part was run by Harry Sheehan. Again he was a very inspiring teacher, but it was very practical and there was a marvellous opportunity there, but you just had to take it yourself. The quality of clinical teaching was very variable, one or two outstanding teachers, a lot who were not so outstanding and things like the district midwifery which I had to do those days, gave you an extraordinary feel for the dire poverty in that city. So it was a great experience the clinical school in Liverpool, from that point of view, provided you made the best of it yourself. You are not going to get very heavy teaching or be spoon fed in any way.

PSH. Would it be fair to say that the value of bedside teaching and learning from patients directly was something that really became part of you at that point?

DW. Yes I think so, although a lot of what I saw in my teachers at the bedside I found quite disturbing actually, but I think yes, the feeling that each individual person was a challenge almost, and as I later came to think of it every individual person was almost a research project in themselves. Extraordinary diversity of disease and little bits of general practice I did to fill in just after qualifying, in the slums in Liverpool, gave me an enormous feel for the importance of public health and social aspects of medicine.

PSH. When you got to the stage of qualifying had you become any clearer at that point about the kind of medicine you wanted to do or was it still very much wide open?

DW. No, I think by qualifying I had probably got some inkling that it was going to be something hospital based or hospital university based, rather than general practice, but I hadn't the faintest idea in what area it might be.

PSH. And then you say that you managed to get your MRCP before you went into the Army so you must have done a fairly wide range of medical jobs to get that.

DW. Well I did a year's house jobs, one in medicine and surgery, and then just the one year senior house officer in medicine and then the membership and then the Army.

PSH. Going into the Army with a qualification must have meant you were able to use your specialist or at least your hospital medical skills rather than just be treated as a squaddie.

DW. Yes, the British Army in 1958, they were coming more or less at least getting on top of the long 12 year war in Malaya and they were desperately short of medical specialists so, although I applied to stay in the UK because I didn't like flying or snakes or fighting, they immediately posted me to Singapore as a kind of junior medical specialist with two years qualification and put me in charge of the paediatric ward in the Singapore British Military Hospital. I did that for a year and then went up and looked after 80 medical beds by myself in a hospital near the Thai border in a place called Taiping, which was a fantastic experience.

PSH. So was that where you first encountered thalassaemias?

DW. Yes. I had worked as a houseman for Cyril Clarke and heard a lot of talk about genetics, but it never occurred to me that it would be of any particular interest to me in the future, but purely by accident in the children's ward in Singapore we had a little Gurkha child, who had been kept alive on blood transfusions. She had previously come down with her father who was a Gurkha sergeant from Nepal and nobody had been able to make a diagnosis; I had taken to spending half a day a week at the Singapore General Hospital and met a chap called Frank Vella who was a biochemist and he had become interested in haemoglobin disorders in Malaya and we looked at some of the literature and thalassaemia had not been described in Nepalese before, but there had been a recent paper with the title 'Mediterranean Anaemia in Thailand' and at that time starch block electrophoresis had just come out and

you could actually diagnose the carrier status of thalassaemia, beta-thalassaemia, much more accurately, so we got covered in starch for a few weeks and did these family studies with this child, and it turned out it had thalassaemia and that was my first interest.

PSH. Yes I've got that down as your first published paper, am I right, in 1960?

DW. Yes. It was a disaster paper really, because as soon as it came out I got hauled up, phone call from the Director General of the Far East Land Forces, no less, come to my office and he had this British Medical Journal out and he said "Is this yours?". Well you know I could hardly deny it and he said "You didn't get permission from the War House to publish this". I didn't know what the War House was, that was the War Office and apparently he said that publishing information about British or British attached personnel was a court martial-able offence. "Don't do it again" and then he said "Either way" he said, "its damn bad form to tell the world that Gurkhas have got bad genes" So it wasn't exactly a major triumph.

PSH. Were you two years in the army or more?

DW. No two. Bare minimum. It was great. That switched me on. I did manage in my spare time to do a lot of haemoglobin electrophoresis and I became interested in neonatal jaundice and glucose -6-phosphate dehydrogenase deficiencies. The problem in the military hospitals was there was no equipment and so we built a simple filter paper electrophoresis set-up with car batteries and then, if I thought I found anything, I used to send it through to Herman Lehmann in Bart's who was the great British haemoglobin king of the time.

PSH. How did you manage to make a link with him, because he was very much the key person there? Was that through your first paper perhaps?

DW. I think what happened was, shortly after I got to Taiping I found a child with a fast moving haemoglobin and so I think I just wrote to him and said could I send you a sample of this just to see if you agree, and after that I sent him one or two samples and then, when I finished in the army, I went dutifully to see the great man at Bart's, who told me that I shouldn't continue in that field because there was nothing left to do, and go and work on red cell enzymes, but he was very helpful. He was a delightful character.

PSH. When you were in the Army in your medical post did you have to be your own pathologist or was there a full-time specific pathologist who did the lab work?

DW. No, in Singapore, no in both places actually, all the military hospitals had a small lab and they would have a general pathologist, who did a bit of everything, but the problem was they were very poorly equipped, so if you were really interested, I mean I did learn how to look at blood films and look for malarial parasites and things like that myself and I did all the bits of lab work with the G6PD and with the haemoglobin myself, but that was you know,

really you had to do it with very primitive equipment and just make the best you could out of it.

PSH. In a way it sounds quite a good atmosphere. It sounds as if you were encouraged or at least welcomed, if you wanted to follow up on something doing your own basic lab work.

DW. Oh yes, yes.

PSH. You were given the chance to do something rather than having a totally different set-up do it.

DW. Well of course a lot of the people in the labs were national servicemen like yourself, for example in Taiping the first pathologist was a chap called Bernard Knight, who became a very famous forensic pathologist.

PSH. I know Bernard Knight.

DW. Who used to disappear at night. We thought he had a woman. He was actually already in those days writing thrillers, and then the second pathologist was David Evans who became a very distinguished nephrologist in Cambridge, so you know, there was no problem. Even in Singapore with the regular Army pathologists, if you wanted to go in the lab they made you quite welcome. There never was any problem.

PSH. So when you finished in the army did you go back to Liverpool?

DW. No. I kept in fairly close touch with Cyril Clarke while I was in the army and about 6 months before I was due to be demobbed, he wrote to me and said that Liverpool had started some kind of arrangement with Johns Hopkins and that David Price-Evans was there and Victor McKusick had said that they would be very happy to take somebody else from Liverpool, but there wasn't anybody obvious to go, would I be interested in going. So I thought, I still didn't know what I was going to do, although I had become interested in haematology a little bit in the army and genetics, so I thought well yes, fine, so I just slipped through Liverpool to see my parents and then took off straight to Baltimore.

PSH. Now were you working with Conley mainly, or was it with Victor?

DW. No the fellowship was with Victor and I had wanted to study thalassaemia in Baltimore and Victor said fine, but I think Victor had his head in the clouds sometimes and when I got to Baltimore there was only one patient with thalassaemia known to the whole of Johns Hopkins and this child lived in Washington anyway, so it was not a rich source of thalassaemia. But I went into work with Ned Boyer who didn't have a research fellow, and he taught me starch gel electrophoresis at the time and we decided to look at genetic mutants to try to answer some questions about the haemoglobin genes and their arrangement, and then I had read a small report suggesting that black babies have a fast moving haemoglobin called haemoglobin Barts, which there was some controversy whether this might be a thalassaemic marker, so I decided to do a major survey of newborns in Baltimore and try to

relate this haemoglobin Barts to thalassaemic phenotypes in the family, and so I did get that chance to work on thalassaemia in my first spell at Hopkins. So that was really an initial crack at trying to understand the genetics of both the normal alpha chain production and the alpha thalassaemias.

PSH. How long were you there that first time, was it two years?

DW. Not quite two years, but I knew by the end of that two years exactly what I wanted to do, but the fellowship finished. I did spend just a short time at the end of that fellowship up in Lock Conley's department, because they had access to much more material. It was much easier to do the cord blood survey up there with him, but I had to come back to Liverpool. I had only just got back, about four months into a locum senior registrar post, when I get this letter from Hopkins inviting me back for a faculty post with Conley. I knew what I wanted to do, it would be very difficult to do at Liverpool at the time because there was no lab, there was no equipment. The Nuffield Institute had not been built then, so that's when I got my bit of career advice from Cyril. I just went and asked him whether I could go back to the States for a couple of years, because everybody told me it would wreck my career and I must follow the line and go through all the years of registraring. He didn't even look up from what he was doing and he said "What do you want to do?" and I said "I would like to go back at least for a year or two". "Well bugger off then" and that was it, so I buggered off and went back to try to develop some way of measuring haemoglobin synthesis in the test tube, which would start an interesting two or three years' work.

PSH. Before we get to that, can I just go back to Cyril Clarke, because you must have known Cyril for a good long time during your Liverpool years. How did you first get to know him?

DW. Oh, as a medical student I think. I wasn't on his firm as a student, but I did a locum in my final year, a student locum for his houseman and so I worked a couple of weeks with him on the firm. And that went OK, so that was my only exposure to him as a student, so since I had done his locum I decided to apply for his house job and I got his house job, so I got to know him. In those days you really did get to know your boss, it was very much you and him and then the more senior registrars and senior registrars kind of came along, but he had a very close relationship with his house staff.

PSH. Was that at the Northern?

DW. Mmmm, yes. He was a very eccentric physician, but he really did expect you to know the patients and he would come at any time of the day or night, well day, he went to bed very early. You could never ring him for advice after about 8 o'clock. But although he was eccentric and I suppose by modern standards he would be perhaps a very unusual clinician, he did have a genuine feeling for medical care; he felt enormous responsibility for his patients I think and he expected you to have it, so it was just God help you if you didn't. You didn't go out at weekends and he did expect that kind of continuity, that's quite interesting and that's all gone now of course.

PSH. The other thing with Cyril I feel, again seeing things as an outsider, he always struck me as being totally different from the Liverpool establishment by having an enquiring mind.

DW. Yes, I think that was my view of Cyril as well, and what he taught me was an enquiring mind, it was a kind of hopping around enquiring mind. He was interested in everything. And this enormous enthusiasm, when he had this conversation with Philip Sheppard who worked with him on butterflies and I think this idea that there might be something in genetics for medicine evolved, but once that evolved and then they got involved with blood groups and disease and had read Aird's stuff from Hammersmith about blood group A and cancer, an extraordinary kind of enthusiasm evolved and that was really quite infectious, the whole place was buzzing. Crazy ideas some of them but, you are right, he was one of that old generation of physician naturalist, really you know, he was in a curious way a bit of a polymath. Not an intellectual perhaps in the usual sense, I don't think Cyril ever read very widely or was interested in music or the arts at all, but he had this extraordinary kind of bridge between medicine and biology.

PSH. Had the rhesus work started at that point before you went off to Baltimore again?

DW. No. I think when I was going off to Baltimore, yes the first idea had started to glimmer I think, because when I got to Baltimore, Ronnie Finn was in Baltimore at the time and I think he had done his thesis on ABO incompatibility and protection against rhesus and, of course, right at the end of the thesis, the famous Kleihauer papers and the Toronto papers showing that you could identify fetal cells in the maternal circulation had come out, and so there was still a lot of doubt when that suggestion was first made, but that was probably about '59, so I got to Baltimore in about'60, the end of '60, so it was just taking off I think.

PSH. I had forgotten, in fact I don't think I ever realised that Ronnie Finn had done a fellowship in Baltimore. Had he been sent out by Cyril specifically to work on that area, or was that an idea that Victor had when he was out there?

DW. No, I think Ronnie was specifically sent out to work in that area and although he was formally with Victor, I think Victor put him onto Julie Krevens, who was out at the City Hospital, because Julie had a lot of experience in blood transfusion and so on and I know he worked primarily with Julie Krevens and they had started some of those so-called volunteer experiments in the Baltimore Jail.

PSH. Yes, because it has always intrigued me that the Americans used prisoners whereas the British used policeman, which somehow I feel reflects a fundamental difference. So how long were you in Baltimore for this second spell?

DW. The second spell, it was just about two years. I struggled away and managed to get human haemoglobin synthesis going in the test tube and then ran into the problem of separating the globin chains. I won't bore you with the details, but I tried counter- current distribution and hybridisation with animal

haemoglobins and so on and found there was unequal labelling in thalassaemia, but one needed to make this quantitative; I very fortunately ran into John Clegg who had just come from, well he'd been sacked by Neurath on the West Coast.

PSH. By who?

DW. By Hans Neurath.

PSH. Oh right.

DW. John Clegg was a student with Fred Sanger and Mike Smith in Cambridge and then when he had done his PhD he went out to work with Hans Neurath the German protein chemist, in Seattle. Neurath was very distinguished, but he ran a very rigid laboratory and they had to be in at 8.30 every morning for a journal club and this was not Clegg. Clegg has to work in his own hours, like they did of course in Cambridge so he didn't turn up and he had only been there a month or two when he got a note on his desk, "your presence is disturbing the morale of my laboratory, please leave by the end of the month." So here was an impecunious young British post doc with nowhere to go. He did know Mike Naughton who had been Fred Sanger's technician, done a PhD and then moved to Baltimore to Dintzis's department so he rang Mike and Mike got some money for him and he joined them. He had a terrible project to start with. He was trying to pulse label insulin, in other words to get counts into living pancreas and see how insulin was synthesised, and it was going nowhere, and I used to meet him occasionally for coffee. I'd tell him my problems with globin and he said, well, he had just done his PhD in Cambridge on fibrinogen chains, which are separated in mercaptoethanol urea columns and it might be worth trying, so we did try and it worked beautifully, and then he took over the structural end and I continued with the biosynthesis and that was when we were able to really define some of the basic pathophysiology of the thalassaemias quantitatively and so on, and also take it a few steps further in trying to pin down the level of the biosynthetic defect and so on. And then I came back to Liverpool and John went back to the LMB, and he did two years with Cesar Milstein, but he wanted to work on thalassaemia so we managed to get a senior Wellcome Fellowship for him and then he came up to Liverpool.

PSH. Now when you went back to Liverpool this second time, what post were you in then?

DW. As a clinician, I mean in the University, I think I was a lecturer in medicine and by then there were some labs based in the Nuffield building.

PSH. So the new building must have just about opened.

DW. Yes, and when Cyril wrote to me in the States and said that there would be some kind of lectureship coming up and if I got it I could try and set up a lab in the new Nuffield building. So he did that and John came up to join me after a year or two, and we had a small group up there which was really quite successful. A number of quite nice things we did over the next year or two; so in the meantime I had to spend part of my life setting up a haematology unit in

the Royal Infirmary and mixing the clinical work in the Royal with building up this lab in the Institute. We ended up with quite a nice lab and quite a nice group, and we were doing some quite exciting things really I think, and then of course we got this phone call from Oxford.

PSH. Yes. In Liverpool, am I right that haematology wasn't really split off from medicine, or at least the clinical end of it, because I feel you have been a haematologist, and a physician and a geneticist, and in most places these roles have got all separate but

DW. Oh you couldn't do it now anywhere. I'd be unemployable. In Liverpool there was a kind of standard laboratory pathologist who might have some interest in haematology, but they'd all been trained in pathology I mean, so they had to be a bit of everything and there was nobody really interested in the clinical end. Of course coming from Conley's department at Hopkins, it was largely run by clinicians who were also to some degree internists, and the idea of a full-time laboratory haematologist, maybe not in the teaching centres really, maybe in the peripheral hospitals there might be ones who did nothing but the laboratory, but it was a more clinically based specialty. So coming back to the UK, I mean once you were at consultant level in medicine and one had been trained to some degree in haematology, one could set up a haematology unit fairly easily, but I got a bit involved in the politics of haematology. Gradually it became clear that haematology was a separate specialty and in the end haematologists would do both, look after their patients and run their labs. And that's how it is now. But when I got back there it wasn't a clinical specialty at all really.

PSH. Can I ask David, how much during your time in Liverpool and in Baltimore, how much of broader medical genetics had you kind of absorbed over this time.

DW. Well in the period with Victor McKusick, I suppose a fair amount, because I would obviously sit in on all the research meetings and go to all the seminars, and I went out to quite a few of the teaching sessions at Homewood over that 18 months. Not formal, and probably very patchy, and then in my second period at Hopkins of course, unusually for somebody from the UK, I did get exposed to protein chemistry and to some degree the beginnings of molecular genetics, because they didn't have even the equipment to work with in the haematology department at Hopkins and I got a part-time appointment with Howard Dintzis in biophysics, where Naughton and later Clegg worked, so at least one got exposed to the basics of protein chemistry, fingerprinting as it was, amino acid analysis then, and then, the basics of protein synthesis. There were a number of people working in protein synthesis in Howard's lab so you could talk to them. I suppose what I would say is, I've not a great education in genetics or molecular biology. I just managed to pick up the parts of it which were most relevant to my clinical research interests.

PSH. One of the things which has always intrigued me and, thinking in terms of how all of us have been influenced, Cyril had this idea that genetics was part of all parts of medicine, which I have always felt he was right but about 30

years too soon; but then he had other ideas that because genetics was part of medicine you didn't need to have medical genetics as a separate specialty, and there I felt he was profoundly wrong, and in some ways I have felt that you have been the person who has inherited that bit of Cyril's mantle of having genetics as part of everything. But then I felt well, apart from a place like Oxford, it's very difficult to make that work, or at least it has been until now. What's your feeling about Cyril's ideas and indeed, your ideas on how medical genetics should or shouldn't relate to genetics in medicine?

DW. I think it's a very fascinating question that. To be quite honest, Peter, I'm not sure Cyril thought this through. I think he was a kind of honest archetypal amateur at everything. He loved to dabble . If you put this into the real world, it seemed to me that, once genetics had taken off, it was clear in the 50s, I mean it was amazing there was no realisation apparently in the British medical scene what was going on in the 50s. As medical students we never heard about Watson and Crick, you know, this extraordinary discovery, and it was not until I got to America in the early 60s that it was bubbling with possibilities in the medical world. But I think what one realised and I think it was quite clear that genetics was going to influence all specialities, so one had then the problem of educating doctors with at least enough genetics to be able to appreciate its importance, but it was going to be far too complex just for generalists to play around with and you would have to have a speciality in clinical genetics. I think where the problem was, that there were certain diseases which somehow traditionally the clinical geneticist just didn't get involved with, like genetic blood diseases, the haemophilias and so on. There was this curious kind of divide and the other thing which I – sorry – many clinical geneticists really had very limited clinical practices in a sense and perhaps they would make the diagnosis and prognostications, but then perhaps hand over to the specialist in that general area. I think that has always been one of the problems with clinical genetics in a sense, but as its abutting more and more across into general medicine, there is still, I think there's an enormous place for specialists in clinical genetics, but I often wonder how satisfying that life is for the ones who are very much more patient orientated.

PSH. That's true, and I suppose most of us in who have been a bit in that position have held onto one or other area of our expertise where we have been practising clinicians, even though we obviously can't do it in everything.

DW. Yes.

PSH. Which I suppose in some ways is what you did in the blood diseases.

DW. Absolutely. That's right yes.

PSH. Coming back to your move from Liverpool to Oxford, I mean how did that come about?

DW. It really came about because of two reasons I think; firstly, although they wanted me to stay on in Baltimore, I got married and I didn't feel particularly that I wanted to become an American citizen or bring up my potential children in that way and I really wanted to get back. I suppose that was the primary

reason actually, and then this post came up in Liverpool and I just had to make up my mind and decided to come back. I never make up my mind on a very logical, you know to lots of logical conclusions, just do what I feel like on the day, but I didn't want to be an American, and I felt that if you were going to stay there you really had to go the whole hog.

PSH. And how long was it then before you moved to Oxford?

DW. I moved to Oxford, so I was back in Liverpool from '65 to . . . nearly 10 years, I moved to Oxford, I was appointed in '73 to the Nuffield Chair of Clinical Medicine and then moved down to Oxford in '74. That was a difficult move because I had tended to become more a haematologist in Liverpool, done less general medicine and I didn't really feel that one could be a Professor of Medicine and not be a part of the general medical scene, so I had to do a bit of quick re-education and that meant cutting down on haematology: I did very little specialist haematology work in Oxford except in the red cell stuff, and so managed to kind of keep my general medicine presence right through the whole period as a Nuffield professor, and limit the haematology very much, otherwise I would have done no research at all.

PSH. Am I right John Clegg came down with you?

DW. Yes, John, we had a very excellent working partnership right through and he, having been trained in Cambridge I think he always had quite a yen to come back to one of the old Universities, so he came down with me and at least two of my students, by then had got their PhDs, Bill Wood in particular came down and one or two others.

PSH. I know very little about the Oxford structure, but I get the feeling that the Nuffield chair of medicine has always been the more investigative chair. Is that right or am I not?

DW. Not really. There had only been two Nuffield professors before me. The first one was Leslie Witts and the second was Paul Beeson, the American from Yale, who came to the UK towards the end of his career and I think although there had been a tradition of quite strong clinical research, both of them had been primarily clinicians who had made their names and reputations as all round clinicians and teachers, both of whom had encouraged people in the department to do research, without possibly doing a lot themselves.

PSH. When did you get the idea of setting up the Institute of Molecular Medicine.

DW. Well what happened was, I got to Liverpool in '65 and the work had gone pretty well actually in that last period and just after moving so in '79 the Medical Research Council suggested that we might have a small unit in what was rather hopefully called molecular haematology, and we started that in 1980. In the early 80s it was really starting to be clear that this area, molecular biology, was going to have some serious impact and so people from around the medical school started to spend more time with people in the unit and, by then I had brought in one or two other groups into the department of medicine who were starting to think about using this technology. It then became a

matter of space and the broader issue, if you were going to introduce molecular biology into clinical research, how on earth would you do it? How would you train your people? Could you persuade non-medical PhDs to come and work in departments with problems for their careers and so on. And also the plant was so expensive. So at that time, I think about the mid 80s, the building called the Nuffield Institute for Medical Research, which had been the fetal physiology department under Geoffrey Dawes, who had just retired, became vacant. The University wanted to close it, and so that's when I really had the idea, well couldn't we produce an institute where people from different departments using the same technology would come together and where it might be possible to produce a kind of critical mass of both MDs and PhDs in the American sense, and so that's when it started really. I proposed this to the MRC and they liked it but didn't have enough money, so we went out and found some partners and we used that old building but we built a kind of equal-sized extension to it and so on and opened it in '89.

PSH. So when did the present building open there?

DW. Well the present building opened in 1989.

PSH. So it was sort of on the foundations of the previous old building.

DW. There was the old Nuffield Institute, but then an extension was built completely afresh and new and they were joined by link corridors, and that opened in '89. By about the mid 90s it was getting crowded, and there were already over 400 people working in there, and there were one or two outstanding groups which, you can't keep everybody obviously, but it seemed to me that they must have the opportunity to stay and so coming up to retirement I was involved in the GIF exercise and some other fundraising, and so it was possible to extend the building and improve it.

PSH. Of the different groups who've worked here, apart from your own group, which were the founder groups that formed part of the institute?

DW. Yes, well I think that was quite important, the reason I think we got the support was we did have strong founder groups. We had Kay Davies, who'd joined me in the department of Medicine and she was desperately short of space, so she was a fairly obvious founder group and then we had Andrew McMichael and a variety of people with him, who were very very strong in immunology and to some degree in imuno-genetics, and then we had made two appointments based on the possibility of the building. First was in neuroscience and John Newsom-Davies came as one of the founder groups and he was one of the few neurologists I think who had been really doing absolutely top class science, again with an immunological bias. Then I was always very keen to develop a parasitology group. I had started to make sure the School had a big tropical link programme with the developing world in the late 70s, so we must have parasitology and infectious diseases in the Institute and so again, one of the founder groups was in malarial genetics and molecular parasitology with Chris Newbold, and then the other appointment we made at the opening was Richard Moxon in infectious diseases. He had been trained in molecular microbiology in Baltimore and had been head of paediatric infectious diseases there, so that was the kind of foundation. Oh

and then, right at the end just when we were starting to build, the ICRF came along and said they would like to be in, so that extended the building and so we had Adrian Harris and Walter Bodmer and several other very good people. So that was the core. I didn't want to have a kind of building that was directed at one area. You don't want to compete with places like the LMB. The idea was that people who were working in applying these technologies in different fields of medicine would find a kind of common environment where in the longer term it would be possible to share equipment and all this kind of thing, and make sure there was a big tea room and try to make sure there was lots of interaction between the groups.

PSH. We were talking earlier about genetics and, as it's becoming applied to common diseases, also about some of the kind of hype and maybe not so much over-optimism but as excess expectations. You've been involved in the genetics of common diseases from the very beginning. How have you seen this? How do you feel it's developing.

DW. Well, I've been involved in a very common monogenic disease which perhaps shows my kind of deficiencies. I have tended to stick with that, even coming up to the end of my career. Having worked in Sri Lanka for the last eight years, I followed the same group of patients with one form of thalassaemia. I'm still not sure I can even define what a mild or severe phenotype is. Now that may be an exaggeration, but I think the phenotypic definition of even monogenic disease can be very very complicated and when one looks below the surface, I mean I don't know about other monogenic diseases, but we have totally ignored the environment which is, when you think of the millions of pounds being spent on snip analyses for genetic markers in sickle cell disease at the moment, nobody has ever done a twin study and I discovered to my horror that nobody had in cystic fibrosis and then I was shouted down at Hopkins last year, when somebody got up and said "we are starting one".

PSH. That's quite late in the day.

DW. Yes. So when I think of the gruesome complexities of monogenic disease and then transport that to common diseases, I have a problem. It seems to me that the epidemiologists and public health people, the W.H.O. has now got sensible targets for trying to reduce risk factors; nobody knows how successful that will be but it probably is worth tackling the genetics of multigenic disease, particularly where you haven't the faintest idea what the molecular pathology may be, just for hints. For example you could argue that doing that for Alzheimer's has produced, just from the rare familial Alzheimer's, perhaps the best indication of where the molecular pathology of Alzheimer's might be, you know it may be way down stream from the common form, but those three different genes that have turned up in the familial forms. I think that has been enormously valuable and I find that approach of relating rare monogenic forms of much commoner diseases a potentially very valuable approach. The genome hunt. Well I'm persuaded, particularly for the diseases where we haven't a clue still, that it really is worth a go and that that may give us some clues in the long term about the molecular pathology of diseases. That also could perhaps direct the pharmaceutical industry in the right direction. But given the enormous complexity of genotype and

phenotype I think it will be a slow cutting away at those diseases but as I say there may be some useful fall out. But the kind of broader picture of personalised medicine I would have thought very unlikely. Well very unlikely in the foreseeable future.

PSH. One of the things that's always intrigued me is that you've combined really major basic research work with applications in the developing world. I suppose malaria is maybe the best example. Can I ask, what has been the main thing that has driven you to keep that side of the work going alongside the basic science, which could so easily have monopolised all your time.

DW. Well, when I had the opportunity when I came to Oxford, I think because of my military service, then just after I got back to Liverpool, the WHO asked me to go on a very long trip for them all over the Far East and to report back on the inherited anaemias and facilities and so on. And you see a lot more than thalassaemia when you visit these places, and as I say by the late '70s I was convinced that we should be doing more for the developing countries and we got the opportunity through the Wellcome Trust to set up units in Bangkok, and then later in East Africa and in Vietnam, and we had some good youngsters and we pushed our students and medical students into interest in that area, and that was fantastic and I thought these units would last six months. You know we had the 30th anniversary of the Bangkok unit recently. The work out in those units of course was very much more clinically based research, and was very successful and still is, but being in the haemoglobin field it was obvious to kind of follow-on into the developing countries, because you knew that once you could measure globin chain synthesis in the test tube then it was possible to do prenatal diagnosis and that was taken up very successfully in Sardinia and Cyprus. Then once DNA technology became available, first trimester prenatal diagnosis, surely this was an area which should be taken into the developing countries. And it was!

There have been a huge problems, I mean by-and-large governments aren't interested in genetic disease. In Sri Lanka when I first went, OK we've got a few thousand kids. If we treat them it's going to take 5 percent of our national health budget. Why not let them die. We've got bigger problems. And it's been a long haul, but it was the obvious place to take simple DNA technology and by developing north/south relationships it has really taken off in many developing countries and many of them have prenatal diagnosis programmes and so on. So it was obvious and then, more recently of course, the whole question of DNA diagnostics for the developing world has become a major issue. There are certain diseases like dengue, and leptospirosis particularly and one or two others where you really do need early warnings. I mean SARS was the perfect example. To have got that organism and all its sub-types within a few weeks completely sequenced. So those were the two major areas I think, in the genetic anaemias, in the DNA diagnostics, though not necessarily in that order of importance. It was just a fairly obvious extension of what we have been doing here already.

PSH. I seem to remember at one point you said something along the lines that, almost all the abnormalities or what we have learned in the molecular basis of human disease had been based on the haemoglobin disorders, or at

least could be, and there wasn't going to be much to learn once one went outside those. Do you think that is still a reasonable view or . . . ?

DW. It sounds like a very pompous view. I'm sure I did say that at one time. It reminds me of Henry Cohen's famous remark, who hated specialisation, "a specialist is somebody who knows everything about a field except its relative importance". No I think that very exciting time in the late 70s early 80s, when these mutations were pouring out by the week, and you got this kind of whole spectrum, from regulatory mutations to what you'd expected from microbial genetics and so on, that it was going to be a reasonable kind of preview of what would turn up in other diseases. Perhaps I overstated it, but of course if you look at the totality of molecular pathology, OK, it didn't certainly disclose the kind of single gene neurological diseases with those boring extensive bits of DNA, and obviously there have been lots of other exciting molecular mechanisms but I suppose what it did at the beginning, it showed the extraordinary diversity at the molecular level. I didn't do a countdown over time but within about four years or so, there had been about 60 different mutations found in the thalassaemias – there are now over 300!.

PSH. Do you think that Lehmann lived long enough to recant on his advice to you? You must have spoken about it later with him.

DW. I did actually. I went on a wonderful trip with him to China, not too long before he died, just the two of us. We went off for the Chinese Academy of Sciences and they sat me on a train with him from Hong Kong up to Canton, and I reminded him of that and he flatly denied he'd ever said it! But he definitely did say it.

PSH. I have been asking everybody I've seen, David, two things, and one of them is, is there one person you can pick out in terms of influence on your medical and scientific career that had a particular effect, or is it a more broad range of people?

DW. No I think it's a more broad range of people. I often wonder if I hadn't been Cyril Clarke's houseman, whether I would have been so at least aware of why studying that child in hospital in Singapore would have been so interesting. I honestly don't know. You can't help feeling that the atmosphere at the Northern hospital did actually make you feel that there was something interesting here in genetics without a doubt. So yes Cyril, and the second person was undoubtedly Howard Dintzis, who you may not have heard of actually. He ran the biophysics department at Hopkins. He was one of the cleverest men I have ever met and perhaps appointed too early to a heavy administrative job, but there was an atmosphere in that lab. It was a place where I think I saw more imagination but also more stringency. I think it's been, by and large there's an awful lot of sloppiness in clinical science, and there was a level of stringency that one saw there that completely changed your level of thinking. Other than that and I think the other person that I certainly admired enormously, whom I crossed paths with quite a lot over the early years, was Vernon Ingram, who of course is still around doing experiments, at MIT [He died in 1999]. That's a bit unfair actually because I think so many people influence you, but those three just come to mind immediately.

PSH. The other thing I've been asking everybody is whether you can single out any one particular piece or phase of work which you especially identify with or feel proud of in some way, over or and above the broad range of things.

DW. Well I think it was the phase, say between the mid 60s and the mid 70s, because we were able to develop the technology for measuring globin synthesis, and so many people could take that on, and then probably, say within about 5 years it had already been applied to fetal blood sampling and so, from a kind of simple laboratory test to being something that was used out in the field, really in less than 10 years, and also that technology enabled one to go the next step into the RNA level, and then the finding of one of the first molecular defects before one even got to the DNA or the DNA level with the chain termination mutants in the early 70s, and then actually instigating this experiment with John Paul's group up in Glasgow to demonstrate a direct deletion for the first time in a gene. I think that period, there was a lot concentrated into that 10 years, which was great fun.

PSH. David thanks very much. Before I finish is there anything you feel that I have not touched on. There must be many things but is there anything you specially want to say that I have not covered at all today. I've not tried to be comprehensive.

DW. No I don't think so. It's just, I find this kind of thing very difficult. You can have a lot of regrets post retirement that you didn't do things differently. I think it's very difficult to mix a life of clinical world and the basic science world and several specialties and all that. Maybe I was just lucky, being able to do something reasonably useful during that period when the field was just developing. I think it would be very difficult now for somebody to do it yet again, nothing to do with ability, just because the breadth of technical complexities have changed so much.

PSH. David thanks very much. I will stop the recording there.

End of recording.