Bernadette Modell

Personal Details

Name	Bernadette Modell
Dates	Born 01/08/1935
Place of Birth	London
Main work places	London
Principal field of work	Haemoglobin disorders Community genetics
Short biography	See below

Interview

Recorded interview made	Yes
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Personal Scientific Records

Significant Record sets exists
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Summary of archive

Biography

Bernadette Modell graduated in 1952 as a biologist and did her PhD in Cambridge when molecular biology was in its earliest exciting stages. She then studied medicine, and after graduating focused on management and prevention of haemoglobin disorders, as a model of genetics in the community. As a Wellcome Principal Research Fellow she developed the basic scientific concepts of Community Genetics (a fusion of public health and primary health care aspects of medical genetics) in collaboration with WHO. She is retired in theory, but hardly in practice.

INTERVIEW WITH PROFESSOR BERNADETTE MODELL, 14th DECEMBER, 2007

PSH. It's Friday December 14, 2007 and I'm talking with Professor Bernadette Modell at the Galton Laboratory in London. Bernadette, just to start with, when and where were you born?

BM. I was born in London on 1 August 1935.

PSH. And can I ask, do you come from in any way, a medical family?

BM. Not at all. My family were Irish immigrants over the previous two generations, with very working class backgrounds in St Helens and Oldham in the north.

PSH. So were you the first in the family to go to university?

BM. No I wasn't actually. My mother often spoke of her family, and they came over before she was born from Ireland because of poverty, rural poverty and her father worked in St Helens in Pilkington's Glass factory, but they were not literate because in those days the Irish were not allowed to learn to read and write, but her mother taught herself to read and she used to read stories to the family. My mother remembers the family gathered around the fire in the evening and her mother reading Uncle Tom's Cabin and her father sobbing away, and in fact we saw something which he had signed with an 'X', but as you can see the mother was absolutely dedicated to education as the way out of being the bottom of the pile.

PSH. That was your grandmother?

BM. That was my grandmother and all her children became teachers, practically all, the ones that survived the 1914 war and the various other things that happened, but my mother was the only one to go to university. After the 1914 war there started to be scholarships for university and she was the first girl to get a scholarship to Liverpool University. She was very proud of that. She studied English and she became an English teacher, an extremely talented teacher.

PSH. When you say the first girl, do you mean the first girl there had ever been?

BM. To have had a scholarship.

PSH. To have had a scholarship, to Liverpool.

BM. Yes I think so.

PSH. That's really quite a . . .

BM. Quite something isn't it?

PSH. It really is.
BM. Now they were of course Catholic and the nuns at her convent were very worried, and they said that she would lose her religion. They were praying against her that she wouldn't get the scholarship in case she lost her religion.

PSH. Luckily, from Galton on, the studies on the efficacy of prayer have not shown it to have a huge effect!

BM. Well, it wasn't very effective in this case. No, she was quite a remarkable woman, my mother, but again, you know what happened to women in that generation with the recession. Each family could have only one job and my father, who was paid less than her, of course had to be the person who kept the job and she had to give hers up. So she was back into poverty again, with four children, until the Second World War.

PSH. And then in the Second World War I suppose, women were desperately needed to fill all jobs.

BM. They were, but she still had four children at the time, but after the war, yes there was a tremendous surge, soldiers coming back from the war, the government was committed to providing them with education and opportunities, and she started teaching in a night school in London and then progressively came back. She ended up teaching English in the school where I was, the convent school I went to. She was a very, very good teacher. So what we are talking about now is the change in the position of women in society, and for people of this kind of class, which is the majority, it's not something that happens over one generation. In our family it has taken three, I would say four really. I think that my daughter is really emancipated. I don't think I was.

PSH. What got you interested in science or medicine in the first place? Can you pinpoint anything that took you in that direction?

BM. Yes, I can pinpoint the exact moment when it happened actually. I have asked other people about this and it doesn't seem to be very common, particularly with men because they tended to be in an education system that was promoting science. But when I was in the fifth form, so I suppose I was 14, I was sent with a message to the science teacher, who was a nun, in her class, about something, and she was teaching four sixth form girls who were looking down a microscope, and she saw me looking because she knew me very well and I was always curious. Insatiable curiosity was my characteristic, and she saw me looking so she said "Do you want to look down" and I said "Oh yes". So I looked down and there was a cross section of amphioxus, can you believe it, and I realised there was another world down the end of a microscope and I wanted to do science from that moment onwards. There just wasn't going to be an alternative really. So it was the nun, it was the teacher, and you know there are always crucial moments in people's lives when a teacher makes the most fantastic difference. I recently went back, and she is now retired but she is still alive, this very good nun. I went to see her because I felt people perhaps don't give the feedback to teachers they

might need, and I told her how important I thought she was, not just for me but for all the children she taught.

PSH. So did you go on to your highers or A levels, or whatever they were then, in science?

BM. The whole education system was going through one of its upheavals. There's no need to go into great detail about it, but my class ended up taking their 'O' levels early so that the clever ones wouldn't be caught and have to wait a year later. So everything was a bit untidy because we went into the sixth form early. But my mother was inclined to go off and get me books from the library and she cheated me really, because she said "well you know at Oxford and Cambridge, they really ought to encourage the school to try to send children to Oxford and Cambridge and you know they've got their own entrance exam, they don't take too much notice about 'A' levels. So she sort of primed me to apply to Oxford at the same time as doing 'A' levels and things and I just got a scholarship. It wasn't a problem really.

PSH. What subjects had you been doing?

BM. There was a problem and there still is a problem, that if you are really interested in biology you've got a problem with, you can't do botany and zoology, physics, chemistry and maths. You've got to choose and botany and zoology were absolutely top for me. I did lots of chemistry, a little bit of physics and alas no maths and I've missed it ever since. Tried to reconstruct it.

PSH. And you went to Oxford then,

BM. And did zoology.

PSH. Which college?

BM. Lady Margaret Hall.

PSH. Oh, you went to Lady Margaret Hall.

BM. And again we were some of the first scholarship girls. We were waiting outside, I think with some apprehension.

PSH. What year was that you went?

BM. 1952.

PSH. You must have been a close contemporary of my sister. She did English literature and she must have gone there about '53 or '54.

BM. She'd have been a couple of years behind me. I was the only zoology student there and all my friends were historians or doing PPE. None of them were doctors, because one never saw the medics. I found out why later. It was because they'd got such a committed course. You know every hour of the day was pretty structured in the medical course. The rest of us, I mean I

found my exam papers from Oxford. I've still got it. First of all, we didn't have any exams until the end of the third year. And then when we had the exams, the papers, there would be thirteen questions and we only had to answer three. So the thing was structured so that you could pursue your own line of interest through your three years. It was very good.

PSH. How did you find the Oxford zoology department?

BM. Oh well I enjoyed it enormously. Some of the people were a bit funny; particularly there was E B Ford, who was completely peculiar, the most bizarre character, especially he didn't like women. If he saw any of the girl students coming down the corridor, there was a rather narrow corridor and when you were coming down, if he appeared at the other end intending to come and he saw you coming he would make a spitting noise and disappear until you went past. He taught us quite well though. I learnt statistics from him and I'm very pleased I did.

PSH. It was a wonderful department, because I was there just a few more years later and the whole approach to evolutionary biology and population biology I found inspiring.

BM. Well Hardy was good. We had Tinbergen, we had Fischberg who was good on embryology. Did we have David Lack? No he was somewhere else.

PSH. And Charles Elton and David Lack, I think they were down at the Institute of Ornithology.

BM. That's right. That's where they were and oh yes, we had a wonderful time there. Part of the reason was that we got friendly with the entomology, me and another girl got friendly with the entomology postgraduate students who lived at the top of the museum. There was a tower and the entomology department was there. Did you ever visit it?

PSH. Yes.

BM. And they were working on locusts, this lot, and they had a whole lot of locusts in the room and, when you went in you could hear all this munching, and one of them was from Sri Lanka and we used to go in there at the weekends and have curry parties, in this building which had all the moths and different insects, all stored in these beautiful wooden boxes, in a wooden building with loads of camphor and we were lighting our Bunsen burners and currying kippers. Can you believe it? So we had a good time.

PSH. After you had done your zoology degree, did you go on and do a PhD, or did you decide then to go into medicine?

BM. No, no, I had decided to go to the States for a year because I had got very interested. By that time I had a wonderful tutor, who later on built up the school, or department, of human biology but at that time, being that women were still in somewhat inferior positions at Oxford, her name was Wilma Crowther, and I realised, one day I got excited to an enormous degree because I liked embryology and then suddenly I realised that it was genes that

did it, and that the whole of embryology must be determined by genetics. So I got very excited about genetic embryology and started reading all the literature, of which there was a surprisingly good amount there. There was, what was the name of that. Anyway we won't go into it. I became very excited in my second year. My tutor said no, leave it until your third year and then you can really study that. So I became very interested in the role of the nucleus and the nucleus/cytoplasmic relations, and I saw an advertisement for a scholarship in the States at an Institute in Philadelphia where, the Cancer Research Institute, where two researchers called Briggs and King were researching in enucleating frogs eggs and so on. I got the scholarship and went and spent a year there learning about enucleating frogs' eggs and the development of haploid embryos. We were trying to study that. They always got stuck. It was interesting to know. I used to section them and try and find out why they got stuck during their development because they were haploid. So yes, that was a good and illuminating year. I was very young.

PSH. And you came back then from America?

BM. I had fixed up to come back to Cambridge to the Strangeways Research Laboratory run by Honor Fell, and she wanted me to do some work on disaggregating tissues and seeing the way the cells behave to find their way back to each other, but actually with the equipment available it wasn't going to work very well, and in order to do this you had to take the epidermis off with trypsin. And I thought, well here's the epidermis. Here's a pure tissue. Let's try putting it back on different types of connective tissue. So I started something that's been pretty typical really which is, that I was supposed to do one thing and I did something else, but it ended up producing very interesting results, namely that different types of connective tissue determined the way the epidermis then went on to develop. So that was nice. But during that time at Strangeways there were some wonderful people in Cambridge, well, I am a beneficiary of Hitler's anti-Semitism, because Cambridge of course was full of German Jewish scientists and particularly the Strangeways. There was one there, Jacobson was his name, who worked on B12. No, he didn't work on B12, he worked on folic acid, and I recently was rapporteur for a meeting, on public health aspects of folic acid and I would really have liked to have dedicated it to him, to his memory. He died recently. He was a wonderful scientist and also a clinician, and working there with him, I understood what medicine was about for the first time, and that was what made me decide that I really had to go on to do medicine, because I felt that all of this knowledge that we were getting, really there should be a way to use it in human health and of course at the time there wasn't any medical genetics anyway. It didn't exist. So we were taught that there were these . . . So that led me on to do medicine. It wasn't that easy to get myself set up to do it, but it happened.

PSH. Had you published any work by this stage?

BM. Yes I had a couple of solid peer-reviewed publications, and then the work attracted quite a lot of interest. I had already got, oh I don't know, I think by the time I got into medicine I already had about 8 or 10 publications.

PSH. What name would you have published under then?

BM. McLoughlin. Maybe even C B McLoughlin, yes.

PSH. Because looking up lists of publications, this causes confusion with people changing their names.

BM. Changing their names, yes. I heard later somebody say, well what happened to McLoughlin. She seems to have disappeared. And I did indeed. I mean doing medicine is so strenuous, it was a complete separation from what I had done before, except I must say, that everything you do later of course is built on what you did earlier, and thinking of the various things, going right back to Oxford, my tutor, because of this very liberal way in which the education there was structured, I bet it's nothing like as liberal now, but for people in research it was absolutely perfect. She said, well, in the middle of the second year, you just have to take a term and do something different, some other interest, and I said I wanted to do anthropology. I spent a whole term, I was just thinking about it this morning actually. She found the right person for me so I had tutorials once a week, didn't have to write any essays, didn't go to any lectures, gave me a structured reading list which I read sitting in a punt on the river. But it was vitally important, later on, the concepts that I picked up then in the subsequent practice of medicine. So that was one. The other one was that at the Strangeways Research Laboratory the research I did was on chick embryos, which were at exactly the stage of development of the 8 - 10 week human fetus, so that when we came round in the end to first trimester diagnosis I already knew, I had a clear intellectual picture of what we were dealing with and I think that also quite possibly was rather crucial.

PSH. What year was it you started doing medicine?

BM. I did my PhD at the Strangeways. 52 to 55 was Oxford. 55 to 56 was the States. 56 to 59 was the PhD in Cambridge and then at the end of '59 I started doing medicine.

PSH. Where did you do it?

BM. At Cambridge.

PSH. Did you manage to get exemption then from most of your . . .

BM. For, now what was it, physics. I was supposed to have physics which I didn't have, and I got exemption, but it had to be a special thing in the Senate. One of the meetings at the Senate, it had to be read out and approved. Yes I did. And I was only able to do it, because I didn't have any money, you know, my family was not terribly well endowed. The Mistress of my College, Girton, I went to see her to say I really wanted to do this and one had to construct a great big campaign and it was very interesting because a lot of people were willing to help you, but on condition. You know there was always a condition and what they were doing was waiting for somebody to commit themselves and the mistress at my college said 'right, I'm going to commit myself. We are going to give you this grant so that you can do your medicine' and once the mistress of Girton has agreed, after that everybody else agreed and I was able to do medicine.

PSH. So were you able to do your clinical studies at Cambridge, or did you then have to come on to London?

BM. No, I had to come to London and what's more, one of the conditions was that I had to get a scholarship, because Girton grant supported me through the first two years and then the Ministry of Education had agreed, I had never had a straight scholarship because I had a college scholarship, that they would give me a state scholarship if I actually, they would supplement any scholarship from the medical school, so I only had a choice of two really that gave scholarships of the kind. One was UCH and the other one I think was the Westminster, and I was interviewed at both. That was how it happened, yes.

PSH. So you had your three clinical years at UCH?

BM. Yes.

PSH. You must have qualified then about 1964.

BM I did, yes. I've been at UCH ever since, basically, more or less ever since, yes.

PSH. So presumably, once you qualified you got submerged in pre-registration and jobs and things like that. How did things go in the next few years?

BM. Listen to you. You are quite a good interrogator aren't you! Let's see, yes, well, in those days. It would surprise people now. Things were different in those days. You know you apply for house jobs. I didn't apply for the paediatric house job. I got the paediatric house job. They issued me with it, which absolutely terrified me, because you've got to deal with these little things, get needles into them and all that. But we had a wonderful Professor, Leonard Strang. I had always liked him, because he taught physiology at the bedside. He was a great scientist and a great teacher. And so that continued the steep learning curve really and it was wonderful. I very much liked that job, but that was the time when my earlier interest in genetics, the reason why I had gone into medicine of course, came around full circle because I hadn't intellectually grasped the fact that if you want to see where genetics is, it is going to be in paediatrics. But it was just the time when the possibilities for diagnosing a genetic disorder, biochemical diagnosis, was expanding and we were starting to get children with glycogen storage disease and interesting metabolic disorders. And there was also a lot of optimism because of the progress that was made with treating PKU. So it was a very positive time and I think that people were very keen really for me to go ahead and get interested in this area.

But what happened was, that we started getting children with thalassaemia because, as I later found out, calculated it, you know, I've got the data showing it, that was the period when there was such large scale migration from Cyprus to exactly this part of London, around UCH and the Whittington and the various other local hospitals, and these children started turning up

and nobody had a clue how to treat them and this attracted me at once for various reasons. One was that this was a disorder of haemoglobin, about which we knew so much already. It was the way in. Haemoglobin was really the way in to molecular biology. Then it was a disorder of the control of haemoglobin synthesis. It wasn't structural so that was intellectually very interesting. Then it was a disorder which presented exclusively in people from ethnic minorities, and I had always been interested in culture and really would have been very keen to travel. If I hadn't married and settled down I would have wanted to work for an international organisation for this reason really. But I thought well this brings the questions of culture to me. And then the final thing was, partly because of the approach of our Professor Strang, he had a very mathematical approach, we really met on that level. I realised from that and from looking at the literature that actually this disease should be treatable, and it was the case. We could transfuse, we just didn't know how to do it. We were using transfusion terribly. Just keeping children teetering on the edge of the grave like that. And that was the time when the first iron chelating drugs came out. But it was a serendipitous feeling really . And then the final thing, as I said to my husband, I said I really want to work on this. He's a GP and he said yes, and it's common. Then there was another feeling which I had then because I was always fundamentally a researcher, and I still have very much, which is that we had here a disease which was common and caused major problems in the tropics and sub tropics, where they didn't have the resources either to treat it or to develop new approaches for prevention or anything, and now we had a sample brought into our country, which gave us the opportunity and the privilege to use our scientific resources to develop treatment and prevention, but it had to be of a kind which could be disseminated. It had to be simple enough. So those were all the reasons that hooked me on to thalassaemia and as I say, I have been like a limpet with it ever since. Not a limpet, these nasty things that . . .

PSH. Barnacle?

BM. No no no, what the Romans threw their slaves to.

PSH. Leech?

BM. No no worse than a leech, the things that - lampreys. Been like a lamprey. But on the other hand and from the beginning though, I have always seen it as an example of inherited disease. Not so much as an end in itself.

PSH. Before we get into that in a bit more detail, Bernadette, can I just ask you a bit about links at UCH and UCL, because it was very much the centre of all things genetic at that time.

BM. Oh yes. Charles Dent.

PSH. I was going to ask about Charles Dent. How much contact did you have with people like him and people at the Galton and others at that time?

BM. With Harry Harris, quite a lot. I thought he was wonderful. I absolutely sucked up his books. He lived opposite us actually, so I always had a very good sympathetic relationship with Harry Harris and was fascinated by the

work at the Galton. But it was a problem really that I had gone for thalassaemia and it is a systematic problem in genetics, that the people's engagement is sort of structured really by practicalities, and thalassaemia and sickle cell have always been haematological disorders and all the way through the system within the hospital, within the Department of Health and everywhere, they have always been seen in a different category from genetic disorders. So I feel that I never really became part of the world of medical genetics, because the issue I was dealing with wasn't really recognised, practically not recognised as genetics by the official genetic world. In retrospect, if I had been more assertive, I could have done something about that but I wasn't assertive enough to do it, so that gap remained unbridged and I think it's largely still unbridged in this country. In other countries, I have done a lot of work with the World Health Organisation, and there's an advantage to be starting a service from the beginning, and so Middle Eastern countries all see haemoglobinopathies as just one example of genetic disease, and often a good example to start with.

PSH. Do you think that's partly also the result of haematologists feeling quite proprietorial about blood diseases? I have noticed it perhaps even more with haemophilia, where there was a strong feeling that the haematologists should be able to do everything to do with haemophilia, including the genetics and I wondered whether that might have been part of the reason, as well as geneticists not feeling it was an area for them not to get involved with.

BM. I wouldn't say it was quite like that, but I would say the world of science is one thing, but when you have scientific developments which you wish to transfer into practice, you are enter a completely different world, which is the practical world of territoriality and people's job security and all these other issues. And it's not only that, it's even the way that health systems are structured, so that there are already haematologists and everybody expects them to deal with it and there are chest physicians and people expect them, after the paediatricians, people expect them to deal with CF for instance. And then the clinical geneticists, on the whole, have not been interested in common disorders, because those should be somebody else's responsibility because their special skill is diagnosing and helping people with how to handle rare conditions. So yes, I think we suffer to an extent, because we are such a rich and developed society we suffer from excessive sub-division of labour. I think where this actually is most important, within genetics it has generated a fragmentation and naturally the clinician's interest in genetics has started with the patient so that you have people who work on children with metabolic disorders, haemophilia, because you have got to bring your own particular skills as a clotter, as a red-cell person, and so in practical terms, genetics tends to be divided up into hundreds and hundreds of different areas, because you have genetics in practically everything. So there is a failure to grasp that if you start off at the genome and you deal with everything to do with the transmission of genetic variation, everything is more or less identical until you get to the clinical manifestations in homozygotes or patients, and there's still a failure to grasp this enormous commonality. Which is a pity, but we will get there.

PSH. Can I just ask, before we get on again to research, had you got married and had a family by this point, and how did that sort of fit in with your career side?

BM. Yes, people sometimes say to me I should write my biography and one of these days I will.

PSH. You should.

BM. If I don't become demented, because it took me quite a while to realise in retrospect there weren't many women in medical research. So, let's see, I came back from Bolton and then I got married that next year. I did a wonderful house job in Bolton District General Hospital, surgery, where I was the only white and the only woman and I ended up cooking curry for the entire mess in the diet kitchen at weekends. So I came back from Bolton and got married the subsequent year, and started a family right away because time was passing. I was 30 by the time I married and I was determined that I was not going to work full-time, because there was a contradiction between that and having a family, and nobody had ever heard of such a thing before. I was on a Beit Memorial Research Fellowship and I asked them if I could work part time. And they said 'No we don't have any allowance for that. That would create a precedent' and they had to be very cautious, but we wouldn't mind if you re-arranged your hours, which was extremely flexible of them. I have always had this problem that you were saying, if people were paying you to do something you feel you have to account to them, and I felt I could not actually work on something saying I was full-time, and then not working what I considered full-time, which was very full time. And so I sought funding from a body that was prepared to support you part-time and for ten years the Sir Halley Stewart Trust supported me for part-time work while I brought up my family. It was just as well, because my second child became very seriously ill when he was five months old and what he had was a congenital malformation of the lower end of his ureter, and he nearly lost a kidney and in fact he could have - if we hadn't had the knowledge we have now, if it had been before the war, for instance, he would certainly have died. But he had a brilliant operation at Great Ormond Street with a re-implantation of the ureter and he has been perfect ever since, but I really dropped my sessions down to two for about a year, while I looked after him through that rather difficult period. That gave me, it reminded me of my patients I already had. The paediatricians when I started to do my research, the paediatricians were terrific and they said, well you can have all the thalassaemic patients, you can create a clinic. My clinical work then became running the thalassaemia clinic, which increased by leaps and bounds because the Cypriots were having more and more children. And I remember my families, of course families obviously develop a very close relationship with you in this kind of situation. And I remember them saying 'oh you are pregnant' when they saw me coming. 'Ah now you are going to understand' they said, hopefully, and of course you do. It does help quite a bit.

PSH. What was the first area of actual research you took on?

BM. Treatment of the patients. When I was a house physician, the convention then, we had two patients only. The convention was that you

didn't want to transfuse them too much, because then their bone marrow would stop trying to make blood and they would get iron overloaded and that would kill them. The result was, later on, I listed it, I wrote a book called The Clinical Approach to Thalassaemia, in which I quoted what the parents said to me subsequently, but I could see that the kids came in, the parents were supposed to bring the children in when they weren't well. They brought them with a haemoglobin of four. They were absolutely at death's door and hell to transfuse because all their veins had collapsed. You would sit there you know, when you got to sticking the needle in the tenth time before you could get the drip up. It really was not a good experience. That had stimulated me to go and look up what was available information and I had found one paper describing high transfusion, what they called, but it really means normal transfusion for thalassaemic patients, and I thought I would like to do that. We should try that when I came back from my surgical house job. And by the time we came back from the surgical house job, one of our patients was dead and more were coming. So we tried transfusing this other child properly, meaning transfusing up to a haemoglobin of 9 and taking it up to 14 at sort of 5/6 weekly intervals, and he just became a normal child It was a complete conversion from a child who was absolutely at death's door to a normal child running around. And everybody said, we had a meeting where we reviewed what had happened to this child over a 6 month period and people said, 'You've cured him.' And people from the Whittington Hospital, who had more patients were at the same meeting, and I said we haven't cured him because now we've got the iron problem. But in medicine it is always best to have one problem. In the past with the low transfusion we had multiple problems of all kinds. Now you have a transfused patient and we've got one problem, which is iron overload. So then the next step was to try and look at the use of the iron chelating agents to get the iron out, which was pretty challenging because they had to be given parenterally. But before I could turn around I heard the Whittington Hospital had just gone home, and they decided to high transfuse all their patients, and that was great. Now one of the reasons that was great was that it transformed the Health Service's attitude to the patients because before, everybody knew that this was a hopeless situation and when they appeared everybody got depressed and nobody felt energetic or positive about doing something about the disorder. But you get a lovely dark eyed Mediterranean child prancing through the door and everybody thinks, oh we've got to do something for this child, so it just changed the whole feeling about the disease and the optimism and the attack. So that was great. Now that paper that I read was published by a chap called Wolman in the States, but you know we are so narrow in our literature. When I write my history of thalassaemia I shall give due credit to the French person, Orsini in Marseille who had done the same and published it, and to the Greeks who have been doing it for years but hadn't published it. I visited Cyprus to see what was going on, because once we felt we were getting things under control here, and we had 10% of all the Cypriots in the world in the UK, I wrote to Cyprus and I asked them what do you do about thalassaemia in Cyprus, because some my patients want to come for holidays and things, and they wrote back the most stupid letter saying of course everything is perfectly done with thalassaemia. I thought this is nonsense. I'm going to have to go and see for myself and I did. There was the British Army base at the time and a chap called Colin Bate there, who had also read something that I had written about thalassaemia saying, in some throw-away thing. I said the only mistake you

can make is not to be aggressive enough, and he at that time in his military hospital had two or three little children with thalassaemia at the last gasp. He read the article and thought, righty ho here we go, and transfused them. And the same thing happened and he built up of course, rapidly, a big clinic. And there was a meeting of the BMA in Cyprus once and they visited around and they came to visit the Military Hospital and they saw all these thalassaemia patients and some Cypriot doctors were there too, and Greek, and they said 'they haven't got thalassaemia.' They had.

So what I am trying to say is, that you are asking me about my contribution and I'm very aware of that, but throughout, and it has been a bit of a struggle, but throughout the whole history of trying to tackle this disease and learn broader lessons, there has been a string of quite exceptional people who have done quite exceptional things and I feel enormously privileged to have met. You know, the ones like Colin Bate I am telling you about, he just transformed the situation in Cyprus, not so much by publication as by actually demonstrating. You know there is nothing better than showing a child that nobody can tell has got thalassaemia. All the other parents would immediately want to have the same treatment and that message, because he treated Greek and Turkish Cypriot patients; after the Turkish invasion of Cyprus of course, for a while everything fell apart and particularly the Turkish Cypriots, practically lost their chances of treatment, except the bases continued to treat them. The Greek patients, the Greek Cypriot patients, having seen what was possible, very quickly got up on their hind legs and demanded that they should have a proper service, because once people know what's possible, they will go for it, especially parents.

PSH. When did it become clear to you that one needed to think in terms of prevention as well as treatment?

BM. At a very early stage, but before we come to that, there's the iron chelation therapy which was very difficult to show that you could do. There's quite a bit of literature on that now, but there was a problem because there because was a drug which in principle might get iron out but which had various problems. First of all we'd got to show it could, and we didn't know what level of iron was safe, and we didn't know if patients could tolerate having one or two intramuscular injections a day, and so forth. And there were two possible approaches and at Great Ormond Street they decided to do a randomised trial; ultimately it showed that you could keep liver iron down but they just felt it wasn't down enough and so because they were pessimistic they didn't really carry on with that. Whereas I thought "well, if we wait for the results of a randomised trial the patients will be either toxically overloaded or dead". I mean you could calculate that if they were going to survive until about 30, they would have about half a pound of elemental iron on board. It wasn't likely, so I just decided to treat all my patients and follow what happened, but at the same time I had for various reasons to get the epidemiology right and so forth. I had contacted all the hospitals in London and they had all given me permission to review their patients, they had all listed their patients, given me permission to view their notes, so I had a handle on all the patients everywhere in the country, and people were so co-operative that I was able to sort of create a database and relate outcome of treatment to all the patients in the country. And I treated all mine, but you see what happened was that the

doctors confronted with this problem fell into two quite distinct groups according to their temperament There were some like me who said, well the patients haven't got a chance unless we do this very punishing treatment, so let's get on with it and there were another half who said we had no right to inflict this nasty treatment on our patients unless there is good scientific evidence that it's going to work so let's wait; and the country just split about 50:50 really, and I followed up all the patients and at an early stage I was able to show that the ones who were on the chelation therapy were surviving and the ones who were not, were not. So we were able to define the natural history of unchelated thalassaemia and show how patients were peeling off. It was that, actually, was the finding that converted people, everybody in the country, to putting their patients on desferrioxamine and across the whole of Europe, Italy and Greece as well. So that was a very interesting observation, I think, because it wasn't the randomised trial that produced the result. It was the consistent follow-up of a whole national cohort of patients.

PSH. It must be very unusual to be in a situation where there is a single national cohort of patients.

BM. Yes, now there were a relatively small number of patients and so I felt it was feasible for one centre to do this. The other was that I was very interested in trying to get the best treatment for all the patients and not just for our group of patients and you know, I listen to people and I constructed a policy about this, because you know that people are afraid of having their patients taken away so actually I went, if somebody wrote to me about a patient, I went to visit and interviewed the patient together with the doctor on the spot and then wrote a report with recommendations. But what I gained from that was in a sense, the co-operation of the doctor in the long term follow-up of his patient and they were wonderful. I would ask to see the patients' notes and you know these patients' notes, they would send them to me through the post and I guaranteed to return them within 48 hours, so the system worked. Now that continued, I continued to run a UK thalassaemia register until 3 years ago, 2003. I thought it had proved its worth very well in terms both of research and of service, and that we had demonstrated that this was the kind of instrument you need to provide equitable care for rare disorders. We ran into two things, firstly there isn't any source of funding in the NHS to continue this after I retired as Wellcome Principal Research Fellow, so it sort of carried on on a shoestring from here and there for two years, and the other was the beloved Ethics Committees. I foolishly listened to people who said that, now you are going to have to go to an MREC, because I had ethics committee approval from UCH from long, long ago and of course the MREC in spite of our having written why it wasn't feasible, decided we had to have written signed consent for all the patients on the register which we had predicted would not be possible. Not because people didn't want to join but because the clinicians didn't have the time to sit down with a consent form, with a Pakistani woman and an interpreter and to explain to her why her written consent was needed for something which she thought was obviously for the benefit of her child anyway. She expected it to be part of the service. So the register collapsed having fortunately, having just demonstrated that the survival of thalassaemic patients now, with a oral chelator available, is coming up to approach the normal, which is just great. A lovely message.

PSH. Did you write, I should know, but did you write what one might call a summing up paper from the register, taking it from its beginning to its conclusion.

BM. No, I have never written an overview paper of the register. That might be a thought. I have been trying to publish this last data and the trouble is here we run into a medical controversy. The field was sort of split by a very unpleasant controversy about the oral chelator deferiprone which is being used here, and it's very difficult to get stuff published if you even mention the name of that drug. I think that's improving now because very hard evidence is coming out, but that certainly held up publication of this paper. We are trying again now but for the last time. The register ran to the end of 2003 and I submitted it first in 2004 and it's now 2007. It still hasn't been published

PSH. When did you start the register though?

BM. Now let's see, when did I start, '64, '65, '67.

PSH. So that's 35 years.

BM. It's 40 years now. Yes. Without any complaint.

PSH. That would be a very fascinating account of the history of that register over this long time.

BM. Yes but where would you publish it?

PSH. I think you could publish it most . . . well, it doesn't really matter, as long as it's published. As long as it's written and published.

BM. We have a lot of papers.

PSH. Before I come back to prevention, at some point your work shifted from the Cypriot community to involving the Pakistanis as well. What was the time scale of this evolution?

BM. Well it is actually related to prevention. Shall I go ahead with prevention then?

PSH. I was just thinking first though, when did the Pakistanis, what year did it start to become a significant problem for the Pakistanis?

BM. Well now, when I was at Bolton District General Hospital, there was another woman doctor there, that's right she came as a locum. Together we used to cook for the Indians. Now I therefore, at the weekends, we used to go around visiting all the other Pakistani and Indian doctors and we went to Leeds, Now that was the time there was a very large scale migration of Pakistanis to work in the textile industry, the car tyre industry and so on and there were a lot of them in Leeds. But what happened with the Pakistanis, unlike the Cypriots and the West Indians and most other groups, is that the men came first and it wasn't for an average of ten years that their wives

appeared. So everyone was aware that there were a lot of Pakistanis here, but there wasn't any Pakistani thalassaemia because no children were being born. And then ten years later, so that was in the seventies, the first Pakistani children with thalassaemia started to be born and they were outside London, they were in the North and also they weren't so concentrated up in one place. They ended up being more concentrated in Bradford, and I was, by that time, collecting census data, to see where ethnic groups at risk were and so on and I realised that this group at risk was in the North, but nobody was recognising that they had a problem with thalassaemia, partly because they were separated, there were two different regions which barely communicated with each other, because there was Yorkshire and there was Lancashire and they were in all the mill towns. They were concentrated in mill towns in the middle. So I contacted a haematologist there and said that when you next have one of your regional meetings can I come up and talk about this. And I did and there I met a doctor called Kay Hunt from Bradford, and she was the one who picked up on it, and she immediately started looking at the issue and trying to do something and so I worked with her for some years then. That was extremely illuminating to me, but I could come back to that later.

PSH. What about prevention now? We've skirted around it.

BM. Well, we had better do the prevention. Well it started very early, because I had only been looking after, I had set up my thalassaemia clinic, had been looking after the patients for a short while, when I realised that I started getting phone calls from mothers saying "I've missed my period. Can you arrange an abortion for me". And they were very frightened at the time, because they didn't know what the law was about abortion in the country, and of course the abortion law had been passed by then, and they didn't realise that this was something that they had a right to really. So I found myself organising terminations of pregnancy and later on I did the statistics on this, and they were recent migrants and they could not communicate well. Let's say there were many communication barriers and their use of contraception was not that perfect. So anyway, I found later that 70% of them if they got pregnant requested an abortion right away and it only took a few of them to make me realise that this was absolutely tragic because they had, in each of these aborted pregnancies, a three quarter chance of a healthy child they were desperate for, but they just didn't dare. They were too terrified of the disease. And I thought at the time, well what a pity, because we had been working, there were so many useful developments at the time. Now let's see, it was the late 1960s, early 1970s the automated haematological analysers, the particle-size analysers were just coming in and we were experimenting with them at UCH, or they were, and this gave you the possibility of detecting the carriers by their microcytosis and then following on with A2 estimation. And I did, in fact in collaboration with our lab here, I had done a project with Charles Payling-Wright, who was at the Galton, and we agreed, we were thinking, if we could detect carriers and give people genetic counselling in this population. Well first of all we worked on the prevalence of thalassaemia and I worked out, using the Hardy Weinberg, collecting all these births. This is how I started the register in a way I suppose. That's right. I collected all the births of thalassaemic children in London from all the hospitals, found out which areas of London they came from, then went to the Registrars of Births, Marriages and Deaths and asked for permission to look through their registers

so that I could pick out all the Cypriot names, so that I could do a Hardy Weinberg calculation of what the carrier prevalence was among Cypriots, and Charles and I did that together. We came up with a minimum of 14% and this seemed such a large figure that we felt we ought to confirm it. So he and I together went to the Greek Orthodox Church, two Greek Orthodox churches in Camden and asked for the cooperation of the priests in getting their congregations to volunteer to have their blood taken, so that we put it through the coulter counter at UCH. And people thought we were mad, they said, because there was so much, you know there were all these prejudices about these ignorant foreigners and how nobody would agree and all the rest of it. And so Charles and I went with our needles and things to St Andrew's Church in Kentish Town and the priest, after we'd had some discussion he said yes, one of our priests has a son with thalassaemia. He stood up and preached in all his golden glory in the church crammed with Cypriots, encouraging them to give blood so that we could do this study. 200 people lined up. It took us hours to get all the samples, and once again when I saw the number that were microcytic and were thalassaemic I simply couldn't cope with it. It seemed so enormous an issue. And then I went to discuss it with the Medical Officers of Health, there used to be lovely people called Medical Officers of Health, who had power in those days. They said, this is an important public health issue and they were very prepared to support some efforts to approach the community and inform them and offer screening. But I had my doubts, because I thought if we haven't got anything better to offer, what are we going to do?

Anyway, coming back to the people coming and requesting abortion. So we were working across the spectrum really at this time and I was thinking, what a pity, here we are; we can detect the carriers and we can't do prenatal diagnosis. And for some reason I was used to the idea of prenatal diagnosis, I think probably because our paediatricians obviously were very interested at that time in prenatal diagnosis for neural tube defects, and also our obstetricians, particularly Denys Fairweather, had a deep interest in prenatal diagnosis. He had started working on rhesus disease and the prediction of seriously affected fetuses from pigments in the amniotic fluid. So we had interest at UCH in prenatal diagnosis and to me this seemed a very natural thing. And I went to a meeting in the States where Y-W Kan stood up, and he had looked in the literature and discovered a paper by an obstetrician who is probably still alive, an Oxford obstetrician, it was from the 1950s, where they had looked at fetuses after, because in those days they used to do abortions by hysterotomy. They collected all the aborted fetuses and analysed the haemoglobin and showed that human fetuses have got about 7% on average of adult haemoglobin from about 12/14 weeks on. So YW Kan had looked at this paper and thought, well in that case we should be able to do prenatal diagnosis, but he had increased the power of the method by radioactive labelling at the time, and he presented this paper and he showed that one should in theory be able to do a diagnosis by globin chain synthesis, using Weatherall and Clegg's method. Again it was one of those times when I knew we just had to do this. At that meeting I ended up with a collaboration with Blanche Alter in David Nathan's group in Boston. When we had a request for an abortion, I would follow up and collect fetal material, and we would label the mixture that came out and ship it to them for globin chain synthesis

because I hadn't got that in my lab. Didn't have a lab. So we set up a collaboration.

At the same time, you see, this is very integrated with patient care. At the same time I was trying to push the parents of my patients to look carefully to family planning, to their contraception. Some of them were asking me for sterilisation, and I just felt this is too awful for words, so I said no. Do your family planning properly, because there is hope in the future we will be able to do prenatal diagnosis. So they all knew what we were working on. I should say in the States, but not in England at the time, there was a chap called Frigoletto and a couple of other obstetricians who were trying to develop methods for obtaining fetal blood, and one method was blind sampling and the other method was trying to develop fetoscopy, so you know there was action there going on. And we set up our research collaboration. And then one day, one of the parents of one of our patients, who was actually a British Pakistani doctor, with one boy with thalassaemia major, said to me "How are you getting on with the research?" "It's beginning to look very hopeful" I said, "come into the lab and I will show you." And I showed her the first five results, of which I think, two looked normal and three looked heterozygote. It looks as if it is going to work. And she said "How nice" and went away. Six months later she rang me up and she said, "I'm pregnant and I want you to try and do prenatal diagnosis". She said "I know you haven't got a method to get fetal blood but if you won't try I'm going to have to terminate this pregnancy and the worst you can do if you try is to cause an abortion". So I said "Ah". I rang Blanche Alter in the States and said this thing has happened to us and she laughed. I said "That is very unkind. You don't realise the gravity. " She said "Oh don't I? It happened to us yesterday too". So I said "what are you going to do?" She said "we're going to try". So I said "well we should try". I said I will go and talk to our Professor of Obstetrics, so I went to talk to Denys Fairweather, our Scottish Professor of Obstetrics and explained the situation to him, standing in front of his desk. And he thought, he kept quiet for a full three minutes and then he said "Well, when we do an amniocentesis we sometimes get fetal blood. Why don't we try to do on purpose what we sometimes do accidentally." So he was prepared to try blind needling, which meant that you try to orientate yourself and we didn't have real time ultrasound. We had B scanning which gave you a static picture. But he was one of those obstetricians with unbelievably fine sensation in his fingers and he was very expert in amniocentesis, and I watched him carefully and it was a very fascinating thing, because when he put the needle in, you could see him feeling very carefully and then he put the needle. I said what happens when you put the needle in? And he said "I hear a pop." Some of these surgeons have wonderful skills and he had.

So he was prepared to do it. So we had to find a method for sorting out what was fetal cells and what was maternal cells. One method was proposed but it didn't work, but we quickly found we could do it with a portable Coulter counter. So he used to stick his needle in and prick the placental surface, and take a little sample of blood-stained amniotic fluid and I would quickly look at it (while his needle was still in) on the Coulter counter and I would say maternal, maternal, aha, mixed maternal/fetal, that one will do. As the fetal blood was so much more active it synthesised haemoglobin much more quickly than the maternal blood. You could actually sort out fetal haemoglobin synthesis and

so we went ahead and started doing it, but my goodness it was tough, and worrying, and we didn't know how many abortions we would cause. So the counselling for the couples was quite educational, but they felt that this was the only way. It was very interesting what you learnt from talking to couples like this, because what they said was 'I could not knowingly bring a child into the world to suffer.' It was the knowledge, the knowledge of risk that made them stop, and you knew that if they knew they had done their best to avoid the tragedy and it still happened, that they would be able to cope better because they would have done their best, even if they still had an affected child, but of course they desperately hoped for an unaffected child. Anyway, it was a very interesting thing and it was them who pushed us, in spite of the fact that we didn't know the risks, we didn't know if we could get it right and then this is where you come up against statistics, and I always feel one should teach students this way. I mean, you must have had the same experience with, a 1 in 4 chance. If you do 4 you should get one. We did 18 before we got a homozygote and I was on the point of saying this probably doesn't work for Beta plus thalassaemia, which I knew we had, when we got our first homozygote. Well after that 19 was unaffected, 20, 21, 22, 23 were all affected. But it took us eighteen months of work before we knew this was a service that we could offer.

PSH. How long was it that you were offering fetal blood sampling before the possibility of CVS and first trimester.

BM. Too long. We started in 1974. By 1979 we really knew this was a service we could offer, I would say by 1978, we were offering it and we were pushing the Department of Health and the local Region to fund the service. But we had the feeling, and I haven't always lived up to this principle, but I certainly, you know, you and I were in the same generation and many of the things that one thought after the war, was about the use and abuse of science, and what responsibility does a scientist have for the use to which their discoveries are put, like the poor chap who discovered the extra chromosome in Down's and then found that people were doing prenatal diagnosis. It was a bit tough on him because of his convictions. So one has a feeling of scientific responsibility if you initiate something like this. So we followed our families. We accompanied them through the whole thing, including the abortion. You see we had done the procedure over a couple of years, before we actually had an affected one, and this was the first time we had an abortion, and so there was one possibility, which was to hand the woman over to the obstetricians. The other possibility was to accompany her through the whole process and we chose to accompany the woman and that again was another learning experience, very much a learning experience for us and for the midwives.

I remember sitting by this woman's bedside feeling absolutely terrible, with a 21 week termination and she was the one who was supporting me, because she was saying I am so grateful, I'm so grateful, as she was delivering her dead baby. And from that again, one learned how to handle, nobody knew how to handle a late abortion then psychologically. You know, did you just hide it away, what did you do? And so we also went through all of that, and lots of interesting things, like discussions with the Church of England Chaplain about the position of these women and how unsupported they were by their

religious advisers. I'm very proud that, now at UCH the Chaplain gives a little blessing ceremony and so forth for late abortions because of the feelings of the parents. So we always accompanied them through. Now if you do that, then you can't have any illusions that this is a satisfactory solution, and so we were highly motivated, and again I think this is terribly important in medicine. We had a unit where we tried to have everybody in contact with what was happening at the patient end, because after all, even the scientists, they come to the lab because they want to help, and throughout the health service now it is such a pity that the laboratory is separated from the patient interface, and I think everybody loses from that. It certainly kept us on line. One day I came into our laboratory which was in the obstetric unit, we thought we would call it the Club Mediterranée because we had lots of people from abroad fighting their way in. I came in, and we had a lot of columns set up there and the people who were working there came out from behind the columns and they said this is terrible. We've got to do something better and they had run four diagnoses that week, three were homozygotes and the fourth one we lost the baby because of the procedure. All around 20, 20 something weeks, and at that time I had a vision then, had an egg, an ovum with a polar body. I thought, what's the polar body there for. It's just like cross-matching, so we must be able to do something better. We've got to go earlier than this. We organised a meeting with the obstetricians, we had Ann McLaren, did you interview Ann by the way.

PSH. Very sadly . . .

BM. You missed her.

PSH. I missed her.

BM. Yes that's sad. Anyway Ann McLaren was there, and we started a discussion of whether anything would be possible in terms of IVF and what's pre-pregnancy genetic diagnosis. And Ann said well in China you know, they are getting bits of chorionic villus material. So I said 'Oh really', and it's another one of these things, once people like the parents know that you can treat thalassaemia they are going to get it and I said, oh really, then we should be able to do that. Now in Anshan, The Steel Corporation paper, they were doing this blind, very early, and it seemed to us obviously not good enough, and especially because of my early knowledge of embryology, you've really got to steer clear of embryogenesis and that would take us to about 9 weeks gestation so we studied everything we could find out about 9 week fetuses, and I talked to the obstetricians. I said we've got to do this, and they said it's been tried before, can't be done, too many problems. But I knew my obstetricians, and obstetricians think big and I thought, they are thinking big chunks of stuff. They don't appreciate with molecular biology how small a sample is needed, and I really should run back, to Bob Williamson, but I'll carry on with this. So I thought what I've got to do is get an instrument that I can think might do the job and show it to them, so I got hold of a needle company and we talked about it and we created a small instrument with a hole at the side, where one might suck, and I gave it to Humphry Ward our obstetrician and I said "That's the kind of thing I am thinking of" and he looked at it and he said "Oh that won't do". Immediately the whole question of whether it was feasible or not had disappeared. So he said, "No no that won't

do", and he got hold of Portex and set up a collaboration with them, where we would start researching how you could get chorionic villi with minimum trauma during abortions at the hospital, at the Temperance Hospital here. We got an ultrasound machine and we had all our foreign workers, I had lots of foreign workers, and every week we used to take this up to them. We had to wheel it up to the Temperance Hospital, a whole lot of us would process up and Humphry would have got permission from some of them, not all of them would give permission of course, but from some of his ladies terminating and the theatres were very helpful and obliging and we began to get samples. Now this takes us back to Bob Williamson, because of course the molecular biology started with a meeting which David Weatherall set up with Bob Williamson in Oxford, about the possibilities of molecular biology and you know, all the future possibilities, it was very fascinating. A wonderful meeting we had. I think it was at St John's College. I met Bob there and, now I can't remember the date.

PSH. 1979 or so?

BM. No, no, it was before that. It must have been 1974, when Bob was still using the biochemical methods. They were still using biochemical methods to try to sort out the messenger and the binding of DNA and so on, and Bob was still working in Glasgow, but I thought this was extremely interesting and what we were doing was so, I mean it was a heavy load actually, and the molecular biology struck me, as I said, it was light entertainment as far as I was concerned, and I would love to be involved in it just for the pure science, to elevate our minds a bit, mood-enhancing I thought. I said "Well, I've got loads of patients and you need material to try and get your message out for alpha and beta thalassaemia and so forth, so what can I do to help?" So he said "If there are any splenectomies we could do with a spleen". So I said fine. The operations then were done at what was the, oh help, I have forgotten the name of the hospital, but it was at Mornington Crescent , St Pancras Hospital, paediatric operations were done there, at that time. And so I had a sit-up-and-beg bicycle and I went on this bicycle with a container of liquid nitrogen in front of me, would go into the operating theatre, we had a lovely surgeon and he would say "Oh yes, Dr Modell's come", and get me to explain what it was all about, and as soon as the spleen was out, it was straight into the liquid nitrogen and then it went on the night train up to Glasgow, packed in dry ice. And in many other ways, in other ways I did everything I could to provide Bob with his stuff and I didn't realise at the time that this was going to be what we really needed. It took quite a while for the penny to drop once he was successful, that the one thing that really mattered was to move prenatal diagnosis into the first trimester and this was going to be the way to do it; and once the penny dropped of course we started working together.

He had come down to London by then, and we used to send him blood samples so that he could do his DNA stuff on them in parallel with our carboxymethyl-cellulose diagnosis. And I remember the first time he rang me up and he said 'We've got it'. It was by RFLPs. It was complicated linkage. So I dashed over and he had a beautiful electrophoretic picture, that was all, in those days and I took it straight back to the obstetricians because I knew how obstetricians worked and talking to them about molecular biology they

would say 'Oh but I'm just a plumber' and they would be frightened of it. You show them a picture and say 'Look, that's affected and that's not.' And they'd say, oh yes we can do that. So that was what led me to get hold of the instrument, which led Humphry to do the work with Portex, which led to the work at Temperance here, and actually we did our first procedure here and then Bob wanted to move on, because he was going to tackle CF and he felt didn't want to get too close to any kind of service commitment. So this was the point at which we went to John Old and David Weatherall and said - who were obviously deeply into this whole area - and said look, how about it? And they thought that was fantastic. So we then started a collaboration over many years with John Old, who was again another one of these wonderful people, because he was so reliable, and so determined to get the answer right. So we started taking samples, experimental samples and sent them to him. And then what happened? The same thing.

Now I had got involved with the Pakistanis, as I said. There was this doctor in Bradford who was contacting us and I became very interested, but I realised that I wasn't going to be able to research with British Pakistanis on my own. I mean I had learnt enough from working with Cypriots that one needed a Pakistani collaborator, and I had read a nice, a very fascinating book called Between Two Cultures which was about the experiences of families of different ethnic origins in the UK. It was anthropology largely, and in there there was some articles about Cypriots, but there was an article about Pakistanis by Verity Saifullah Khan, which I found fascinating. So I contacted her and said "Do you know, by any chance, a British Pakistani Muslim sociologist?" and she said I've got just the person for you and introduced me to Aamra Darr, who as student had worked with her and was doing some other job, so I contacted Amra and said, are you interested in working on this. I'd got a grant from the Department of Health and Amra immediately dropped the job she was doing, which she didn't find so fascinating, and started to work on this. So we then created a little team and went to meet the doctors and the families in Bradford and started working quite closely with them and she was visiting the families. I mean it was almost participant observation, finding out what their attitudes, feelings and experiences were, leading to a PhD thesis and it was a big learning experience for me. I always respect people if I learn from them and I learnt an awful lot from her, the way she went about and what she elicited, and I'm still learning actually because she is still much in this field.

So now among these families, there was one, and actually he was an Imam, a Mullah, and they had a child with thalassaemia. They were one of these families that came down to London for prenatal diagnosis, mid trimester prenatal diagnosis and they came and the fetus was affected and they had a mid trimester abortion and they felt obviously terrible, as one does. And she got pregnant again. Aamra had told them about our efforts for first trimester diagnosis, so they came down to London to see us, and said they wanted us to try and I said to him, I asked him whether he felt that by doing this they would be contributing to developing techniques that were acceptable to their community and he said yes, they also thought that. So that was our first real case and we did it here at the Temperance Hospital, in the same operating theatre where we had been doing the research. This was interesting because sometimes you are so focused on what you are doing that you don't

realise what's going on around you. The theatre sister burst into tears. She said, it was wonderful seeing something good come out of all of this. There are so many good people and they become so involved in the objective that you are trying to reach and sometimes you don't see them because they are behind you, not in front. Now that fetus was affected too and she had an early abortion. And when Aamra went to see the family later in Bradford, she said "It's wonderful. I can't tell you the difference". And they got pregnant again and it was alright the next time. When we finally published on the first series, in the acknowledgements, I felt I had to acknowledge the 22 brave ladies who had made all these decisions which led us on and on to getting something which was better. Then after that, I'm talking about Mary Petrou, who is the person in our lab who did all this work, and at first the amount of work involved was huge because everything was done by RFLPs, you needed extended family studies. She would go to their home. She found out where they lived abroad. She contacted to the people abroad. She got the samples sent and always at a level of emergency really, because she was always trying to get the answer quickly. It is just incredible what dedication people have put into developing these things.

PSH. When did it . . .

BM And weren't we pleased. I remember when I heard the first description of PCR at a meeting in Berlin which was the International Society of Human Genetics, and some chappy from California stood up and described this method and I immediately stood up, couldn't help it, from the audience and the questions and I said, you have just described the method that is going to make these services available world-wide. And they are. Mary Petrou again, there has been a tremendous demand, of course, for teaching and learning these methods in the countries where thalassaemia and sickle cell are common and she has trained, I cannot tell you how many people and supported them at long distance world-wide. And what you knew was bound to happen at the beginning, that if people know these things can be done, people want them and they will inevitably spread and they are, you can see the creep across the globe continually of new services being set up, and this comes back again to thalassaemia just being an example, because if you introduce DNA technology and genetic technology for this in their country, you open the door wide for all the rest of it. Says she, preaching!

PSH. At what point was it, Bernadette, that this then led to systematic screening. Now you had the possibility for prenatal diagnosis. Had the screening already taken off with mid trimester prenatal diagnosis, or was it really only when you got it to the first trimester that you started screening populations?

BM No, No. You see the Medical Officers of Health had already got quite interested in this, and long in the past, before prenatal diagnosis was on the cards, they had had a couple of meetings and they had called some meetings with the Cypriot community and they were thinking of some kind of educational campaign together with the doctors and so forth. When the invasion of Cyprus happened in 1973 everything fell apart then, because the community wasn't focused on these things any more, and that was exactly the moment when prenatal diagnosis looked as if it might come along, so I

thought fine, let's let it lie until we know where we stand with prenatal diagnosis, so we didn't push for involving the community any more. Now again, this is where your colleagues you see, are so impressive, because at the North Middlesex Hospital the haematologist was George Marsh, who died unfortunately quite a few years ago. Now he was the one who contacted me, because he said you know, we understand you are working on this, but look, I have been screening these people in my hospital now for years as part of the obstetric service, for the differential diagnosis of iron deficiency and for anaesthetic risks for sickle, and we'd not been telling them anything about their genetic risk and I think that is quite wrong and we've got to do something about it, and now you are getting something to offer, I am going to start seeing the people who are carriers in the antenatal clinic. I'm going to set this up and we are going to identify the couples who are carriers and we are going to tell them that your service is, or that you are doing this research and offer them the choice. And he started doing that, and hey presto, at risk couples started being prospectively diagnosed. Previously all the people who came to us, and from abroad to this country, had an affected child, but he turned the whole thing around and started using the antenatal screening, which they were already doing, to provide genetic counselling to the community really, and the couples started arriving and sitting down and having discussions with us, and later on we were able to show that 96% opted for prenatal diagnosis. And you may remember, I realised from the information that we had and the notes, that we would be able to get statistics and say how these people behaved, and so we produced a paper where we were able to show how, once they knew their risk and before prenatal diagnosis was available, they reduced conception rate by 50% and 70% of conceptions were aborted which makes what, makes 85% reduction. And then once prenatal diagnosis was there, all these families demanded, we had a sort of outburst, and then everybody started reproducing to achieve their target family again.

But anyway George Marsh did this. Now that was a major initiative and we had a good relationship. It wasn't easy to get our papers published. I hadn't realised the amount of opposition that would arise from trying to introduce something like this for a whole population. Really it was very difficult, because I found my grants were stopped. I couldn't get my papers published. I lost my reputation, because there were certain people who were frightened about it, or felt that we must be doing something wrong. Well, it was a bit stupid of me not to realise that this was a really very controversial area. It didn't seem very controversial to me. I thought if this was what the patients needed, this is what we should be doing, but not everybody could see or understand it was what the patients needed. I couldn't get grants, definitely couldn't get grants. But in the end we were supported through this difficult period and right on past getting the first trimester going, by grants from various Saudi Arabian potentiaries, because the Saudi Arabian ambassador at the time, Sheikh Faisal al Hegelan had a son with thalassaemia, and his wife was one of the most civilised and educated people I know, and she twisted his arm so that he asked various people who came to London to support this charity and we were supported by, particularly Prince Sultan Bin Abdul Aziz who is now the defence minister, Sheikh Yamani, Prince Salman and a number of other people. I always think I would like to write to, I plan to write to Prince Sultan again, because he took us over this very difficult period and at the end of it we wrote to him. We sent him a big card with lots of

photographs of babies on it and thanking him for his support and at the time he responded, sending us another $100,000 just like that. So we were supported exclusively from Saudi Arabia, over a number of years, from particular charitable individuals, and I think that sort of thing should be known about them, because you only hear one side of these things.

PSH. What was the time scale in terms of the incidence of homozygous thalassaemia coming down? I'm trying to get a picture in my mind of the sequence in terms of Cypriots and others.

BM. You asked me, actually we have to look at the UK and other places separately. In the UK you asked about screening. Now George Marsh started the screening and we started doing the cases, and we felt that the only way we could overcome the, let's say whatever it was, the amount of difficulties that we had, I said to myself we live in a community where when you produce evidence, people accept it - controversy continues in science in the absence of evidence. What is needed is evidence. Once we've produced the evidence, then probably we will overcome our problems. So we shut up, didn't say anything, didn't do anything, except just did the work, and by 1980 we were able to publish a whole lot of evidence and by that time because the news was getting around, most of the hospitals in the Greater London Area where there were clusters of patients with thalassaemia, particularly thalassaemia, started screening in the antenatal clinic. They started because their local doctors thought this was the right service to offer to their population. But not everybody did, and that happened up and down the country, like Kay Hunt started screening in Bradford for instance. It was exactly the same as with the desferrioxamine, that the country was divided into people who started to do it and people who didn't do it, and that went on and it was totally unaffected by introducing first trimester diagnosis because it wasn't that sort of decision. It was a decision that was based on, I don't know what it was based on, and it was not clear to us.

The fact that people started screening made a big change to me because I had been in the Department of paediatrics, and once we were somehow on top of thalassaemia treatment I had to move into the department of obstetrics and I was on soft money. Soft money has many disadvantages, but one advantage is you can move and take it with you. I moved into the department of obstetrics. We set up the lab and prenatal diagnosis service and started working with all these exciting people. Once that was done, and it was all published, what we found was that people were still not getting the service, so we started doing audits. We had a prenatal diagnosis register and we had a patient register and the patients were still getting born. So we started following the WHO recommendations, doing enquiries into why the patients were born, and had the parents been told, and no they hadn't been told and the service was reaching fifty per cent of the people who needed it. And that went on, and there was no way of shifting it. The only thing that changed a policy, that made a new district start a policy, was if somebody sued them, unfortunately, and very few patients sue and still very few patients sue actually, even when they are missed. So there was going to be no change and we kept saying there was going to be no changing unless there is a national policy instead of it being a regional policy. And somebody at the Department of Health has got to change the attitude, "because it is

heterogeneously distributed, it's not our responsibility. Let each Trust or each region make its own decisions", which was their attitude. And what brought about the change in attitude, I think is quite interesting, because there are two groups at risk The group at risk for thalassaemia and the group at risk for sickle cell and they are about equal size actually now, but the group at risk of sickle cell is at higher risk and they are more coherent. They are very coherent with the sort of black identity of Caribbean and African, so they have a political voice, whereas the thalassaemia groups are very diverse and they don't have a single voice and they are not at such high risk, most of them, just the Cypriots.

Now change I realise, it took me many years to realise, however good the scientific evidence, however good, change does not happen without political pressure. The political pressure largely came from the black community. There have been various structures built up, The National Screening Committee and so forth, to review issues like screening, antenatal and neonatal screening. Now in the black community, it was largely in the black community that the sickle cell and thalassaemia counselling structure was built up, so there were a lot of dedicated black counsellors, and I remember being at a meeting at Great Ormond Street where the screening committee's decisions about screening for haemoglobin disorders were going to be presented. And a poor innocent chap stood up and said "well we've looked at all the evidence and we think neonatal screening is justified, but not at all sure about antenatal screening" and the entire audience said something. I did too. I said "I don't believe it". Other people said other things. The black counsellors practically got up to their feet. They almost lynched him. He was horrified by the reaction that this produced, but he had got a feedback from the community and they were supported by active groups in the black community, and it was that political pressure that made them hastily decide that they should include antenatal and neonatal screening in the, was it 2001, policy document, and that has made a big difference. But it was twenty years, I was always outraged, it was twenty years from the time that we proved that this method worked, and had clearly shown that it wasn't being properly delivered, it was twenty, over twenty years before we had a national policy on screening .

Now in the interim, because of this, because of this failure to deliver the thing, I'd identified that as an area that had to be tackled, so I moved into our department of primary care to look at the sort of social and policy making aspects really, and what the problems and barriers were to getting a service like this delivered. The basic problem was there wasn't any kind of infrastructure there, or anybody with responsibility for doing this sort of thing. So that's what happened in this country and it was particularly infuriating, because if you looked at the countries of origin, where the patients came from, things were completely different. A very important development in this whole field was the involvement of WHO, which started in 1980 when Anver Kuliev became the Head of the Human Genetics Programme, I think it was, and he is an extremely responsible person, so he looked carefully to see what was going on world wide that could actually be implemented at the public health level, WHO being a public health organisation, and he identified the developments with thalassaemia particularly, as offering the possibility for the first time of completely controlling a genetic disease at population level. So he

attended meetings and hand picked the people he thought it would be useful to bring together in a group, and created a WHO working group on haemoglobin disorders, which was a real privilege to belong to because the people were just so fine. So it had Antonio Cao from Sardinia and Guiseppi Masera, some Italians, Greeks, Cypriots, Thai, various other people and it was that support from WHO which enabled these countries to move forward. It helped enormously for the different countries, particularly the Middle East and Asian countries to get their governments' attention and some kind of support for a prevention programme. Now a few countries stand out. If you look at the epidemiology of, haemoglobin disorders in general, focusing on thalassaemia there are a few countries that stand out where it is so common it has to be a priority health problem; Cyprus is one of them, the Maldives is another one, Bahrain, Greece was also in that category and southern Italy, bits of southern Italy, and they knew that this was a problem. So they already had very active and committed doctors who seized on the possibilities, got grants from their government, came to the UK and got themselves trained, took the service back, held meetings, started the whole process themselves. Each one of them in their way is a remarkable pioneer, and the most unexpected things happened.

I remember after the Italian abortion law was reformed in 1979, I was invited to give a talk in Milan and people here said, you won't get anywhere there. They've got the Catholic Church there. Little did they know what the Italians' attitude to the Catholic Church is. Of course, when I went to Milan to talk about it, nobody wanted to know "Should we be doing it?", the only thing they wanted to know was how to do it. So the thing spread. And in Sicily I went to a meeting there organised in Sicily and who organised it to discuss this whole thing? The Cardinal. In Cyprus, the thalassaemia centre is part of the Archbishop Makarios memorial centre. So throughout this whole service, particularly with the prenatal diagnosis, starting from the very beginning, every expectation that I might have started off with, every prejudice, every idea, has been turned on its head by what patients and people actually do. It has always been very distressing to me to attend ethical, social and legal meetings where people seem to be discussing How are *we* going to control this service? How are *we* going to provide this service?, without realising that it should be led by patients, because they make so many assumptions. If you introduce this service then this, that and the other will happen. You are getting rid of patients and patients will be stigmatised. Well has that happened? No.

What happened in the Cypriot community is that suddenly people said 'ah we thought it was only a few families but now we realise it affects us all'. They get screened, they are a carrier, they join the UK Thalassaemia Society, they raise funds, because they have a family connection with the patients so they care more and not less. In a sense all that is obvious because one just has to see people as feeling, loving human beings and not as . . . So all expectations, including in the Middle East. Now in Iran for instance they have a real thalassaemia problem in Iran and they started pre-marital screening because they felt this was the right thing to do to give people all the choices, but they collected statistics to see what choices people made, and then they found that only a minority chose not to marry and the rest wanted to marry and thought they would limit their family or whatever, and so they say well we

need more choices, so they go and discuss it in their parliament and they get approval for, not very easy because they had to discuss it three times, but they get approval for termination of pregnancy for severe genetic disorders. They are very wise really, the Iranians, because they've always seen this in much wider context. So it wasn't just termination of pregnancy for thalassaemia. It was termination for any severe genetic disorder, and they made it absolutely clear in the Fatwa that it is the parents who decide, now taking it completely away from groups of people who can't help thinking it's their responsibility to decide. I think it's terrific. Don't you?

PSH. I do. Bernadette, we must draw things to a finish now, but firstly, are there any particular areas that you really feel you want to put on the record that we haven't touched on at all. I know there are lots of other things we could, but do you think we have covered some of the main strands of your work anyway.

BM. Yes. There is one thing I suppose that I would like to say about this is that, because of its unique biological position, haemoglobin has had a leading role, first of all in sorting out the structure of proteins, then in the way into human DNA and the revolution in human genetics, but that means that at the clinical level as well, it has always been twenty years ahead in a way, and this is why I have always regretted the distance between haemoglobin and the rest of genetics, because I feel it is very good that the work on first trimester diagnosis, which we did specifically for thalassaemia, you know, we have presented that as something which obviously had to be done, but actually it was more than that. I realise that we had to do it and *we* had to do it, because the current, the commonest technique for prenatal diagnosis at the time was amniocentesis and that was used for biochemistry and would be used for DNA and for chromosomes, and tremendous work had gone into assessing its safety and improving its safety, so here it had a risk of 1% or less to the pregnancy, but the disadvantage of being late. If you, in that context, you wanted to shift to the first trimester, it was going to be awfully difficult to introduce a technique which might have a higher risk for anybody trying to do it. They would run up against all kinds of barriers with ethics and so forth, whereas we had a technique which had a 7% risk of miscarriage, a high risk technique for people who were at high and recurrent genetic risk for a common disorder, and so that we could introduce a new technique with an unknown risk, without major ethical problems.

So that was one thing, that was one reason why I felt we had to it, because there were not many people in a position to go ahead with this and that if we could manage to do that because, as I've explained to you, because, I mean, I didn't have any support, apart from the obstetricians. I didn't have any support at UCH from the haematologists, so we didn't have major resources. But we felt if we could just make this one breakthrough it would be picked up by many people and spread out, that this was just this little thing. This was our function, and we managed to do that and it was picked up and it has been used and it's become the accepted method of prenatal diagnosis for inherited disorders really, and that means that it could expand in many dimensions, it could expand across conditions, it could expand globally. Nobody thinks it is perfect. I remember the reactions of our patients because we had patients who had been through the mid-trimester procedure once, twice, three times.

And then they had this, I mean we used to quiver in our shoes when patients came back. They always came back. They came, they were counselled, they had the procedure. They had lost the baby either because it was affected or because of the procedure and they always came back, because they wanted that baby. We wouldn't tell the obstetrician, especially if they had been twice or three times, because we felt his hand might shake. So we would tell him afterwards. You know it was very stressful on them, and one forgets how stressful it is for the team, the clinical team to accompany people through two or three late abortions.

Anyway, I remember a couple sitting there and the diagnosis was unaffected but the fetus was just about an inch long at the time and they were saying 'it's a miracle, to be able to get the diagnosis when the baby is just so big' and you felt wonderfully fulfilled. Then we started getting couples who had been picked up prospectively, and this was the only technique they knew and they'd say, just like the other ones had said, they would sit there and look at you and say 'can't you do something better than this?' And we would have humbly to say, 'Well no, you know we can't control the situation, all we can do is tell you what has happened' So there was that recognition of that particular function.

The other thing is, when one has time to consider, the heroism of some of the people involved in developing these procedures. For instance, people used to come and visit our centre when they heard of it and we had an Iranian, who had a fellowship, and he was in Birmingham and he was a laboratory scientist. I think he was working on endocrinology. But he came and he saw what we were doing and he said, I'll stay on longer at my own expense. I want to learn this. And so we trained him on the DNA technology for prenatal diagnosis, and he went back to Iran and set it up and started practicing it, and he didn't know what his position would be at the time in relation to the religious police. You know it's quite conceivable, depending on the whim of somebody at higher levels, that he could have been imprisoned, but he wasn't. And when I went there as a WHO consultant and they wanted to know how they could get someone in to train their people, I was able to say well, you don't need to because you've already got experts here, who are practicing in the private sector. They are willing to combine the private and the public sector and he is now one of the people who runs a reference laboratory and is training their laboratories, and there are other people as well. And when you think back, OK it was his job in a way. He was a laboratory scientist. He wasn't a doctor. Why should he risk himself like this? Because people needed it and he knew they needed it. And I think in every country where we see people trying to set up these services, they are not easy. They are controversial in every single country. So I'm just impressed with my colleagues out there.

PSH. Bernadette, just to finish, I have been asking everybody I've seen two questions. One of them is, in your areas of work, is there one piece of work, or one particular part of the project that you feel you specially identify with or are proud of, which you feel, if you had to name just one and put all the rest on the side, you would say this has been most special to you. Is there anything that stands out like that?

BM. Well, you've put me in a hard position there, Peter, because there are two things.

PSH. You are allowed two I think.

BM. The thing I think is most important, obviously, is first trimester prenatal diagnosis obviously, but the thing that makes me happiest is seeing the patients alive. Seeing their improved survival and quality of life. Seeing them grow up. I mean it was such a gamble at the beginning with these patients, that you were just determined. You couldn't see any good reason why they should die. I couldn't see any good reason why they should die. And so you stuck your heels in and tried to treat them, and told them - we had a wonderful clinical teacher, I don't know whether you remember Max Rosenheim.

PSH. Yes, I remember him.

BM. Now he taught us about the placebo effect really. He didn't call it that. He told us about, to be aware of the effect of the doctor on the patient. Were you at UCH?

PSH. No, I was at St Thomas's.

BM. Ah well then, you didn't have, it was right in the introductory course, but these things absolutely stayed with you. He told you how to be aware that when you came into the ward, the patient immediately feels better, particularly when you take an interest. And he said it's not just the medicine you give, it's the way you give it that counts and if you give it optimistically the patient is more likely to benefit. So I implemented this and I said to my families, because they had to put their kids through this awful business of having needles every day and then it turned into something worse, which was an infusion pump for Desferrioxamine. I said to them, "your child will live" and they believed it, because they saw the incredibly improved quality of life with decent transfusion and so they were inclined to believe what you said. And then you said, right now our problem is iron overload with this drug, we'll deal with it. And look you can see. Fortunately Desferrioxamine (and the other oral chelator too) is taken by mouth. It's colourless when you take it and when it comes out it's a deep rust red. So you can see the rust coming out, and this is what is going to give long term survival. And I would tell them, I would show them with pictures that when they grow up they can get married and they can have healthy children. And all of this was a gamble. I was aware it was a tremendous gamble, but unless you gambled it and said it with conviction, you weren't going to get the best results. And by no means all the patients are alive. I went to the fiftieth birthday party of one the other day and most of my patients, who are alive, they're married, they've got children and there is nothing that gives you greater satisfaction, nothing, because they have beaten the disease and I think having healthy children really confirms it for them that they have really clobbered this disease. And it wasn't me, you know. I had to hand over patient care at the time that I took on prenatal diagnosis, because UCH was completely unwilling to have a thalassaemia centre and to focus too much on this condition. So I had to give over the patients, but fortunately there were very good, super clinicians who took them over, and carried on and did better.

PSH. The other thing which I have asked everybody Bernadette is there any one . . .

BM. And I didn't mention the name of Beatrix Wonke. I will now because she has been the clinician who would not let them die! She took it as a personal insult.
PSH. Thinking over your career, has there been any particular person you feel has been a very special influence, that you owe most to, so to speak, in terms of being either a mentor or an inspiration, at any point along the way.

BM. Oh well, there have been a series of people. There's that partly mentoring when you are younger and partly colleagues that it is a joy to work with. Well, there was my tutor at Oxford, Wilma Crowther who was extremely inspiring, wonderful intellectual woman. Then there was my PhD, well he wasn't my PhD supervisor, Werner Jacobson, at the Strangeways Research Lab at the time who was an inspired teacher. It turned out later particularly for post graduate students. He was absolutely wonderful because he made us go to every tea club that was on and at that time those tea clubs were absolutely sensational. We were a bit out of Cambridge and we used to cycle in, there were two postgraduate students and him When Perutz presented different levels of analysis of the structure of the haemoglobin molecule, or Brenner's first announcement of the experiment showing the existence of messenger RNA, or the first description of tobacco mosaic virus structure. They were absolutely, it was a wonderful time and he made us go to every single one. And when some of us couldn't go, one person at least had to go and come back. And I remember I went to one meeting in the early days of this practice and I came back and told them what the thing had been about. So he said to me, "Well Miss McLoughlin, you have given us your impressions. Now will you tell us the facts". So ever after that, I made sure I knew what the experiments were and what the conclusions were based on. He was a lovely man, who passed on, and it was partly because of that relationship that I understood what medicine was all about and so went on to do medicine. Then in medicine there were people, I wouldn't say Max Rosenheim was a mentor but an inspiration, and Leonard Strang particularly was a great clinical scientist. A lot of the clinicians were uncomfortable with being scientific. Then there was Denys Fairweather, the Professor of Obstetrics, who was superb to work with, and at the time we were doing the fetal blood sampling for instance; he was very taciturn. When he was leaving he had a Festschrift. I volunteered to give a talk. So I gave a talk going back over our experiences a bit. I said that I had said to Humphry Ward "I find him a bit nerve racking" and Humphrey had said "Oh don't worry he's a Scot, the first three years are the worst". But Denys was like that. He didn't explain what he was doing necessarily but sometimes you could see, like I told you about hearing the pop. You could see him hearing the pop, amazing. Now he was doing a big job for the International Planned Parenthood Federation. At the time that we were developing this fetal blood sampling, he was the only person who could do it for us, but he was around the world, here and there, visiting innumerable countries and I would see him and say 'we've got a new case coming up' and he would say, 'Well now just let me see, I'm in Montevideo on so and so and then I'm going through to Stockholm. I'm coming in to London - I'll do it between 10 and 11 on Tuesday. Absolutely consistent and dedicated. As I said to him later on, once we had

demonstrated this worked, you just couldn't measure his achievement really, because people always forget. They think of the laboratory side of it, but my experience is the dedication of the obstetricians. So there was him, and later on there was Anver Kuliev from WHO, who was a wonderful person to work with, a fine partner because he was a very good manager and he had a very good practical grasp and he would ask a question like "How many are there?". I'd think "That's an interesting question", and would go away and find the answer. So he was at WHO. There was Marty Wagner at the regional office of WHO in Copenhagen and then Ala' Alwau at the Eastern Mediterranean regional office who was one of the brightest, most stimulating minds that I ever came across, who took the whole concept of genetic services for the Middle East on board, so these people, there's a whole list of people, all of them.

PSH. Bernadette I hope I haven't worn you out. I think it's time we finished and thank you very much.