**INTERVIEW WITH MARCUS PEMBREY, 19TH SEPTEMBER, 2006**

PSH. It's Tuesday 19 September 2006 and I'm talking with Professor Marcus Pembrey at the British Society for Human Genetics Meeting in York. Marcus, let me start at the beginning and ask when were you born and where?

MP. I was born in 1943, 20th April 1943. I was born in Guildford, as my father had just moved back into Medicine and was doing some work in Godalming. It was the war site for St Thomas's hospital

PSH. So did you come from a highly medical family?

MP. Pretty medical, yes. My father was one of ten children and he and two others were doctors, and he was also a priest actually, a Church of England priest, and his own father was a professor of physiology at Guy's and so there was quite an academic tradition really.

PSH. I seem to remember once seeing you show a slide of inheritance of Medicine as an autosomal dominant trait. Was that your family?

MP. It wasn't actually no. No it wasn't. On my mother's side there were no physicians. She was a nurse at Guy's and taught by my grandfather, though he didn't realise he was speaking to his future daughter-in-law. And my paternal grandfather's father, he worked for the Oxford University Press actually, as a translator.

PH. Which got you interested first, medicine or science, or was it a bit of both?

MP. It was biology really. We lived in the country. My father was a wonderfully broad sort of biologist, country walks. I knew about evolution certainly before I went to my secondary school, pretty well. So my explanation really is, I did well in biology and those subjects. I went into the biology 6th form and if you were reasonably bright you did medicine or veterinary medicine and if you weren't so bright you did forestry or something. That partly was the sort of pressure. I really wanted to do medicine as a general introduction to science and in fact I went to Guy's rather early and so I was a second year medical student and not allowed to buy drinks in a pub at just 17¼.

PSH. Bit of a disadvantage being 17.

MP. So I didn't want to rush through my training anyway, and I was very keen to do an intercalated BSc, but I didn't do well enough in the exams.
I'm not an exams type of person. So I had to plead and beg and argue to be allowed to do a BSc, but they did let me and that really fired me up a bit on genetics.

PSH. Now was that with Paul Polani?

MP. No it wasn't. I mean Paul Polani was there at Guy's but this was an intercalated BSc and what little genetics we had was at UCL with Johnson Abercrombie, no not M L Johnson Abercrombie that was a woman, Michael Abercrombie. Abercrombie was one of them and anyway J Z Young gave us a lecture, you know what I mean? And I also, as a medical student joined the Eugenics Society as it was then, for the sole reason that my cousin told me if you join the society, it's virtually free and you can go and have tea with Julian Huxley. So I did that and I went and had tea with Julian Huxley at some meeting or something. So I had become interested in genetics and that sort of thing.

PSH. Can I ask, those first years in medicine, were they mainly based at Guy's hospital or were they mainly based at places like University College.?

MP. No, not UCL. So during my medical student elective period, just before taking finals, I chose to go to Great Ormond Street and sit in on Cedric Carter's genetic counselling sessions and so forth and so on, and that persuaded me that that was an area I was interested in. So when I qualified I did one job at Guy's, a combined surgery and casualty job, it was pre registration in those days, and a physician's job at one of the Guy's related hospitals, the Miller General Hospital near Greenwich . I did a bit of general practice, that was tied in with in courting my wife Heather, because she lived on the Mersea Island near Colchester, where the population doubled in size during the summer because of all the caravan sites and so the GPs needed someone to help them out in summer, and so I did that for a couple of summers. I did paediatrics at the Evelina Children's, and I was really quite torn between paediatrics and general medicine, because at that time there wasn't really a clinical genetics discipline to go into. During my paediatric time at the Evelina as an SHO I started going to John Fraser Roberts' genetic counselling clinics and relating to Paul Polani's, Paediatric Research Unit.

PSH. Now, am I right that by that stage John Fraser Roberts had retired from the Institute of Child Health and was working at Guy's.

MP. At Guy's yes. He came over in '64, something like that, 1964 thereabouts and continued to do his clinics around the country, and the one I particularly was involved in on a long term basis was the Colchester one.

PSH. So which was your first, so to speak, work that was directly related to medical genetics at all?

MP When I had just qualified and had done my pre-registration, I was looking for SHO jobs so I applied to an SHO job at Broadgreen Hospital in Liverpool, because Cyril Clarke was there, and he said meet me at the College and we will talk about it. And he said you don't want to come and do that job. What you've got to do is go and get the membership. And then come and see me again.

PSH. That's exactly what he said to me.

MP. So I told him my ideas for studying thalassaemia. I have beta thalassaemia trait myself. It runs in the family so my interests initially were how to cure that by switching on fetal haemoglobin. I went away and got the membership actually fairly smartly and I have to say it was marvellous. He rang me up about two days later after I'd got it, 'I see you've got the membership. Come to Liverpool.' So I said well I have just got to do my paediatrics. I've got a paediatrics job lined up. He said 'well come after that.' So it was terrific to have a mentor who steered you straight away.

PSH. So is it fair to say that your links with Cyril Clarke actually developed before your links, on a large scale, with Cedric Carter and John Fraser Roberts?

MP. Oh yes.

PSH. So when you went to Liverpool, was this as a medical registrar?

MP. No it was as a Research Fellow. He had organised a Nuffield fellowship, in those days it was all very straightforward. I didn't have an interview or anything. He said I've got this Nuffield Training Fellowship for you, and that was for two years, I think. Yes I think that was for two years and then, no a bit longer, maybe it was for 3 years, and then I did have to have an interview to get it extended a bit. So I went up there and he introduced me to David Weatherall - I didn't know about David Weatherall. I should have but I didn't. But I had listened to Fessas give a talk when I was a medical student about haemoglobinopathies, and I knew I had beta thalassaemia, which is a story in itself if you are interested.

PSH. I'll come back to that.

MP. And I'd heard Fessas say that a combination of beta thalassaemia with this inheritance of persistent fetal haemoglobin makes it milder. He had said, if only we could switch on these genes, which everybody has, or just not switch them off, and that fired me up and I thought right, that's got to be my first research project and indeed it was.

PSH. When you went up to Liverpool, then, were you working directly with David Weatherall or mainly with Cyril Clarke?

MP. It was agreed I would work with David Weatherall and I would take part in the registrar rotation coverage of the haematology ward, so I did the occasional on-call and so on, and I did my MD thesis on maternal fetal haemoglobin in pregnancy and the whole question of whether this was bleeding across from the baby, or actually the mother switching on her own fetal haemoglobin. Turned out to be a selection of cells mainly, fetal haemoglobin cells. But Cyril, I did do a few projects with Cyril as well, and my first paper was on thalidomide. He believed these biological systems are never 100% and there must be somebody out there where the mother had

taken thalidomide at the critical period and yet didn't suffer from the abnormalities.

So we set up a little study and ascertained such a person and the evidence seemed pretty compelling, at least the Lancet took the paper anyway, and there weren't any abnormalities. The child was carefully examined. So that again got me interested in developmental genetics, both the haemoglobinopathies and that. And doing that in 1969/1970, the first study was very informative really because I then uncovered that Willy McBride had completely made up his published data, not his first one-paragraph piece of data which was in the Lancet. When Distillers said they would gather all this information, they actually gathered it to suppress it. McBride eventually felt he had to publish a paper in the Australian Journal of Medicine, Australian Medical Journal I think it's called, in about 1964. I think it was three or four years after the thalidomide story broke and he didn't put thalidomide in the title and the diagram he had of when the mothers took thalidomide and when they didn't bore absolutely no resemblance to what we now knew, because of Lenz's work on the critical period. And then of course it made sense why he had hidden it in the middle of other data and so on. So I put this all in the discussion of this Lancet paper and Cyril Clarke was very excited about it. He said you will get called to the court hearings in Germany and things like that. But it didn't happen really. I tried to correspond with Willy McBride, then of course he was found to have fabricated other data and had his institute taken away as you know. So it was quite an eye-opener.

So there was that I did with Cyril. And then the other thing I did with Cyril . I started to be a bit interested in twins and he said, all this twin stuff is terribly boring, heritability and so on. What's much more interesting is identical twins who are discordant for a common disease and why don't you study those? So I set up a little twin register and tracked down quite a large number of twins who were discordant. I sort of advertised and went and visited them and took careful family histories and produced a little series of five papers in The Practitioner of discordant identical twins, just speculating on what differences in their history might have accounted for one getting asthma, one not. One getting breast cancer one not, and so on. And those were the studies I did with Cyril.

PSH. How did you find Cyril as somebody to work with?

MP. I would have, I think, found it difficult had he been my main supervisor. He would have these ideas, throw them out, and if you didn't pick something up and run with it, that would be it really. If you picked up the idea enthusiastically, he would always spare you time. This is the point. It was all done in the spirit of terrific fun and hand waving. It was very helpful that David Weatherall's approach was, if I were to be critical, and I'm not really of David Weatherall at all, but if anything this was almost incremental science. We had to be so careful that you got one step right before you moved on to the next. And it turns out that I think Paul Polani was the best between the two. Cyril was too much chasing butterfly ideas really and David Weatherall's approach I think too incremental and sort of stolid really, and Paul Polani

suited me just fine. He was prepared to listen to slightly wacky ideas and would work out what type of studies one could do.

PSH. So how long were you in Liverpool? Was it three years?

MP. No. I was there for two years. From ’69 until ’71 and again I think it will ring true for those who came to Liverpool. Cyril said ‘what are you going to do now?’ He said ‘well, you had better go back and finish your general medical training because you’ve got to be a proper doctor’. And there still wasn’t any other real clinical genetic set-up that I could join, so I went to St Thomas’s as a lecturer in medicine and it was good training in general medicine, you know, you were an admitting physician in a busy casualty and given far too much responsibility. I didn’t like Bill Cranston and his approach to things. He was again very conservative. When I wanted to bring McBride over, to challenge him on these data and so on, he said ‘oh no, you shouldn’t do that sort of thing. Get your head down.’ So I did general medicine for a year at St Thomas’s, didn’t particularly like it, so I was looking for a way out and then David Weatherall rang me and said we have now got a collaboration established with Eastern Saudi Arabia where the sickle cell seems to have raised fetal haemoglobin, you can have first refusal. And I jumped at the chance.

PSH. When you were in Liverpool, did the suggestion ever come up of going to Victor McKusick in Baltimore?

MP. No it didn’t. Victor visited when we were there and it was discussed, because a number of people had come and gone. I think Rodney Harris was just coming back when I was leaving Liverpool and had gone to Manchester and so on.

PSH. I was there.

MP. You were there. That’s right. No it was discussed, but I think I never seriously thought about it. It might have come up if this trip to Saudi Arabia hadn’t arrived just at the time I was finishing and wanting to get out of St Thomas’s.

PSH. Tell me how that happened. What happened.

MP. In the Saudi Arabia trip?

PSH. Yes.

MP. Well basically, when I was doing my work on fetal haemoglobin, obviously part of the drive for understanding the regulation of fetal haemoglobin was this idea that, if you switched it on, you could protect against sickle cell and thalassaemia. I mean the initial story was thalassaemia but it seemed sickle cell was milder in eastern Saudi Arabia. Dick Perrine and a guy before him, whose name escapes me right now. I

might remember it, Dr Gelpi, in the Arabian American Oil Company, had reported some cases.

PSH. How do you spell that?

MP. G.E.L.P.I. I think it was, something like that. They had reported a few cases of what they called sickle thalassaemia, where they were rather mild thalassaemia and they seemed to have a lot of fetal haemoglobin even as adults. So this excited David Weatherall's group and a senior registrar in haematology went out on one trip just to visit and link up with Dr Dick Perrine who was the physician there. A terrific guy, a general physician with an interest in this mild sickle cell syndrome. So they did a sort of two week trip and came back and said, yes they would co-operate. There are some facilities of sorts there and so David said, would I like to go out and try and sort it out. So I went out with the family, well with my first born Lucy, and we were there for four months and I would go and visit the families in the Qatif oasis and Al Hasa oasis during the day and I would do the experiments at night in an un-air conditioned cupboard.

PSH. These were Bedouin tribes?

MP. They weren't Bedouin tribes. No the Bedouin don't have much sickle cell at all, which is an interesting selection. No it is pretty rare in the Bedouin population. These are the oasis dwellers in the Eastern province, the Qatif oasis and Al Hasa oasis; the Bedouin and the oasis dwellers sort of drink the same water almost, but actually are quite separate populations. And there's endemic malaria there. It's caught inside these oases. Mosquitos can't go more than 400 yards out into the desert and oasis malaria is what's driving a whole lot of haemoglobinopathies, but particularly the sickle cell.

PSH. Remind me it is falciparum malaria?

MP. It is yes. Well they had both, but it was falciparum malaria.

PSH. So after that, what happened next in terms of your own work?

MP. Well that work was interesting, so I came back. That was again funded on this Nuffield Fellowship, and I stayed on that funding until about 1976. As I say, I only had one interview in all that time and it was slightly mysterious. I decided I wanted to then do medical genetics, and was trying to get back from this period in research, which didn't quite have the caché of having come from Johns Hopkins or something. I mean, messing around in the oases of Saudi Arabia. But Maurice Lessoff, who is a physician at Guy's and a good supporting friend of mine, and Paul Polani, were very helpful and they said, come back and we will sort out a salary for you for the first few months and then we will see what we can do in terms of getting a grant. In fact I got a grant from the Arabian American Oil Company, and so I spent a little time in the Department of Medicine but going over to the PRU, and then gradually moved more over to the PRU and started taking part in the genetic counselling, basically as a sort of registrar.

PSH. Did you continue your haemoglobin research at the PRU?

MP. I did. I worked with a technician called Paul Rutland, who came over with me to Great Ormond Street when I finally moved. Working on assays for fetal haemoglobin and it was a slow business but we made some progress. We published this assay and so on, and in parallel I continued my trips to Saudi Arabia and that was funded by money from the oil company at that point, and so we did some good studies
and we clearly showed that fetal haemoglobin persists in the sickle cell patients and with Dick Perrine looked at all the clinical features of it and so on. We then did a pretty good paper, in fact the largest series at the time, on beta S thalassaemia , Bill Wood I was working with. He was in David Weatherall's lab. And I used to do, in those days they were chain ratios, the alpha beta chain ratios for diagnosing some of the thalassaemia cases like alpha thalassaemia we had out there. I would carry all this stuff out to Saudi Arabia under dry ice and through customs. . . I wouldn't be allowed to do it now. And do the first part of the incubation out there, and organise blood samples to come back.

PSH So how long were you at Guy's?

MP. I was at Guy's from the end of '73 when I came back from Saudi Arabia, until the end of '78. I took up the post at Great Ormond Street I think in March '79, something like that.

PSH. So almost five years must have given you a really good chance to get to know Paul Polani

MP. Oh yes, I knew Paul really very well.

PSH. You are really one of the few people who has worked with all of the main founders of medical genetics. What are your feelings about Paul's special attributes as one of these founders?

MP. I think that Paul's special attributes were that he believed in, and he set this up at the Paediatric Research Unit, having a very broad basic science base that would interrelate with the clinical practice. He saw these things as critical and working together so he would have Matteo Adinolfi on the immunology side but he was involved in alpha-fetoprotein because of its application. You had Philip Benson on the metabolic disease side. Again not clinical practicioners themselves, but very definitely feeding into a clinical service. You had of course all the cytogenetics, and then people like Mary Seller doing work on malformations, or in the early days on the neural tube defect, you know the Dick Smithells study and so on. So he was absolutely certain , certainly in those days, you needed to practice clinical genetics in a broad basic science setting like this, but with genetics as the common theme. That was his key thing. A library was essential He was a great believer in having a resource library. Guy's couldn't match in any way Great Ormond Street for the number of dysmorphology cases, but nevertheless there was

very careful documentation, clinical photographs and records of dysmorphic cases that came through. So that was the thing that came over absolutely clear to take it forward, that this wasn't something separated from the science disciplines.

PSH. I'm always amazed, and I still can't quite understand how, being based in a primary paediatric setting, how he managed actually to carry off this huge venture.

MP. He was a most remarkable man. You have probably heard stories, well you've spoken to him I think in the past. The circumstances during the war meant he was running the Evelina Children's hospital more or less single handed. Either during the war or just after and the stories were that, having done the operations in the morning and the ward round in the afternoon he would play cards until late at night and then carry on the next day. He slipped out and was missing for a whole afternoon and people didn't know where he was, and he had gone to do the membership. He was one of the brightest people I ever met and he was just a terrific clinician too. When we were medical students, he would have a Wednesday afternoon ward round on the paediatric wards and unfortunately he was a busy man and they were often cancelled and it would be a great disappointment. He would go and just see one or two selected cases. I remember congenital dislocation of the hip and he would examine the child and then he would discuss the theories relating to this. Relaxin I think he even talked about, and there's this interesting epidemiological evidence. You see again, in the Paediatric Research Unit he had Eva Alberman in there. He would draw on epidemiological evidence on a ward round and would talk about congenital hip dislocation in the same way as he would talk about molecules and genetic traits. So he was really very skilled at clinical science. I think he attracted a good group, quite a lot of Italians with special research interests.

PSH. Very, very good Italians.

MP. Exactly. Precisely. Francesco Giannelli and so on did great stuff. So it was a wonderful environment, and at the same time John Fraser Roberts was there and so I helped him do the last couple of editions of his book, and learnt the basics of how he did genetic counselling.

PSH. Before we move on to John Fraser Roberts there's one question which I've not resolved in my mind, is that compared with people like Cyril Clarke or Cedric Carter and some others, Paul Polani didn't actually train very many people who went into clinical genetics.

MP. No he didn't and I think, he very definitely believed in running a genetic service, and he set up this big south east region study and so on, which suited me fine. He thought people could train themselves really and to be honest, one of the appointments on the clinical side was a disaster really and I think that shook Paul. Paul was a bit detached from what was going on and I think didn't realise how bad things were until quite late on, indeed he called me and asked me to write a confidential report.Of course when Caroline Berry came

things improved. So that may have been a very critical and harmful period for that aspect of training clinical geneticists.

PSH. Because I have always felt that it is rather a shame that more clinical geneticists didn't have the chance to get exposed to Paul in their early years.

MP. I agree, I agree, he definitely believed in clinical genetic services but really thought that he had done that job by having John Fraser Roberts there. And John, I am I suppose one of the few who were trained by John Fraser Roberts. He was not in the business of training anybody really. He was already retired and was just trying to complete his follow-up as to whether genetic counselling made any difference to people's behaviour.

PSH. Tell me a bit about John Fraser Roberts because, am I right he started his career in Bristol?

MP. I don't quite know when he was in Bristol, but his career originally, and some of his research was in Edinburgh on sheep and I think the Witness Seminar mentions this work.

PSH. That's right. The badger faced sheep.

MP. Old badger face, as Haldane would call him, and those who knew John Fraser Roberts, knew he didn't like that type of joke. He had a good sense of humour but he was a fairly prim and proper type of person. And also the story of how he came to get the Colchester Clinic was very interesting.

PSH. I don't know that.

MP. Laurie Smith is the key person here and I am just quoting this person, but he was appointed as a technician when he was 16 or 17 in the Eastern Counties Hospital under Penrose, just when they were beginning to screen all their people with learning difficulties, urines for PKU. Then the war came and the superintendent of the Eastern Counties Hospital decided that Penrose had not played his part properly in the war and he physically, this is what Laurie Smith said, and I think that Laurie might still be alive, he physically barred his entrance to the hospital when he came back after the war. He was sent off without actually even collecting some of the things he wanted to collect, and Laurie Smith, who was still working in Eastern Counties Hospital which was right next door to the station, Laurie Smith would gather up sets of notes that Penrose was working on and sneak them out of the hospital into the waiting room of Colchester Station. Penrose would come down on the train and they would work on the notes and Laurie Smith would take them back. Now Laurie Smith rose to be head of the sort of technical side, technical head of the laboratory services, and one job he always hung onto was the looking after the genetic counselling clinic which was done there. So what happened was that when Penrose left, they found John Fraser Roberts who had an impeccable war record, to take over the clinic. So he took that over from Penrose really and I used to go down to Colchester, once every couple of months, once a month eventually, with John Fraser Roberts and then I took

over from him. And when Laurie Smith retired at 65, I was able to give him a retirement card that had a picture of Penrose signed by Shirley Hodgson, who is his daughter, a picture of John Fraser Roberts signed by John Fraser Roberts, (he was still alive then) and myself and him in the middle, having served all these people continually in terms of genetic counselling. Penrose did do counselling, Laurie made it quite clear. He did counsel families and people within the hospital to try and give them some sort of advice on the chance of it happening again.

PSH. So John Fraser Roberts was in Colchester then after the war

MP. No visiting Colchester, he already had, he did definitely have, as you rightly said, a link in Bristol, because he did his studies on severe and mild mental retardation there, and John Fraser Roberts I think was the first to show in a very formal way the interesting fact that, if you took severe mental retardation, there was relatively little family correlation, the parents were essentially normal distribution of IQ, whereas if you took the mild mental retardation you found the parents were down on the population mean.

PSH. When did he move to Great Ormond Street?

MP. As I understand it, he was at the London School of Hygiene and Tropical Medicine for some reason, after the war as well. I think that's where his base was, and then the first Dean of the Institute, before the Institute building was built, you know, when it was a sort of thing created after the war within Great Ormond Street, asked him to start doing a clinic at Great Ormond Street. So I'm afraid one would have to double check the dates, but I would have thought it was the late 40's that he would be doing a clinic at Great Ormond Street. Certainly in the early 50s anyway.

PSH. He must have been, well from what you say, he was in his 70s perhaps, 60s or 70s when you knew him.

MP. He then got the MRC unit of clinical genetic research, or some such title like that, I think in the mid '50s, and then that went through, Cedric Carter was one of his juniors and that went through to, I think it was '64 when he retired, so he might have been born – I will need to check on these dates – but it might have been about the turn of the century.

PSH. But you knew him when he was based with Paul Polani?

MP. Yes, so he retired from running the unit at the Institute but had kept on all the peripheral clinics. He didn't do anything at Great Ormond Street but he kept on his peripheral clinics.

PSH. What sort of person, I never properly met him. I sort of vaguely met him but. I didn't know him personally. What kind of person was he?

MP. Oh he was a wonderfully kind man, quietly spoken, would listen intently, but would be quite firm if he didn't believe what you were saying, or would

gently suggest that there might be a better explanation. For much of the time he would be in these conversations, taking a bit of snuff from his snuff box. He was married to Margaret, who was not his first wife. She was his secretary at the Institute of Child Health. His first wife was a comedienne. I have forgotten her name and I think he was somebody who was greatly troubled by family complications and those sort of emotional things. He was a person who bottled up his emotions. But he was very kind to the patients who came to see him. More so, he had more empathy in counselling I think than Cedric did, and it was only really when he became too old, that he didn't understand the common parlance and so on, I think he lost his rapport with the families who came to see him. He was very organised, he was almost slightly obsessional. Maybe at an older age you get a bit like that. But he would worry whether everything was organised for the clinic properly, had we got the notes. What he would always say was 'I qualified in medicine in order to be able to have genetic advice clinics' and so on 'and the day I qualified I hung up my stethoscope and never used it again and therefore I have always chosen to work in a tertiary centre,' he didn't use that phrase, but in a hospital that had good clinical support.

PSH. So he didn't try to make diagnoses off his own bat?

MP. No he didn't try and make diagnoses at all. He would always seek advice. He was pretty good at knowing who he should get a diagnostic opinion from, but he was purely concerned with the empirical recurrence risk. And of course he had run the MRC unit researching a lot of the basic early empirical recurrence risk figures, the sort of thing that Cedric carried on and so he would use these in counselling.

PSH. When was it you kind of took on, initially with him, his book?

MP. I think it was probably the sixth or seventh edition of it. It would have been in the 70s.

PSH. While you were still at Guy's?

MP. Oh yes, it was really only while I was still at Guy's. It had become really out of date, it hadn't got any molecular genetics in it. Paul Polani had helped with the cytogenetics side and Phillip Benson with the metabolic side, but I came in and fortunately, I was able to use the haemoglobinopathies to demonstrate the various principles. But it was always very practically based. We used to have lots of meetings about revisions and so on and it was all done at a very gentlemanly pace, there's no question, which suited me fine, and he was always very kind and said, two co-authors couldn't think more alike. We always seemed to agree. And I think the only point he disagreed with me was when I was trying to judge some phrases about the ethical aspects of prenatal diagnosis and I used the word 'solution', not 'final solution' but I used the word sort of, let's say, 'temporary solution' or . . . and he said no no we shouldn't use the word solution (with its Nazi eugenic connotations) in relation to these things. I remember him defending Cyril Burt and saying that a lot of what Cyril Burt had done was perfectly valid and so

on, he was a respectable man, I can't really believe that he made up all this data; and he was very upset and angry with the young journalist who made his name exposing Cyril Burt's stuff. So he thought the best of everybody and he was just a slightly old fashioned gentleman in that sense.

PSH. When was it then you developed links with Cedric Carter. Was it before you went to work at Great Ormond Street?

MP. Not greatly, no. What happened was, I had done my elective there and then when I was in Liverpool the Clinical Genetics Society was created of course, in 1970 I think it was, and so Sarah Bundey who was at Great Ormond Street then and Cedric, we would meet at meetings, I knew him and continued to go to meetings of the Eugenics Society. So I knew Cedric from meetings basically. There were occasionally cross referrals between Guy's and Great Ormond Street for various things. Really the main contact was when they were getting the Mothercare money together through a fund raising effort and Mothercare gave a lot of money which they decided to put it into genetics and they created this post. He rang me up you know one day and said, if we were to create a post would you be interested, and I said I probably would. It was the final period of me being involved in junior hospital doctor politics. I was at St Thomas's in 1972. That's right, perhaps I had gone to him about advice and he told me to buckle down and do some more research or something; anyway the day after I had been on the front page of the Times leading a march to the General Medical Council, and he contacted me again and said he didn't think that was a very sensible thing to do and I said don't worry I'm getting back to it, I won't be doing much more politics. So he was clearly slightly nervous about that side of my life. Another example of Cedric's nervousness in that respect was when I did get the job there. The first week he said, now we must go to the hospital, to the consultants' dining room to meet everybody in the hospital because it was an important part and I said, absolutely, and next day I said how about it, and he said -tomorrow. Then the next day it was tomorrow again you see and on the fourth day I said well look its Friday, if we don't go now and I don't want to leave it otherwise it gets embarrassing, new appointee, and he took me aside and said "I think you should wear a suit." I was wearing a tie, a jacket, a smart sports jacket. So from that moment on I always wore a suit. From then on it didn't matter to me at all what I wore, only it upset Cedric if I didn't wear a suit. So I wore a suit. We then went over.

So Cedric was particularly nervous, more so than, I mean Paul was not like that and even John Fraser Roberts was much more relaxed. Cedric had this concern for some reason. So really it was I knew Cedric and he knew I was getting a training of sorts. I think the only other interesting point in that period of my history was that Cyril Clarke became President of the Royal College of Physicians and we used to, Heather and I used to go to dinners occasionally. I remember one occasion there had been a lot of publicity from my junior hospital doctors activity. He would say 'Marcus, come and sit right next to me. That will shock them.' And he rang me up, he told me 'look you had better get organised with accreditation' he said. He didn't really believe in accreditation but he knew it had to come, so he was supportive. He said write

to me and get accredited. He said well you can get accredited in General Medicine, because I had enough of that. Get accredited in clinical genetics as well. And I said how do I do that? He said "just send me the stuff ". So I sent what I had done, and I was told I was accredited for both, so I started putting it on my CV. And two or three years later, it was definitely not just months, it was years later I was rung up by the college and they said "we are looking into accreditation for medical genetics and much to our surprise, you are already accredited in medical genetics. Could you tell us what your career was?" you see. 'Perhaps we could use that as a starting point.' So this was obviously a back-door accreditation through Cedric, not back-door but he just started the ball rolling. So I was the first accredited clinical geneticist, for about three years, the only one. And all the other people had grandfather clauses which meant they didn't have to get accreditation.

PSH. I don't remember ever being accredited.

MP. There you are. I have one up on you.

PSH. I don't think so. But that's interesting. Particularly at Great Ormond Street, there was the formation of the Clinical Genetics Society and then it must have been four or five years after that that training posts and such like started to evolve.

MP. They did. Cedric was very important in this. I have a lot of time for Cedric, and a lot of this is in his obituary I wrote when he died. He was the first of the advisors to the Chief Medical Officer, in Medical Genetics, and there was a little book with a green cover with some very crude chromosomes on it produced by the Department of Health in the 70s. I remember him coming in with real enthusiasm about recognition of clinical genetics as a specialty, I think it was in 1980. It was in the overlap period between when I went to Great Ormond Street and he retired, which was a 3 year overlap period.

PSH. You went in about '79.

MP. I went in '79 and he retired in '82, so it was about that time he came in really excited because for the first time there was clinical genetics or medical genetics on this listing of people in training, in the manpower statistics.

PSH. That's a really important landmark.

MP. It was and he saw the importance of that. He had really wound down his research and saw that as an important contribution.

PSH. Can you remind me, was that accreditation initially as a sub-specialty of paediatrics.

MP. It was. I think that's the way it was organised. They didn't quite know where to put it at the time they started accreditation.

PSH. That's how I remember it.

MP. Yes I think you are right.

PSH. I have always found Cedric quite an enigma in a way. He was a very sort of quiet person.

MP. Ah yes.

PSH. What did you make of him as a person?

MP. I think Cedric was, it's difficult to know what it was that held him back from opening up. He was a very private person. I think Kath Evans, the family counsellor, was probably the only person who ever knew him well, of the group there. He was very keen on having a formal tea in the afternoon and they were very good sessions, we would chat. I think he was never actually very comfortable doing his clinic. They would prepare, look at the notes beforehand and so on. That tradition was established by then. If the family, the mother started crying, something like that, he just didn't know where to look. He found that aspect difficult. So I think that he sort of retreated a bit into just giving the statistics. But he was very concerned by the follow-up results that people were treating what he regarded as low risk as high, they were too frightened by it. He actually tried to counter that a bit and, although it was John Fraser Roberts who introduced the idea of a yardstick of what was the normal risk, the current prevalence of an error of development that would be visible at birth or soon after, a 3 per cent figure, Cedric actually had a bit of a campaign to alter his counselling slightly, so that he would play down the smaller risk and say look this is really a small risk, you should be reassured by this. Because I think he felt badly about people reducing the size of their families or withholding having children because of genetic risk. I think he was a bit tied up in this sort of eugenic bit, not in a very extreme way. But he said, with the contraceptive pill, if that is taken up selectively by the brighter population, then we could be in for trouble. And he did have a very curious, odd way of behaving where his children were concerned. I mean I remember him once introducing one of his sons who came up, by his IQ. He said "This is my son. His IQ is" . My heart went out to this, he wasn't a boy, he was probably a young man in his twenties. Cedric was also very proud of the fact that he won the boxing thing in the Army. He was a very bright guy but this reservation didn't allow the discussion of what we did and didn't know and what our competencies were. So Sarah Bundey did her classic study. I don't know whether she'd left by then, when she sent around these calculations to everybody.

PSH. I remember them well.

MP. I was still at Guy's so that's right, she might have still been at ICH, I guess it was '78 when she sent those around. So I tried them at Guy's, but I didn't get them right, because we hadn't got into any of this. When I arrived Joan Slack was in the department, and remained. She was convinced that because she was a woman, Cedric would not tolerate her being a consultant.

PSH. Do you think that she was right?

MP. I don't know whether it was because she was a woman, that was her interpretation. That's what she said. It may be that he was worried what she might say, but when she did do some genetic counselling, he insisted right up until I and Michael Baraitser arrived, that she had to show him her clinic letters. He wouldn't allow her to practice independently. Even on the things she knew about, you know the lipid stuff. Joan Slack of course was pretty good on the statistical side. She could think these things through and I sat down with Michael and Joan Slack when pedigree calculations came up, I thought I was going to own up straight away. I said, look, I don't know how to do this really. Michael said, well I don't know how to do it, but there's a young chap who is working with me called Robin Winter who knows how to do it. And Joan said, well I've had a go at it but I don't know. I said well look, lets just make it a rule from now on every pedigree we will do it, right there in front of everybody. We'll work it out. We've got to learn, we've got to get our heads around this. So it was completely open. It was the first change that happened. So when Cedric came in, it was the overlap period, we said "Cedric can you help us on this? We've decided the three of us are going to really get this sorted. And we assumed that he could do this because he gave that indication. He said oh no, this
needs a wet towel round my head. So there had been a lot of pretence, really I think about this. And I couldn't get my head around the μ method, as we called it. I thought it was absolute nonsense to put in μ and then cross it all out again in the calculations that Robin Winter was telling us how to do. And I was home with flu one day, stuck in bed and I worked out another method, which didn't last very long but got into the last edition of the textbook for doing simple pedigrees. It was extremely fast. For most of the pedigrees we saw, especially the X-linked ones, Duchenne and so on, people at the Tuesday meeting which is when these thing would happen, they would do it either by my method or the μ method. If we both got the same answer we could be pretty certain we were doing it OK. And much to my amazement, when Andrew Wilkie came to work with us temporarily, he didn't know about the μ method. He had read my textbook and taken on my method and advanced it rather considerably. He could do much more complicated things through my method, and even Robin Winter in the end agreed that for simple pedigrees these two methods could be used. But I only tell that story to illustrate the way the atmosphere changed. There was no opportunity to admit what you didn't know in Cedric's regime. I know that sounds harsh, but I think it was the style. There was quite a lot of style attached to that approach, although I must say, Paul Polani wasn't like that.

PSH. What do you think Cedric's greatest contributions were?

MP. I think Cedric's greatest contribution was to keep the empirical recurrence risk studies going. I think that John Fraser Roberts was the real leader in this, and of course Penrose, but more John Fraser Roberts I think in terms of the MRC unit, that's what they did to just get empirical raw data and recurrence risk. What else are you going to use until you've understood it.

PSH. Nobody's done anything like it since.

MP. And Cedric took that to heart, and there were a very large number of studies he did, and occasionally, like with the pyloric stenosis, he would then try and start formalising models and so on. But I remember Cedric advising me. He said "Look, don't worry about all these models so much The key thing is to get the data. You've just got to get the empirical data and what's more you've got to publish the empirical data and he insisted on that. There was this tradition of putting these appendices in with all the raw data. It was sad that there was that unfortunate period in publication, between journals getting overcrowded and therefore these appendices not being printed, and the arrival of the electronic journals, where of course the supplementary information allows them to be printed again. I don't know that they always are printed in supplementary data, but there's no excuse now not to put the empirical raw data in, although I suppose nowadays some people might worry about confidentiality if there were certain pedigrees, I don't know. That I think was his greatest contribution scientifically and he understood these things well. He did good studies. Kath Evans was terrific and Becky Coffey, who stayed on with us. There were some good family visitors who collected this information. He was fairly obsessional, so the stuff was very well documented. He then saw the importance of training and trying to get clinical genetic services recognised. With regard to the dysmorphology side, Michael Baraitser was already doing the odd clinics at Great Ormond Street in Cedric's time, not full-time though. Dysmorphology, he was very interested in this but he never really quite got it together. I think it was partly because there was a well-known radiologist, Sutcliffe, I think his name was, who again had amazing knowledge of all these syndromes, but again it was just in his head or in a few books and articles. Cedric was pretty keen on the case report you know, and I know, I only met a neurologist with an interest in spinal things, for personal reasons, a couple of weeks ago who said "Oh Cedric. I wrote a paper with him in the 70s on some family who had some rare spinal problem. So he did dysmorphology. You might say well anybody, you'd be very foolish not to start doing dysmorphology there, but I think his main contribution was clearly to keep going with these family studies for complex diseases.

PSH. What year was it that you took over from Cedric?

MP. 1979 I arrived, and we worked in parallel, officially, together for a 3 year overlap. Part of the handover was to give me some MRC money to finish some of the studies that the staff were doing and to initiate one or two more. With regard to the clinic, Michael Baraitser was appointed. Cedric had worked hard with the region to create a new post, which came through in 1980 and Michael Baraitser got that post and as soon as Michael arrived, we decided that Cedric should stop doing the clinics, because we were getting into a slightly silly situation. This was the formality. He would say well, if the letter is addressed to me then I should see them. And we would say well they are likely to be addressed to you. We haven't even informed people of the change over. So eventually he said well, Michael, perhaps you would see this patient. It's a difficult one, and we could see him getting more and more

nervous about the clinic situation, and it is clear as a bell in my memory, the day. We said who's going to tell him and Michael said I'll tell him, and he said, look Cedric, I think you should stop doing the clinic. We have got Joan Slack, Marcus and me here and things are getting more technical, and more things to do and the counselling clinic list is getting longer. He found that quite difficult. I think he was relieved in the end. So the clinical side moved over. I think in the last year, he didn't see any patients but would be finishing off some of studies. And then the sad thing of course was that he decided in his retirement he would keep fit, and he ran this half marathon and whether it was to do with it or not, I rather suspect it was, he was unwell during the night, felt particularly unwell in the morning and died from a coronary. So he never had a retirement. He had said of his retirement, which surprised me immensely it would be quite a relief to be retired because then I could follow my interest in various things in the Eugenics Society. He felt while he had an MRC hat he shouldn't wear that hat. He was conscious of the anxieties that some people had about some of the Eugenics Society history really, not what they were currently doing, but he also said I will then be able to relax and read Nature and things like that. So it's almost that he held back his curiosity in various directions just to keep going with the studies he had started to do .

PSH One of the things which I have not been able to get clear on is what happened to archives and correspondence or anything like that? Have they been kept?

MP. I think there's some stuff there at Great Ormond Street, but they moved fairly recently and I flagged up things that I think ought to be kept. It's difficult to know what to keep really. The old notes with all the clinical letters and everything, they are all there still, you know, no old notes have been thrown away. But with regard to the research side of things, the little cards on which information was collected, there are some sets of those and it just struck me that a set or two of those, captures the way they did things, and I think I've got a few letters from him.

PSH. Coming on Marcus just now to your own contributions at the Institute. The year again? 1983 or thereabouts?

MP. I had got really established by 1982 there. By 1980, by the time I had been a year, I was sort of operating independently really. I was a senior lecturer from when I was appointed and, technically when Cedric retired, they stopped the department, and I was incorporated into Growth and Development, which was Jim Tanner's department. Jim Tanner was absolutely marvellous and just said, go ahead and I won't interfere. He was just formally in there. The only period when I had any little disagreement with Jim Tanner was that Robin and I had been working on haemophilia. As you know we did mapping of haemophilia very early on with the DX 13 probe, and a lot of haemophilia bloods came through. Robin Weiss, the virus guy from the ICR came and gave us a talk about this HIV stuff in the early eighties, and as I listened to all this I started thinking, bloody hell, you know. We've got all these haemophilia bloods we've been handling so I grabbed him after the lecture and said come up and have a look at what we're doing because we

were all squeezed into a corridor. And he said “no no, you have to have a sample preparation lab which is separate from this, and once you have extracted the DNA, or once you’ve done whatever you do, then it’s going to be alright, but you have to do that’’. And the only room available on the corridor was a waiting room of Jim Tanner’s. This was for the rare families that used to come and see him, young girls used to come for height predictions, whether they were going to be ballerinas or not, whether they would be too tall. And this waiting room was used sort of like two hours a week and he was away on holiday. I slept on it and realised there can be no contest, so by the time he came back from holiday this precious waiting room of his was turned into a blood reception and so on. I had a good story of course. He was not pleased. He said you could have waited two weeks. I said my conscience couldn’t wait two weeks.

Then when Jim Tanner retired, I think I was a department on my own. We moved into the Cardiac block and then rather late on, June Lloyd had arrived at the Institute and with Charles Scriver they had asked me to write a thing on the new genetics. I had got quite well known for my Lego demonstrations and explaining these things simply, the RFLPs, which of course modern people don’t know anything about, and as I understand it, June Lloyd said, shouldn’t we do something about Marcus’s career. I must say I’m not that sort of person, all I wanted was the freedom to get on and do what I was doing. I was having a great time, interacting well with Robin, and Michael was there and so apparently she organised for me to be put up for a chair, so I never was a Reader. I was an overlooked senior lecturer, and I think it was ’86 I became a Professor I think. So I had been leading the Department.

I suppose the two early things were critical. When I first started, I planned to do a little bit on Mary Seller type of stuff, congenital malformations. It seemed sensible at the time at Great Ormond Street, and neural tube side of things, you know, folic acid and the trial that was on at the time, we might take part in that in our region. But then Selim Zilkha who was the head of Mothercare who had given the money for my post and unit, came to visit. The Dean, Alistair Dudgeon, took me aside and said look you’ve got to speak very simply about these things. Make sure, you can’t just go on about your research, keep it very straightforward. Selim Zilkha came in and the first thing he said was “I’ve just come from the Salk Institute and they are telling me about this DNA and genetic engineering and how they have created a company. Its just ideas based on DNA, Genentech I think it’s called”, so forth and so on. And I said yes, well we are going to get into the DNA side. Haemoglobinopathies was leading the way, that was my training. In the middle of the discussion with Selim Zilkha which was just over coffee, I completely re-wrote my programme, with the Dean and the Secretary wondering what I was talking about. The Secretary missed the big trick when Zilkha said well you know, what do you need to get this thing off the ground? I turned to the secretary and instead of saying I think £300,000 will do us nicely, the Secretary said “well I will put a budget together” and the moment was lost.

So Selim Zilkha as much as anybody made me persuade myself that well, look, I have had this training in haemoglobinopathy, we should start using

DNA in relation to other things. I had been interested in Fragile X as a cytogenetic phenomenon from the year I left Guys and had said to Bob Williamson, if you can actually see it down the microscope, at the DNA level is going to be blindingly obvious, so let's do a study on Fragile X. Kay had just got her X Library and DX13 was the probe. Presumably it was the 13th probe she pulled out of her DX whatever, or something like that, and we started on Fragile X, collecting Fragile X families. Someone who had been involved in haemoglobinopathies in Saudi Arabia, Kathy Harper, I got on a grant. I got a quick Action Research grant I think, to get all the initial work off the ground. Went to Bob's lab. I thought I'd better try and do a bit of this stuff. I had done quite a bit of laboratory work and all I remember is my gel wouldn't set and realised I hadn't put agarose in it Anyway I had sort of learned enough to take a formal interest in the lab side, and we started a little lab at the ICH with John Cowell, who had come in to look at cancer molecular genetics. When we weren't getting very far with Fragile X linkage, I wasn't into the formal statistics at that time; I did it all terribly long hand, sort of early in the morning at home, trying to work out what were recombinations and what weren't. Robin Winter said, I have been interested in collecting haemophilia families because I wanted to look at this mutation. He was interested in the mutation rate between males and females and was using haemophilia families to study it. It's nearby, lets see if it's linked. It was, very strongly linked, so we went in terribly fast into clinical practice after that. One might have been a bit more cautious now. That happened the same year, 1984, as I'd then thought we were getting nowhere with Fragile X and suddenly realised that the offspring of normal transmitting males in the pedigrees might give us a clue to things. I remember, I got someone else to do my clinic, stayed in the library and pulled out all these normal transmitting males pedigrees, plus a couple of pedigrees I knew of that weren't published and totted up 149 daughters of normal transmitting males and there was only one of them that was mentally retarded. I thought, wowee, this can't be ordinary genetics. So that was a bit of a purple period. We came to the Clinical Genetics Society meeting and Kathy Harper presented the linkage for haemophilia, which we were already using in clinical practice, because we had been doing prenatals for haemophilia with Charles Rodeck doing fetosocopy and blood sample measurements and so on. So now we used the haemophilia probe. Then the Fragile X hypothesis which, as you know, I like to have a slightly off beam hypothesis on the brew at any time and that was 1984, so it really was a sort of a golden year. Robin of course was involved in all these sort of things, and it was quite clear that Robin was destined to come to ICH if only we could organise the funding, and that was eventually done.

PSH. Because you and Robin were the first to put forward really a pre-mutation hypothesis quite well before Stephanie Sherman put anything forward.

MP. Yes I think there's a paradox. Her paradox was just that. It was a paradox but they were still thinking in formal genetics and Newton was saying the mutation rate must be phenomenally high. No, our's was a good idea and it's an interesting publication actually. We sent it off to Nature initially, and they didn't like, we put in one pedigree with some linkage stuff that we thought

might support it. It was sort of over-icing the cake a bit and they were right to say that that bit really didn't add very much, and anyway that was rejected and eventually we sent it off to John Opitz' Journal and he sat on it for about a year, you know. It didn't worry me too much but Robin was more irritated , "this is ridiculous you know. And now Stephanie Sherman was talking about a paradox and so forth and so on. We really should chase this." So I chased John Opitz and he rather remarkably said, well we will publish it but very slightly revised. I didn't even know what the revision was. I've got the two manuscripts, one I sent and one how it appeared. It appeared just before the Dunk Island conference on Fragile X, with this one page apology. Very rare for a paper to be published with an apology, this from John Opitz saying well, of course we had all thought of pre-mutations in other sorts of things, and it seemed a good idea but the referee really didn't think the data was valid. Then Opitz thought he would give it, at my prompting, to another referee, who I think was Randy Hagerman's husband actually, who thought it was really a rather good idea. Opitz says a phrase like 'maybe there is a place for publishing armchair speculation' which of course would eventually be shown to be right or wrong, which I thought was a bit unfair since there was good pedigree data there. I had drawn attention to the fact that the daughters of transmitting males weren't mentally retarded. When I looked back at the paper, and I've only done that recently, I realised that he had inserted an extra line in the introduction about John Opitz' own speculations on pre-mutations in achondroplasia or something.

That was exciting and then the Dunk Island conference was very interesting because Robin and I had by then written a slightly tetchy, I admit, letter to Human Genetics I think it was, in response to Stephanie Sherman's paper, saying we've drawn attention to this. Obviously our CGS meeting abstract had been published in J Med Genet the year before, and on Dunk Island Pat Jacobs, right at the beginning, she announced, as she can, well I think we should keep all hypotheses and speculation until the end and just go through all the data. And we did. It was a wonderful small conference. Beautiful setting of course. We went through all the data. I did hear Dr Ted Brown, saying, looking at a poster of mine and not knowing I was behind him, "This Pembrey guy, he doesn't generate any data. He just takes other people's data and re-analyses it'. And I think psychologically that might have been why I got involved with ALSPAC. No one can ever accuse me of not generating data. Anyway, the conference finished and we had discussions about mechanisms and pre-mutations were raised and John Opitz drew attention to this important paper, ours, that came out the same month. And we were finishing the conference dinner at the end and Gillian Turner was sitting at the end and I was sitting next to Pat Jacobs and there was a terrific noise going on with everyone drinking and chatting away and then Pat turned to me and said "Why did you write that silly letter in Human Genetics?" "I don't think it was a silly letter at all. It was just drawing attention that we'd prior claim in a sense", and the whole room stopped. You could hear a pin drop and we thought, oh dear, are we going to fight or not. I said, well you know how it is when it's a pet idea, you want to hang on to it.

PSH. But it was important Marcus.

MP. It was important. I knew it was important at the time and it was great.

PSH. It actually had a lot of influence on me in terms of looking across to anticipation and myotonic dystrophy, and I think it influenced Grant Sutherland as well.

MP. I think that Sarah Bundey wrote to me and I've still got the letters about some curious phenomenon in myotonic dystrophy, tied in with some phenomenon in Drosophila or mice or something. Anyway you might be interested to see that. And those things followed that hypothesis. The point was it was a hypothesis that was not too far away from being technically possible to look at. That was the key thing. We were wrong I think, I'm not sure that anyone completely knows how the expansion goes . . . We were wrong in assuming that it was recombination that moved it on. I think there is a recombination element to the progression but its not the main mechanism.

PSH. But you were right in the sense that it was a genuine biological mechanism.

MP. Yes exactly, and I think the thing that people said, well mutations are stable things you know. This idea that DNA changed from one generation to the next . . .

PSH. People wouldn't have it.

MP. They wouldn't have it. Of course I've dined out a bit on that. With respect to my transgenerational studies now I think I get away with proposing these things a little bit, because I was so on the ball with regard to Fragile X.

PSH. Marcus we must finish soon and I think ALSPAC and the Bristol cohort, I think we should maybe leave to a future time. There are two things I have been asking everybody. The first is, which person or people do you feel had the most influence on your work career in genetics, particularly in the early stages?

MP. The early stages, Cyril Clarke had a very strong influence, purely because of the faith that he put in me, as it were, to say, you know, it may seem a bit of a knock down to say go and get membership, but to ring you up and give you a job, so that was good. And David Weatherall taught me what one of my aunts always used to say, that my enthusiasm will overrun and I'll have the long trudge home, very often. So the meticulousness of, and I say it partly as a gentle criticism but it's actually very important, this incremental science of making sure that one step is solid before you progress to the next. Paul Polani really had a huge influence in his saying that you can't really think about genetics without thinking broadly about the different basic science disciplines. And I think John Fraser Roberts, not only from the way he wrote his book, which was a very good way of learning genetics at an early stage, I have always felt very secure in arguing from first principles, which I think came from his training. It put me in good stead with all these population

geneticists and some of the large scale genomics people, who don't always think from genetic first principles. So in the early stages those were the key people. Later, but I was still reasonably young when I went to Great Ormond Street, Robin and Michael taught me an enormous amount.

PSH. And then the last question. Can you identify one bit of your work which you feel particularly fond of, proud of, that stands out from the rest?

MP. Well, this is a difficult one. The Fragile X was an idea but not too much data. We had one linkage paper and that was about it. I think this transgenerational phenomenon which came out of my interest in imprinting. So if I am allowed to lump two things together, the very deliberate decision to study Angelman's syndrome and the imprinting phenomenon rather than Rett syndrome, which could have been just as interesting. We actually made the decision at Great Ormond Street, we had the ability to get two large collections there. We plumped for Angelman's syndrome and imprinting and that led on to the transgenerational view. I think that's the body of work that I'm most proud of.

PSH. I ought really to have let you go on to the Angelman work before drawing things to a close, so maybe you should tell me just a little bit about how that originated.

MP. I think it originated really in that Great Ormond Street was very good at defining syndromes, whether they be purely dysmorphological or a neurological combination, and so we were confident in defining Angelman syndrome. We knew what it was, even when the American community, principally, were rather doubtful if there was such a syndrome, and basically we decided to look at the genetics because I had declared, from when I arrived at Great Ormond Street, that my primary research interest was going to be in those families where clearly it was running in the family but the genetics was not standard Mendelian. This was a deliberate decision. Angelman fitted into it and, partly because Paul Polani had seen a family where there were three children with Angelman syndrome and he had even organised to look at the chromosomes, because he was convinced there would be a small translocation on chromosomes and it wasn't found. So I knew what Angelman was, still, nobody really knew what the mechanism was, and we saw this small deletion reported from standard cytogenetics. When I explored this a bit further, Pat Jacobs said 'Oh no, we've looked at that. This is all part of the normal variation'. Then somebody in Manchester, Maurice Super, had a similar deletion so we published those, no we didn't publish then. We looked at 12 Angelmans that we had and saw cytogenetic deletions, so it was deliberately chosen because of the unusual inheritance, we thought chromosome abnormality might be the first cause. We thought microdeletions might explain it. So we got on with that. Pat Jacobs, it turned out that her one extreme case which was at the end of the spectrum she said they normally saw in all types of referrals, was a case of Angelman syndrome, so it warned me to not pay too much attention when Pat said no, no. And then the thing that really bugged me was when we were beginning to think of mechanisms. I was still a bit hung up on unequal crossing over and I had a

model, which got published at the time of the deletions (1989), that we might have unequal crossing over, you know a bit like the alpha globin gene. But it didn't really fit too well. We were beginning to get onto parent of origin effects and then the guy from the States, Rob Nicholls published the translocation heterodisomy with Prader Willi. I remember, I would read Nature on a Saturday morning when I was working and then I would go and dig my garden. I was pacing up and down my garden saying "bugger this." So I came in Monday morning and said "Right, uniparental disomy, this is what we've got to go for and Sue Malcolm with help from Armour in Jeffreys' lab got a probe a long way away on the 15 chromosome and fortunately we had enough cases to run through. This is the thing with Great Ormond Street and we picked up these couple of paternal uniparental disomies which were published in 1991

PSH. You realised at that stage it was likely to be with imprinting.

MP. Tuesday morning meetings were always rather important, but became big events. Visitors liked them very much and we looked forward to these. We'd go from the clinical, from patients to the journal club and it was always my choice to have Nature to look at and so on. And when Bruce Cattanach's paper came out in '86/'87, '86 I think. I remember Robin saying now this is really important. We don't know really what it means. So we knew about parent of origin affects, and of course myotonic dystrophy and Huntington's, sort of hints of parent of origin effects and other things like that. So that then led onto the imprinting side of things and thinking about epigenetics, and then I suppose Judy Hall's invitation to do the last slot of the imprinting section of the 1994 Florence meeting on Imprinting and Dysmorphology. Imprinting was two thirds of the conference and I had the last slot. She said just speculate on what you think, why humans have still got imprinting and that is when I formulated the idea of epigenetic inheritance being a transgenerational adaptation. So that was a clear step from Angelman syndrome to transgenerational responses, and of course it was very nice, all along, to provide proper genetic advice and prenatal diagnosis for the families.

PSH. Marcus, thanks very much. I've worn you out I'm afraid. I think let's conclude there. Thanks very much.

**End of recording.**