

VIDEO INTERVIEW TRANSCRIPT

## Pembrey, Marcus: transcript of a video interview (05-Feb-2016)

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## Pembrey, Marcus: transcript of a video interview (05-Feb-2016)\*

**Biography:** Professor Marcus Pembrey MD FRCP FRCOG FRCPCH FMedSci (b. 1943) is Emeritus Professor of Paediatric Genetics at the Institute of Child Health, University College London and Visiting Professor of Paediatric Genetics at the University of Bristol. He graduated from Guy's Hospital in 1966 with an interest in paediatrics and medical genetics, then studied benign sickle cell disease in eastern Saudi Arabia while training in clinical genetics with Paul Polani at Guy's. In 1979 he was appointed Head of the new Mothercare Unit of Paediatric Genetics at the Institute of Child Health and Honorary Consultant in Clinical Genetics at Great Ormond Street Hospital for Children. Here he helped develop clinical DNA analysis services, contributing to the Department of Health's Special Medical Development on this. His research focused on irregular inheritance, initially fragile X syndrome and then Angelman syndrome and genomic imprinting. This led to his current interest in transgenerational responses to early life exposures. He helped Jean Golding launch the Avon Longitudinal Study of Parents and Children (ALSPAC) in Bristol, being Director of Genetics within ALSPAC from 1989 to 2005. He was Adviser in Genetics to the Chief Medical Officer UK (1989-1998) and President of the European Society of Human Genetics (1994-1995).

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### [1]. HOW AND WHY DID YOU BECOME A CLINICAL GENETICIST?

Well, how did I get into clinical genetics? Well, as a medical student I didn't want to go straight from second MB into the wards and I persuaded eventually somebody to let me do a BSc where there was some genetics, because I'd always been sort of vaguely interested in genetics. And at the same time I discovered that I had beta-thalassaemia trait, which is a bit unusual for apparently endogenous English family and we were a big family. So I did a little research as a medical student on beta-thalassaemia. So I got into that type of genetics. And then of course one did a secondment as a clinical student and I went to Great Ormond Street [Hospital] to see how they did genetics there, with Cedric Carter, and of course we had Paul Polani who would do the occasional ward round, which were absolutely inspiring. And so I suppose all those things, I ended up qualified wondering whether to do paediatrics or clinical genetics. But there wasn't really much on the clinical genetics side then. You know there wasn't a discipline. I mean John Fraser Roberts had just come over from Great Ormond Street to Guy's [Hospital] as well, so I knew there were people doing what I regard as clinical genetics. Anyway, it was quite straightforward: when I was a houseman I saw an advert for a job, SHO [Senior House Officer] job in Liverpool with Cyril Clarke as one of the people. So I contacted Cyril Clarke because I had read his book and knew about his book and he said, 'No, no, don't come to that, don't apply for that job. Meet me at the College.' So I met him in the College and he said, 'Yes, well that's great. Become a medical geneticist,' he didn't use the words 'clinical geneticist', and said, 'Get back in contact when you've got the Membership,' which since I'd only just qualified...

But in fact he rang me up. I got the news on a Saturday morning and by Saturday evening he rang me up and said, 'Come to Liverpool.' And of course because of the beta-thalassaemia I linked up with Professor David Weatherall who was there, because I had this idea that if I switched on foetal haemoglobin it would cure - it wasn't my idea, I'd heard [Professor Phaedon] Fessas say it. But I was enamoured by the idea of switching on foetal haemoglobin and curing sickle cell disease and thalassaemia.

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\* Interview conducted by Professor Tilli Tansey, for the History of Modern Biomedicine Research Group, 05 February 2016, in the School of History, Queen Mary University of London. Transcribed by Mrs Debra Gee, and edited by Professor Tilli Tansey and Dr Apostolos Zarros.

**[2]. DNA ANALYSIS**

Well, thinking back about my career, about the greatest achievements, as you call it, or what I was most pleased about, I can think of it in two different ways. The first thing is sort of what I might call 'timely impact', where I think I did move, through collaboration with lots of other people, things forward at the appropriate time, perhaps a bit quicker than they would have. And the first of those is the introduction of DNA analysis as an adjunct to clinical genetics. I mean this was an area where the fact that I'd been involved in haemoglobinopathies gave me a bit of an advantage, because that was where DNA analysis really first started and so on, in terms of actually determining mutations and so on. So we were able to hit the deck running at Great Ormond Street and then there was the, and we got the first clinical probe for haemophilia A, a probe that Kay Davies had got from X library. And we started using that long before we had any organised service side of things at all really. And people from Europe sent blood samples and we just got on with it really. And it was great to see the sisters of boys with haemophilia A go from sort of where 'you may be a carrier but probably not,' to 'well, no, you are not a carrier, you know.' And that brought out the element of clinical genetics which I think people have sometimes overlooked, that we give a lot of good news when we have very precise tests.

So, and then of course we were part, asked to be part of the Special Medical Development, which I think the Department of Health were really far forward looking in this respect, and they got Cardiff, Manchester and us at Great Ormond Street, and with David Weatherall doing the haemoglobinopathies, to do a three year project to see how it would work. And, remarkably, people were mapping genes very quickly and we were able to at least use markers close to where the genes are mapped for a process I used to call 'gene tracking'; it was a phrase I introduced to determine from the pedigree whether someone was a carrier or not depended on which markers they got. So that, I think, I was very proud of because it took off in this country quicker than anywhere else, and it had been properly evaluated by the Department of Health. It amused us that the evaluating team from St Thomas' [Hospital] got much more money than us who had actually done the pilot.

**[3]. ALSPAC**

Yes and the other, what I might call 'timely impact', was helping Jean Golding set up the ALSPAC study, that's the Avon Longitudinal Study of Parents and Children. When we first started in 1988, planning it and so on, well, Jean started before that but I joined, it was the, we were the first to build in from day one, genetics and cell lines. We were applying for cell lines but we didn't get those for another, I don't know, 10 years, but none the less we got the cell lines. Because the idea was to have living genomes. So we had living cells in our cell lines, which we could use eventually, and that, I think, is gradually just beginning to show that you can use them for studies. But the other thing is that at the time there was a general feeling that case controls, often in adults, were by far the most efficient, and that we had Biobank and all these things basically, okay, a bit of following, but I never bought that and nor did Jean. We always needed to have a developmental perspective being from conception onwards really. And that has gradually come back in recognition that that is the approach. And epigenetics operates in terms of foetal plasticity and development and, but that, I think, has been the big change in the right direction over my career, that we've gone from. It started of course with the '58 cohort, when I was leaving school at '60, 1960, so but then it went into case, genome-wide association studies are a good example of something which has had a lot of hype and is going to help a bit but only, it's not the whole story at all.

**[4]. ANGELMAN SYNDROME**

In terms of my own research, when I went to Great Ormond Street in 1979, I decided to concentrate on non-Mendelian inheritance, you know, monogenic but non-Mendelian, because it was quite clear that eventually we were going to get sorted with Mendelian disorders with gene mapping. For example, as I have mentioned, we had the first link probe for haemophilia in 1984, and that was going to carry on clearly. So I concentrated on non-Mendelian inheritance. The first was fragile X, which was very strange inheritance of

it, and I was the first to propose a premutation explaining the bizarre inheritance of fragile X in 1985. And then, very quickly after that we were trying to work out the inheritance of Angelman syndrome.

So very soon after the fragile X side of things we got interested in Angelman syndrome. This was a syndrome that had not really been recognised in the States, people weren't quite sure what it was, whereas at Great Ormond Street we were very clear with the neurophysiology and everything else of this as being a discreet syndrome with lack of speech and some learning difficulties and a jerky gait. But the inheritance was very odd. Paul Polani thought it was a chromosomal thing. Anyway, to cut a long story short, we worked out the inheritance of that and it was due to a deletion on chromosome 15. But blow me it was the identical deletion to the Prader-Willi syndrome, completely different syndrome. Identical down the microscope, chromosome deletion on chromosome 15.

So we found this deletion on chromosome 15 but the problem was it was the identical deletion on chromosome 15 that we knew was the cause of Prader-Willi syndrome, an entirely different ~~chromosome~~ [syndrome]. And so we didn't know what to do think of that. And Pat Jacobs, this would be sort of 1989, Pat Jacobs was established as the cytogeneticist in Salisbury and she had done a big survey of these minor deletions around, in chromosome 15, and she said, 'Oh no, we've got one of those. It's part of a normal variation,' the one that we thought was associated with Angelman's syndrome, overlapped with Prader-Willi. She said, 'Here look at the survey.' And indeed there was a survey and she said, 'Well, we've got one as extreme as the thing that you're talking of.' We went and, unknown syndrome, we went and saw the child, had Angelman's syndrome, so that really clinched it. So then how could you explain this, and very quickly imprinting had been recognised in mice in 1985/86, these loci, and to cut a long story short, we soon worked out, together with the people working on Prader-Willi, that if the deletion was on the maternal chromosome it would have Angelman's syndrome; if the deletion was on the paternal chromosome it would have Prader-Willi syndrome. So that discovery of imprinting involving Angelman syndrome, genomic imprinting, then we went into the diagnostics of it in the lab, the DNA lab, and found that a methylation signal was the thing that you could use for telling whether a person was affected with this condition or not. And that got me very much into epigenetics and of course that led on, I speculated in '96, or '94 conference but the publication was in '96, that perhaps imprinted genes might mediate transgenerational responses. By that I mean, exposures to the environment, experiences of the parent or the grandparent might actually change the setting of the imprinted genes and lead to consequences in subsequent generations.

#### [5]. MISJUDGEMENTS AND CHANGES OF DIRECTIONS: SICKLE CELL DISEASE

Yes, things that went wrong. Misjudgements and so on in my career. Yes, I think there was an episode and how it arose was when I was in Liverpool doing my thesis on foetal haemoglobin, that would have been in, I was there from '69 till '71. Cedric Carter, sorry, Cyril Clarke, was really adamant that at my stage I should definitely go back and do general medicine or paediatrics, or a general medical job, you know, and get accredited in medicine and then do genetics. And a job came up at St. Thomas' Hospital and I went there as a Lecturer in General Medicine and it was dire, partly because St. Thomas' Hospital hadn't moved into the current century, as it were, in terms of attitude towards all sorts of things.

I mean okay, one always gets good experience and I got a lot of medical experience, that's true, in the time I was there, but when David Weatherall contacted me and said, 'We're going to do this project in eastern Saudi Arabia to see if foetal haemoglobin is protecting against sickle cell disease there,' I jumped at the chance to leave. And that was end of '71, something like that, and then in '72 we, no it was '72-'73 and then I established a link with the Arabian American Oil Company, went out there and did a lot of research on this benign sickle cell disease in the Eastern Province. And although a lot of people said, 'Come on a minute, you're going to Saudi Arabia when you should be going to the States,' you know, Victor McKusick, various centres like that. Well, I was escaping from St. Thomas' Hospital and it really was very valuable in all sorts of ways. I was completely running my own research, nobody was telling me what to do. I was deciding how to do it. David Weatherall never came over; he didn't like the flying at that time. And we sorted it out and I learnt quite a bit of epidemiology too. And people were very helpful there. So that I think that stood me in good stead, as good a stead as going to the States, I suspect.

But when that came to an end, that initial study, I was welcomed back fortunately to Guy's, Maurice Lessof, Head of Medicine there, Professor of Medicine, and Paul Polani, very helpful. And so I was back at Guy's, continuing my work, research in Saudi Arabia, but learning to do clinical genetics with Paul Polani and in the Paediatric Research Unit. So by that time I was really definitely going to do genetic counselling, clinical genetics.

#### [6]. CHANGES IN DIAGNOSIS OVER THE PAST THIRTY YEARS

The most important changes since I qualified in medicine, say, and that would have been in '66. At that time we basically had chromosome analysis really and beyond that there was relatively little we could do in terms of diagnosing various syndromes and so on. We relied very heavily on the very good work that John Fraser Roberts at Great Ormond Street, and then Cedric Carter afterwards, had gathered these empirical risk factors. If you had deafness, you know, congenital deafness, you know, I think we combined, a lot of it was recessive, but if you couldn't prove it was recessive, was the first one, you would change from a 25% chance down to 10% based on empirical observation. That's all we had. But once the DNA analysis came in, we made fantastic progress and really what we'd gone right through to pre-implantation genetic diagnosis. I mean I know we've had IVF [*in vitro* fertilisation] and all the success of that and so on, and amniocentesis, but that is amazing.

Yes, so John Fraser Roberts initially and then Cedric Carter at Great Ormond Street, collected all these empirical figures of recurrent risk. If the fact that a couple had had a child with genetic, with deafness, one could say well, it was probably, it could be recessive at 25% recurrent risk, but not all were. And they said, 'Well, it turns out about 10%.' You know so you'd use those figures. Well we've gone from that empirical stuff, which was pretty meaningless to a large extent for those families, right through to giving precise advice based on DNA analysis and then pre-implantation genetic diagnosis. So the options for families facing these high risks is amazing now compared, and we're just beginning to get actual treatments now of these recessive disorders from all the understanding.

And the thing that particularly pleases me from a broad sense is that those families at greatest risk get the help, you know. These are often very severe conditions in childhood or later on and these monogenic Mendelian, or non-Mendelian disorders but monogenic ones, where we can help. And so in a sense all the advances, the Human Genome Project, what it's really helped are those with monogenic diseases. And so you have this nice thing that all the science is helping those who are helping those who are at greatest risk of the worst things pretty much. And okay, coronary artery disease, things later in life and so on, well, they're not as bad as having children with some of these genetic disorders, and so that's very satisfying.

#### [7]. WHAT DO YOU HOPE/EXPECT TO HAPPEN IN THE NEXT THIRTY YEARS?

Right, the future, 30-40 years [laughs]. Ten years perhaps but anyway, the first thing is a sort of caution really. I sincerely hope that the way clinical genetics works is preserved. And that a key aspect of that is we keep family-based notes. I think we're one of the few disciplines that have family-based notes as opposed to individual notes, and I fear that people will eventually say, 'Well, it's personalised medicine now where you don't need to keep these family notes.' And that would be a disaster not only for the research but for the service. So that's a thing I hope, what I think is going to happen is the monogenic diseases are really going to be sorted. We will have many treatments because gene editing's going to make it possible to, where you can do transplants to combine the transplants you know, bone marrow transplants, things like that, stem cell transplants, with gene editing that's already happened with leukaemia for example. And that I think we're going to accept gene editing even in the pre-implantation embryo in that time period. And I think the therapies for monogenic diseases are going to improve. From the point of view of the common diseases and personalised medicine, now even in that timescale I'm doubtful it's going to be as big a player as people think. Obviously with cancer, where you're actually looking, it's a sort of tumour that's being genotyped to help with the treatments, and there will be a little bit, I think with cancer it's going to be important and will deliver very well.

Now with regard to the common disorders, you know, like diabetes, coronary artery disease, and mental health disorders and so on, I mean obviously there are going to be one or two monogenic subsets, you know like there are with breast cancer or diabetes. Those will all be sorted with very satisfactory screening for those. But the rest, I think we're going to have to understand the very early embryological development. And I think gene editing and all sorts of other things is going to allow us to do that. We have to remember that the inbred mice used in experiments, they have extremely organised embryo life. The cells just, you know, do what they're supposed to and can be followed through. Humans are chaotic. Their chromosomes are chaotic and so on. And I think that early chaos settles down into a developmental trajectory and it's partly stochastic but it's partly influenced. In my view, I think we're going to see increasingly these transgenerational effects, that is the experiences of either the father or the mother, certainly the fathers as much as the mother, their early life experience whether they started smoking very early, stress, and things like that. And even the grandparents. And how that feeds into that chaotic early human embryo and the outcome from that.

Certain things, imprinted genes, as I predicted in '96, are going to be big players in this, and out of the chaos will come a certain canalised trip developmental trajectory, which works fine. But it's going to be different for each sibling, type of thing. Even difference for some twins. And we may be able to screen children when they're born and know whether they're particularly at risk of something or other in terms of public health interventions, but there's a lot of research to do. But we will be able to do it. So personalised medicine, I think it's going to quietly disappear as the broad answer to everything. It's going to be very important in cancers in terms of getting the cancer, the tumour, assessed, and I think we're going to have to, we've been missing a trick up to now, that's my view.

[END OF TRANSCRIPT]

**Further related resources:**

1. Christie D A, Tansey E M (eds) (2003) *Genetic Testing*. Wellcome Witnesses to Twentieth Century Medicine, vol. 17. London: Wellcome Trust Centre for the History of Medicine at UCL.
2. Jones E M, Tansey E M (eds) (2016) *Medical Genetics: Development of Ethical Dimensions in Clinical Practice and Research*. Wellcome Witnesses to Contemporary Medicine, vol. 57. London: Queen Mary University of London.
3. Overy C, Reynolds L A, Tansey E M (eds) (2012) *History of the Avon Longitudinal Study of Parents and Children (ALSPAC), c.1980-2000*. Wellcome Witnesses to Twentieth Century Medicine, vol. 44. London: Queen Mary, University of London.
4. Reynolds L A, Tansey E M (eds) (2010) *Clinical Genetics in Britain: Origins and development*. Wellcome Witnesses to Twentieth Century Medicine, vol. 39. London: Wellcome Trust Centre for the History of Medicine at UCL.