

CLINICAL MOLECULAR GENETICS IN THE UK c.1975–c.2000

The transcript of a Witness Seminar held by the History of Modern Biomedicine Research Group, Queen Mary, University of London, on 5 February 2013

Edited by E M Jones and E M Tansey

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WHAT IS A WITNESS SEMINAR?

The Witness Seminar is a specialized form of oral history, where several individuals associated with a particular set of circumstances or events are invited to meet together to discuss, debate, and agree or disagree about their memories. The meeting is recorded, transcribed and edited for publication.

This format was first devised and used by the Wellcome Trust's History of Twentieth Century Medicine Group in 1993 to address issues associated with the discovery of monoclonal antibodies. We developed this approach after holding a conventional seminar, given by a medical historian, on the discovery of interferon. Many members of the invited audience were scientists or others involved in that work, and the detailed and revealing discussion session afterwards alerted us to the importance of recording 'communal' eyewitness testimonies. We learned that the Institute for Contemporary British History held meetings to examine modern political, diplomatic and economic history, which they called Witness Seminars, and this seemed a suitable title for us to use also.

The unexpected success of our first Witness Seminar, as assessed by the willingness of the participants to attend, speak frankly, agree and disagree, and also by many requests for its transcript, encouraged us to develop the Witness Seminar model into a full programme, and since then more than 50 meetings have been held and published on a wide array of biomedical topics.¹ These seminars have proved an ideal way to bring together clinicians, scientists, and others interested in contemporary medical history to share their memories. We are not seeking a consensus, but are providing the opportunity to hear an array of voices, many little known, of individuals who were 'there at the time' and thus able to question, ratify or disagree with others' accounts – a form of open peer-review. The material records of the meeting also create archival sources for present and future use.

The History of Twentieth Century Medicine Group became a part of the Wellcome Trust's Centre for the History of Medicine at UCL in October 2000 until September 2010. It has been part of the School of History, Queen Mary, University of London, since October 2010, as the History of Modern Biomedicine Research Group, which the Wellcome Trust funds principally

¹ See pages 143–8 for a full list of Witness Seminars held, details of the published volumes and other related publications.

under a Strategic Award entitled ‘The Makers of Modern Biomedicine’. The Witness Seminar format continues to be a major part of that programme, although now the subjects are largely focused on areas of strategic importance to the Wellcome Trust, including the neurosciences, clinical genetics, and medical technology.²

Once an appropriate topic has been agreed, usually after discussion with a specialist adviser, suitable participants are identified and invited. As the organization of the seminar progresses and the participants’ list is compiled, a flexible outline plan for the meeting is devised, with assistance from the meeting’s designated chairman/moderator. Each participant is sent an attendance list and a copy of this programme before the meeting. Seminars last for about four hours; occasionally full-day meetings have been held. After each meeting the raw transcript is sent to every participant, each of whom is asked to check his or her own contribution and to provide brief biographical details for an appendix. The editors incorporate participants’ minor corrections and turn the transcript into readable text, with footnotes, appendices and a bibliography. Extensive research and liaison with the participants is conducted to produce the final script, which is then sent to every contributor for approval and to assign copyright to the Wellcome Trust. Copies of the original, and edited, transcripts and additional correspondence generated by the editorial process are all deposited with the records of each meeting in the Wellcome Library, London (archival reference GC/253) and are available for study.

For all our volumes, we hope that, even if the precise details of the more technical sections are not clear to the non-specialist, the sense and significance of the events will be understandable to all readers. Our aim is that the volumes inform those with a general interest in the history of modern medicine and medical science; provide historians with new insights, fresh material for study, and further themes for research; and emphasize to the participants that their own working lives are of proper and necessary concern to historians.

² See our Group’s website at <http://www.history.qmul.ac.uk/research/modbiomed> (visited 13 August 2013).

ACKNOWLEDGEMENTS

This Witness Seminar is held under the auspices of our current Wellcome Trust Strategic Award ‘The Makers of Modern Biomedicine’. While building on the style and success of our previous meetings and volumes (listed on pages 143–8), we are now focusing on five main themes in contemporary biomedicine, one of which is clinical genetics (details at <http://www.history.qmul.ac.uk/research/modbiomed/index.html>). Professor Peter Harper is our expert adviser on this part of the project, and the theme of clinical molecular genetics is one we have been discussing for some time. Peter has advised us on suitable participants, as have Professor Andrew Read and Professor Martin Bobrow; the latter also chaired the resultant meeting. We are most grateful to them all for their input.

We also thank Professor Bob Williamson for writing the introduction for this volume. Professor Bert Bakker, Dr Fiona Macdonald and Dr John Old all generously provided archival material for reproduction in the appendix for which we are very grateful. Mr Laz Lazarou also gave material that will be deposited in the Wellcome Library with the records of this meeting. Thanks are also due to Professor Marcus Pembrey who commented on the final proof transcript.

As with all our meetings, we depend a great deal on Wellcome Trust staff to ensure their smooth running: the Audiovisual Department, Catering, Reception, Security and Wellcome Images. We thank Mr Akio Morishima for the design and production of this volume; the indexer Ms Liza Furnival; Mrs Sarah Beanland and Ms Fiona Plowman for proofreading; Mrs Deborah Gee for transcribing the seminar; Ms Caroline Overy for assisting with running the seminar and Mr Adam Wilkinson who assisted in the organization and running of the meeting. Finally, we are most grateful to the Wellcome Trust for supporting this research programme.

Tilli Tansey

Emma Jones

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ABBREVIATIONS

cDNA	Complementary DNA
CF	Cystic fibrosis
CGH	Comparative genome hybridization
CMGS	Clinical Molecular Genetics Society
CVS	Chorionic villus sampling
DMD	Duchenne muscular dystrophy
FAP	Familial adenomatous polyposis
FISH	Fluorescent <i>in situ</i> hybridization
MD	Myotonic dystrophy
mRNA	Messenger RNA
NHS	National Health Service
NSC	National Screening Committee
PCR	Polymerase chain reaction
PKD	Polycystic kidney disease
RFLP	Restriction fragment length polymorphism
SHHD	Scottish Home and Health Department
SMD	Special Medical Development

ANCILLARY GUIDES

Further information on the topics discussed in this seminar can also be found through online resources.

For conditions, diseases and syndromes see, for example, the websites of these organisations based in the UK:

The Fragile X Society

<http://www.fragilex.org.uk/>

Genetic Alliance UK

<http://www.geneticalliance.org.uk/>

Huntington's Disease Association

<http://hda.org.uk>

Muscular Dystrophy Campaign

<http://www.muscular-dystrophy.org>

(includes information on Becker, Duchenne and myotonic muscular dystrophies)

Polycystic Kidney Disease Charity

<http://www.pkdcharity.org.uk/>

Sickle Cell Society

<http://www.sicklecellsociety.org/>

Tuberous Sclerosis Association

<http://www.tuberous-sclerosis.org/>

United Kingdom Thalassaemia Society

<http://www.ukts.org/>

For genes, OMIM (Online Mendelian Inheritance in Man) is a reliable, up-to-date information source for human genes and phenotypes:

<http://www.ncbi.nlm.nih.gov/omim>

For the website of the Clinical Molecular Genetics Society (UK), see:

<http://www.cmgs.org/>

(all websites visited 25 October 2013)

Readers wishing to know more about the techniques mentioned in the text can also consult standard reference books, such as:

King R C, Mulligan P K, Stansfield W D. (2013) *A Dictionary of Genetics*. Oxford: Oxford University Press.

Strachan T, Read A. (2011) *Human Molecular Genetics*. New York: Garland Science.

INTRODUCTION

How different it all was...

I am sorry I could not make it to this meeting, which sounds as if it was a great occasion, but in spite of all the advances of science, Australia is as far away from London as ever. However, I still get great pleasure from spending a lot of my time talking to, and mentoring, really bright young researchers working in human molecular genetics. It is not easy to convey to them how different things were 40-plus years ago, when the field was young. While there is a tradition in clinical genetics going back over 100 years (particularly to Garrod in London, as well as others), beautifully described by Peter Harper in his recent book *A Short History of Medical Genetics*, there was none in human molecular genetics.¹ The doyens of biochemistry, like J Norman Davidson (Glasgow),² characterized molecular biology as ‘biochemistry practised without a licence’, and make no mistake, he intended to make sure we were forced off the road.³ Perhaps more surprising, some of the most senior traditional geneticists, from Lionel Penrose (University College London) to John Edwards (Oxford), had no sympathy with DNA; they disliked Crick and Watson personally, and made it clear that their superior understanding of both statistics and phenotype was the pre-requisite for entry into the field. There were exceptions: I remember J B S Haldane (Professor of Biometry, University College London) being pro-Crick and Watson, and always intellectually open and willing to discuss new ideas with the very young undergraduate I was at the time, as was Peter Medawar (also UCL, Professor of Zoology until 1962), but not the Professor of Biochemistry, Ernest Baldwin, who refused to acknowledge anything that diminished the role of proteins.

We had so much more time to talk and think...

Recalling these days does, remind me, however, of what is perhaps the biggest difference: we all seemed to have so much more time. I went out for a beer with the most senior staff, not only Haldane but also John Maynard-Smith, David Newth, Anne McLaren, John Paul, Pat Clarke, all manner of super-good intellects who had the time and the kindness to talk to us students as if we really

¹ Harper (2008).

² For the frequent biographical references made throughout this introduction, the reader is referred to standard biographical sources such as *Who's Who*, *Biographical Memoirs of the Royal Society* or specific internet searches.

³ For the quotation, see Campbell (1992).

might understand the science they discussed. This was true for clinicians as well; long before I met David Weatherall in 1974, I knew John Dacie (Hammersmith), Tom Prankerd (UCH) and Sheila Sherlock (Royal Free); once again, they were ever-generous with their time, and not only to me. Robin Weiss and Ian Healey and Tony Trewarvas and Patsy Ingold were my contemporaries, and they too benefited. How sad we are all so busy today; I fear this does not happen now as it did then.

International links...

Several of the participants in the seminar mentioned the wonderful meeting that I organized in Crete in 1978, the best meeting I ever attended as well (Appendix 1). Part of the reason it was so good is that EVERY participant was there for the whole 12 days. All fares and expenses for the 80 people were paid, but the condition was that you stayed for the duration. It also was the first meeting to which young scientists from Italy, Greece, Saudi Arabia, Thailand and Africa were invited to come and participate as equals with the Americans and Brits who were doing most of the talking – many collaborations were started there that continued for decades. The WHO, with Bernadette Modell playing a major role, was also present at the meeting in Crete, and continued to fund workshops to introduce the molecular genetics of thalassaemia in developing countries for many years.

We were so much more idealistic...

A lot of us were radical, and politically active (and a lot of science was talked on the ‘Ban-the-Bomb’ marches to and from Aldermaston).⁴ Even those who weren’t political still grew up in an environment of great hopes, and fears, for the future. Everyone I knew was interested in the social uses and values of science, and what we found from our research was immediately interrogated as to its usefulness. Socially, it was a time when we shared a lot more than happens today: no one patented anything. Indeed, when the CF gene was located to chromosome 7 simultaneously by my group at St Mary’s London, and by Lap-Chee Tsui in Toronto and Ray White in Salt Lake City, we were horrified when a commercial company popped up with its infamous claim: ‘We own chromosome 7’. The start of the nightmare!

⁴ The Atomic Weapons Establishment in Aldermaston, Berkshire; a target for opponents to nuclear weapons since 1958, for instance through the Campaign for Nuclear Disarmament’s ‘Ban-the-Bomb’ Easter marches. See, for example, <http://www.cnduk.org/about/item/437> (visited 23 October 2013).

Technology was hard, ideas easy...

We did have an advantage, though: the technology was really difficult, so it was easy to talk about ideas. For instance, when my group in Glasgow was working with David Weatherall and Bernadette Modell to determine if alpha-thalassaemia is due to a gene deletion, it took my post-doc Sergio Ottolenghi NINE MONTHS to make enough alpha-globin gene probe to do the experiment (this was before gene cloning, and before PCR). We knew we could talk about it with impunity; very few groups could attempt such an experiment (apart from that of YW Kan, who came up with a similar result and published side by side with us in Nature). I often think it is now the opposite. The technology has become so simple teenagers do PCR-based gene analysis experiments in secondary school, but ideas are few and far between.

There were unsung heroes...

It is easy to criticize the very English, male-dominated and hyper-intellectual world of the 1960s and 1970s, when human molecular genetics was first being established in the UK. There were some remarkable unsung heroes as well. In Edinburgh, groups around some unlikely and quite eccentric individuals flourished: Martin Pollack and Bill Hayes, Peter Walker and Ed Southern, Anne McLaren and Ruth Clayton were wonderful. So too were people in MRC headquarters like Tony Vickers, who consistently supported human molecular genetics, Sir Gordon Wolstenholme at the Ciba Foundation, Bridget Ogilvie at the Wellcome Trust, and a few others. When the Wellcome Trust blossomed, it created a genetics panel under, I think, David Weatherall that operated in a very adventurous, almost futuristic way. Without this support, human molecular genetics would have died in the same ditch that clinical biochemistry found itself in (but that bit of history, of the demise of much of British pathology, is another story, for another time). Some of the clinicians, in particular Peter Harper, were extremely generous in making their 'collections' of patients available for study, and I learned that a good and trusted clinician like Peter is able to count on support from his patients and their families. On one occasion, Peter got samples from 30 families with DMD in less than a week – a truly outstanding tribute to the affection with which his patients embraced him.

And it was all so much fun...

Was it because we were all younger; the field was very non-hierarchical, it was new and we were all so excited to be there; we were more radical, or we thought we were breaking original ground? Whatever the reason, it was terrific fun.

But it also was fun for other reasons – we had tea and coffee in the labs, beers in the student bar after 5pm (and then back up to work), and we all worked weekends (but also took time off whenever we wanted, during the week). We all shared data, our own and other people’s data, and never thought there was anything wrong with this. The university helped by making funding available (‘to those who hath shall be given’), and the obsessive worry about health and safety that has segued into foolish rules had not yet happened – no one ever caught anything from drinking tea or coffee in the lab that I can remember. Indeed, I feel rather guilty that I helped to establish the environment within which these rules were established, through the Gene Manipulation Advisory Group, a government committee that met for about 15 years to establish ways to deal with a fictional problem. It is astonishing that about 20 of the brightest minds in the UK deliberated for so long how to contain recombinant DNA species biologically and physically, without noticing there were no problems, no ‘sentinel cases’, at all!

And on to today...

The reason why Jim Watson’s book *The Double Helix* is so good is because it portrays with a fair degree of accuracy the three sides of the triangle that I remember so well from the start of human molecular genetics. First, the long periods of talk, of chat, even of boredom, of trying to master material that others thought was important but you suspected was not. Second, the incredible excitement at thinking in a new interdisciplinary way and turning them into practice: being the first to demonstrate that alpha-thalassaemia is due to a gene deletion; showing how the globin genes are organized, proving that cystic fibrosis is due to mutations in one gene, that was only located and identified using the new techniques that I helped to develop. And third, just how much fun it all was. I hope that some of our students and post-docs have every bit as much fun with their projects today!



Figure A: Professor Bob Williamson
Melbourne, August 2013

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Participants*

Professor Bert Bakker	Dr Helen Middleton-Price
Professor Martin Bobrow (Chair)	Professor Bernadette Modell
Dr Rob Elles	Dr John Old
Professor Malcolm Ferguson-Smith	Professor Andrew Read
Professor Peter Harper	Professor Julian Sampson
Professor Pat Jacobs	Dr Rosalind Skinner
Mr Laz Lazarou	Professor Tilli Tansey
Dr Ian Lister Cheese	Professor Sir David Weatherall
Dr Fiona Macdonald	Professor John Yates
Dr Linda Meredith	

Apologies include: Professor Dame Kay Davies, Professor Sue Malcolm, Professor Christopher Mathew, Professor Marcus Pembrey, Professor David Porteus, Mr Paul Rutland, Professor Tom Strachan and Professor Bob Williamson.

* Biographical notes on the participants are located at the end of the volume



Figure 1: Professor Tilli Tansey

Professor Tilli Tansey: Can I begin very promptly please and welcome you all to this Witness Seminar on Clinical Molecular Genetics. I'm Tilli Tansey and I run the History of Modern Biomedicine Research Group, which is now at Queen Mary University of London. This began several years ago under the auspices of the Wellcome Trust who, thankfully, continue to fund us. We try to get together groups of people who have been involved in particular debates or discoveries to discuss among themselves what really happened; not just the dry record you find in the scientific literature but the stories behind the scenes, what happened, what didn't happen, who made things happen? Not necessarily the most famous people and stories that one knows of. So the purpose of this is to talk among yourselves, led by our Chairman, and everything is going to be recorded, edited and published, and will be freely available to download from our website.¹ Nothing you say will be published without your permission.

We've held several meetings on various aspects of clinical genetics, and now under the auspices of a new Strategic Award from the Wellcome Trust we're going forward for another five years to look at a big project on the Makers of Modern Biomedicine. One major theme of that is focused on genetics, for which we have a consultant adviser who is Peter Harper, and Peter and Andrew Read have advised us a great deal on setting up this meeting, as has our Chairman Martin Bobrow. I'm delighted to welcome Martin because he is a glutton for

¹ See http://www.history.qmul.ac.uk/research/modbiomed/wellcome_witnesses/index.html (visited 14 May 2013).



Figure 2: Professor Martin Bobrow

punishment; I think this is either the third or the fourth meeting that he's chaired for me, as well as contributing to several others. He is going to keep you all in order but also try and prompt reminiscences and we're so delighted that you could come, Martin. Thank you so much. So over to you.

Professor Martin Bobrow: Thank you, Tilli. I think I know pretty well everyone, which is a very rare event for me. For those who haven't been involved before: these meetings are different. They're a cross between science, history and a revivalist meeting so you must feel free to get up and declaim things you believe to be true, and things you remember clearly, and want to be written down, even if it's not easy to document. The essence of this is capturing what is in the collective memory of groups of people who have been involved in ventures of this sort: ventures like getting molecular diagnostics going in the UK and in continental Europe. I thought it would help to set some background if I asked Peter Harper to briefly outline which other meetings of this sort have been held or are in planning on related topics, because that will help us collectively to steer away from talking about things that are going to be covered elsewhere.

Professor Peter Harper: Thank you, Martin. Yes, obviously human molecular genetics is a huge area and so we had, not problems, but it was quite difficult to decide what not to include. Some of this was made a bit easier by the fact that we have had other Witness Seminars in this broad field, including the original one on genetic testing, then one on clinical genetics and, most recently, one



Figure 3: Professor Malcolm Ferguson-Smith (left), Professor Peter Harper (right)

on clinical cancer genetics.² So that has taken part of the load. We also decided from the beginning not to try and cover basic molecular research; that would clearly have been impossible – likewise not the Human Genome Project.³

Also, there's a plan that we may have a separate seminar on the Human Gene Mapping Workshops, which I think really are areas deserving in their own right.⁴ Then we also thought we would make a cut-off around the time when whole-genome sequencing started to come in and not to cover that very rapidly developing area. So this in part explains why some of the seemingly very obvious topics are not on the list today. Hopefully that will give us a bit more time to deal with the beginnings of the subjects which are on the outline programme (Table 1).

Professor Malcolm Ferguson-Smith: Sorry to make a rude interjection. I'd like to make sure that when we consider the whole area of genetics in the United Kingdom, we don't exclude Scotland because I'd like to ensure that this is not just about England and Wales; this is about the whole of Great Britain.

² Christie and Tansey (eds) (2003); Harper *et al.* (eds) (2010); Jones and Tansey (eds) (2013).

³ For key historical materials on the development of genetics during the twentieth century, see *Codebreakers: Makers of Modern Genetics*, an online resource of primary archival materials hosted by the Wellcome Library from scientists who made landmark breakthroughs: <http://wellcomelibrary.org/using-the-library/subject-guides/genetics/makers-of-modern-genetics> (visited 17 June 2013).

⁴ A Witness Seminar on Human Gene Mapping Workshops is scheduled for March 2014, in consultation with Professor Ian Craig and Professor Sue Povey.

<p>Technological advances</p> <p>Haemoglobin and its disorders First service applications; haemoglobin disorders</p> <p>Positional cloning: From gene mapping to gene isolation; DNA polymorphisms The X chromosome; Duchenne muscular dystrophy Cystic fibrosis; trinucleotide repeat disorders; other autosomal conditions</p> <p>Cancer genetics/molecular testing</p> <p>Molecular cytogenetics</p> <p>Beginnings of a clinical molecular genetics service: Department of Health Three Centres Study Scottish Molecular Genetics Consortium The Netherlands' experience</p> <p>The UK Clinical Molecular Genetics Society</p> <p>From linkage to mutation: Detection and sequencing</p>

Table 1: Outline programme for *Clinical Molecular Genetics in the UK c.1975–c.2000*.⁵

Bobrow: This is the whole of Great Britain. Scots people unfortunately did not find it possible to fit us into their busy diaries. A lot of people were approached, some of whom just couldn't make the day, some of whom don't travel much any more, and some of whom don't travel at all any more. It's the nature of history.

Ferguson-Smith: We mustn't forget about them.

Bobrow: No, no; you're here to remind us. Okay. So the next thing I want to say before we kick off is that there is a tentative programme in front of you but it is very tentative. We're going to start off on technological enabling advances. We'll handle all of that science development first and then go through disease areas very broadly, But this is extremely rough and if people want to stray across boundaries, feel free. And if we stray from that order, it doesn't matter. So let's start off on underpinning technology and the science.

Professor Andrew Read: I was trying to delve back through my deepest, foggiest memories and they start, I guess, in about 1961. I did my PhD from 1961 to 1964 in Cambridge, in Todd's department where of course nucleic acid

⁵ A draft outline programme was circulated to seminar participants to comment on a month in advance of this meeting. Table 1 is the final version of that programme, used as a framework for this seminar.



Figure 4: Professor Andrew Read (left), Professor Peter Harper (right)

chemistry was the big thing.⁶ And I did my PhD on attempting to get a method to sequence RNA by putting it through a series of chemical reactions that knocked off the 3-prime nucleotide, which you could identify, and then you carried on with the next nucleotide. Of course, everything depended on getting a good quantitative yield at each stage, otherwise you rapidly got everything out of sync; so I spent most of my time trying to do that. I remember Fred Sanger came to my PhD seminar and he had only one question, which was, ‘Does it work?’ At that time I thought, ‘Oh dear, how unintellectual of him.’ [Laughter] I was interested in the beta elimination reaction and the niceties of which amine worked best. I now realise that was part of the reason why he has Nobel Prizes and I don’t.⁷ If you think what the state of the art was back in

⁶ The department was that of Lord Todd (1907–1997), Chair of Organic Chemistry at Cambridge (1944–1971) and Nobel Laureate for Chemistry in 1957. His obituary from the Royal Society and entry in the *Oxford Dictionary of National Biography* are available at: http://www.royalsoced.org.uk/cms/files/fellows/obits_alpha/todd_lord.pdf and <http://www.oxforddnb.com/view/article/64697> (websites visited 17 June 2013).

⁷ Double Nobel Laureate, Dr Frederick Sanger (1918–2013) led the group that produced the first whole-genome sequence. See <http://www.sanger.ac.uk/about/people/biographies/fsanger.html> (visited 14 May 2013). Sanger was awarded the Nobel Prize for chemistry in 1958 (sequencing of insulin) and in 1980, with Paul Berg and Walter Gilbert (recombinant-DNA). See *Frederick Sanger – Autobiography*. http://www.nobelprize.org/nobel_prizes/chemistry/laureates/1980/sanger-autobio.html (visited 14 May 2013).

those days, well, we'd had Watson and Crick. From about 1960, one had some picture of transcription and messenger RNA;⁸ the genetic code was, I think, the big Holy Grail at that time. I remember Paul Zamecnik was working in the laboratory then and everybody held him a little bit in awe.⁹ It was around about 1963 through to 1966 that the genetic code got worked out so, by the time I had finished my PhD, one had quite a decent picture of the DNA-gives-RNA-gives-protein, almost entirely in bacteria and phage.¹⁰ Although, of course, there was the work from Pauling and Ingram *et al.* on sickle cell, which others will be more qualified to talk about than I am.¹¹

Now, at that point I left this area and wandered off in various directions and resurfaced in genetics when I joined the Medical Genetics Department in Manchester in 1977. If you look at what had happened in the meantime, well the basic toolkit that set up clinical molecular genetics had been established in the 1970s. Restriction enzymes, I guess, were first properly described in 1970 and by the mid-1970s there were actually a number of enzymes available commercially of good quality and reliable.¹² So you had restriction enzymes, you had gel electrophoresis, of course. It was a starch gel electrophoresis that [Harry] Harris had been using back in the 1960s for protein polymorphisms, but for DNA variants I think it was in the early 1970s that people started using agarose gel electrophoresis.¹³ Other people may have better memories of that than me. Cloning had come about and probably 1972 to 1974 was the main time when people learnt to stitch together recombinant DNA, put it into a vector, clone it in bacteria.¹⁴ So by the mid-1970s you had clone libraries of DNA from humans and other organisms. The Southern blot, Southern's key paper, was published in 1975, although, of course, the way he did it then was very different to the way

⁸ See, for example, Brenner *et al.* (1961).

⁹ Dr Paul Zamecnik (1912–2009) played a key role in the discovery of both transfer RNA and antisense DNA. See his biographical memoir published by the National Academy of Sciences, USA, at http://www.nasonline.org/publications/biographical-memoirs/memoir-pdfs/Zamecnik_Paul.pdf (visited 4 June 2013).

¹⁰ See, for example, Witkowski (ed.) (2005).

¹¹ See, for example, Pauling *et al.* (1949) and Ingram (1957).

¹² See, for example, Smith and Wilcox (1970) and also Smith (1978).

¹³ Harry Harris (1919–1994) established the Medical Research Council Unit of Human Biochemical Genetics at King's College, London, in 1962. He was Galton Professor of Human Genetics and Director of the Galton Laboratory (1965–1975). For agarose gel electrophoresis, see, for example, Laurell (1966).

¹⁴ Cohen *et al.* (1973).

it was done later.¹⁵ But that gave one a very crucial thing, I think, the ability to look at a specific sequence in complex DNA, like human DNA, provided you had the probe that could detect that sequence.

Sanger sequencing emerged in about 1977, but that was very much a research tool because you've got to have cloned DNA to sequence, so it was never going to be part of diagnostic practice until you had some easy way of cloning the DNA of your patients without having to make libraries and screen them.¹⁶ It was a research technique for defining genes. By 1977 you had the toolkit there to isolate human DNA, to restrict and digest it, to look for specific sequences but absolutely everything hung on having probes for clinically useful genes. One only had one set of probes for clinically useful genes, which were the globins, so I think the story of clinical molecular genetics really starts with that globin work. Certainly I remember the Kan and Dozy paper of 1978.¹⁷ That was the real wake-up call. I had joined the department in 1977 and I had a vague feeling that it was surely going to be useful to know something about DNA, but actually at that point there was nothing useful I could do with DNA. For the first three years I was in the department, I didn't touch DNA at all. I did other things. Meanwhile, the people who worked with globin actually had a probe to detect a clinically useful gene and so I suggest we ask them what they did with it, if I'm allowed to set the agenda, Martin?

Bobrow: I'd like to ask other people to comment on that, and on some of the developments a little subsequent to that. Two things that I would remind you: first, we're a group of people who happen to be around and are willing and able to come into a room to talk about it today. I think the more we mention the names of other people who aren't here to talk for themselves, the easier it will be to tie things together. The mention of Kan and Dozy, and a few related things, brings to mind the story of prenatal diagnosis, because that was one of the very early points when the science of genetics hit the clinical tracks in a big way.¹⁸ Although they're not directly germane to today's topic, I think making those links across would be helpful.

¹⁵ Southern (1975). See also Southern's biography on page 110.

¹⁶ Sanger *et al.* (1977). See also Sanger and Coulson (1975).

¹⁷ Kan and Dozy (1978a). For Professor Yuet Wai Kan, see also pages 19, 20–2, 24, and his biography on page 105.

¹⁸ See for example, Steele and Breg (1966); Lisgar *et al.* (1970); Davidson and Rattazzi (1972). See also note 78.



Figure 5: Professors Julian Sampson (left), Bert Bakker (centre), John Yates (right)

Professor Bert Bakker: I remember a lot of things Andrew said. When I joined my department in the Netherlands in Leiden in 1977, almost the same time as you [Andrew, in Manchester], I was a technician in the lab of Peter Pearson and I worked the first years there with immunoprecipitation and other things. Around 1979 Peter came with the paper of Kan and Dozy and said, ‘Okay we need to find more of these types of polymorphisms – RFLPs (restriction fragment length polymorphisms) – and the unique probes to detect them. We need many of these RFLPs in the genome to follow genetic diseases in pedigrees.’¹⁹ But, at that time, there were no probes and we needed probes. For preparing those types of probes, we had to go a step back and first get human DNA. I got a placenta from the hospital and isolated human DNA from it to digest with a restriction enzyme. We needed lots of restriction enzyme, so I first had to grow the bacteria and isolate the enzyme, then digest the placental DNA, run it on a gel to see a nice smear, and then I ran a sucrose gradient to select fragments, of a certain size, and cloned these in a plasmid vector. We had some pieces of human DNA prepared in a few experiments. All this work I did in Mill Hill, in the MRC lab of Dick Flavell.²⁰ With these probes, we could go back

¹⁹ In 1972 Dr Peter Pearson was Head of the Human Genetics Department at Leiden University. He is now Co-Director of the National Institute for Stem Cell Research in Genetic Diseases, Sao Paulo, Brazil. See http://genoma.ib.usp.br/?page_id=1232&lang=en (visited 10 May 2013).

²⁰ Professor Richard Flavell was Head of the Laboratory of Gene Structure and Expression at the National Institute for Medical Research at Mill Hill, London; http://immunobiology.yale.edu/people/richard_flavell-2.profile (visited 10 May 2013). Professor Bert Bakker wrote: ‘At that time it was not allowed in the Netherlands to clone pieces of human DNA in bacteria.’ Note on draft transcript, 19 May 2013.

to human DNAs on Southern blots. I had to isolate DNA from 30 different placentae, digest these DNAs, run them on gels after digestion with different enzymes – EcoRI, PstI, HindIII, BglII, and TaqI – all in-house and isolated from bacteria because these enzymes were too expensive to buy at that time so we needed to prepare them ourselves. With these probes hybridized to the blots, we could try to find RFLPs and to localize them on the genome. But first I had to select the unique clones, so I pulled the bacteria with human inserts from an agar plate onto a nitrocellulose filter and hybridized those with total human DNA. The clones that were not repetitive didn't show up, so these ones were the ones that were 'more unique' and were used to hybridize against Southern blots to see if they showed a single EcoRI band. When a single band was seen, we knew, okay, this might be a unique probe and then hybridized them against other restriction enzyme digests to see if we could find a RFLP similar to those around the globin genes in the paper of Kan and Dozy, which were the kind of things we were looking for. I found, for 23-odd probes, all types of RFLPs.²¹ In 1981, this was presented at the Human Gene Mapping conference.²² One of these probes, L1.28, was later linked to Duchenne muscular dystrophy.²³ But before that, in 1982, we organized a course in Leiden, in the Netherlands, where people came from all over Europe to learn about this new technology: Southern blotting, cloning and growing these probes, hybridizing and all the things needed to detect RFLPs as tools for genetic studies.²⁴ Some 20 people were at the course, amongst whom were Andrew Read and, from Denmark,

²¹ Professor Bert Bakker commented further: 'At that time these probes detected 30 per cent of all known polymorphic DNA loci.' Note on draft transcript, 19 May 2013. For a complete list of the probes involved in this discussion, see Bakker (1989), pages 17–30.

²² Pearson *et al.* (1982).

²³ Davies *et al.* (1983). See also Professor Peter Harper's comments on linkage analysis for DMD on pages 38–40.

²⁴ The postgraduate course was entitled *Restriction Fragment Length Polymorphisms and Human Genetics*, and took place from 19 to 30 July, 1982, at the University of Leiden. Professor Bert Bakker wrote: 'It was an international (European) course with tutors such as Ray White, Web Cavance, Mark Skolnick (all from Salt Lake City, Utah, USA), and Peter Pearson and me from Leiden. Among the participants were Andrew Read (UK); Tobias Gedde Dahl (Norway); Jan Mohr (Sweden); Marianne Schwartz and John Philip (Denmark) and many others.' Email to Ms Emma Jones, 23 July 2013. See Appendix 2 for a sample of the Leiden course laboratory manual. The full manual is deposited with the records of this seminar in the Wellcome Library at GC/253.

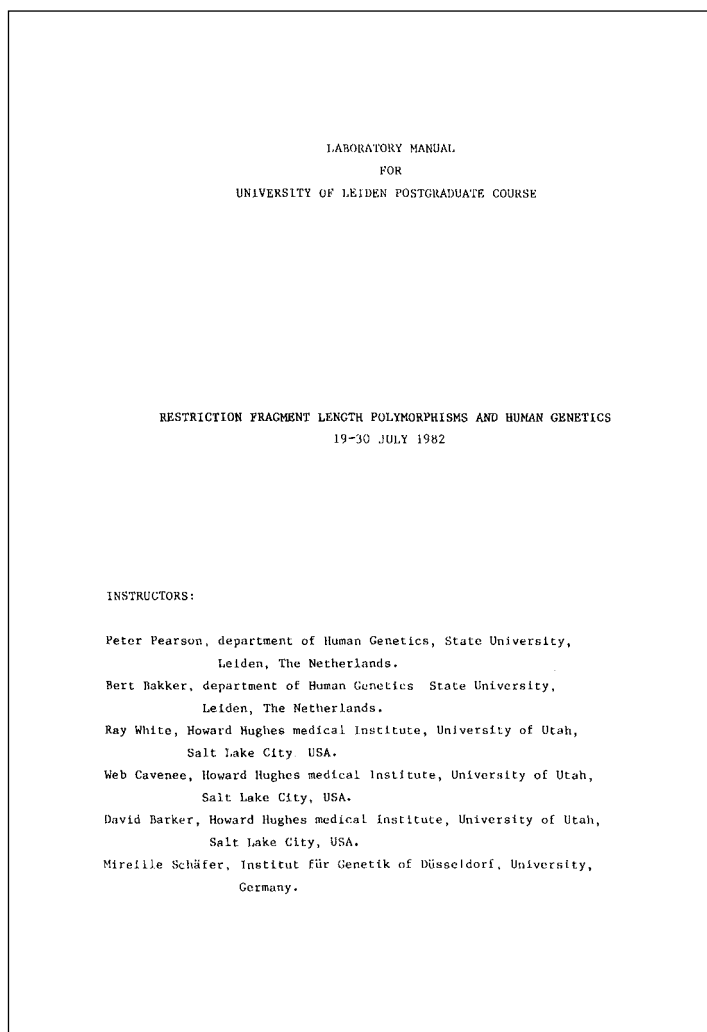


Figure 6: Title page, laboratory manual for postgraduate course *Restriction Fragment Length Polymorphisms and Human Genetics*, University of Leiden, 1982

John Philip and Marianne Schwartz, so there were quite a few people interested in RFLPs at that time.²⁵ We had a lot of probes that could be used for linkage and diagnosis.

²⁵ Dr John Philip was a cytogeneticist at the Section of Clinical Genetics, Department of Obstetrics and Gynaecology, Rigshospitalet, Copenhagen, Denmark. Dr Marianne Schwartz worked as a scientific biochemist at the Metabolic Laboratory, Pediatric Department, University Hospital Copenhagen from 1979 to 1991, then she became Head of the DNA Diagnostic Laboratory. She retired in 2009 and is now Professor Emerita at the same institution. These biographical details were confirmed in an email from Professor Marianne Schwartz to Ms Emma Jones, 29 July 2013.



Figure 7: Professor Marianne Schwartz (left), Dr John Philip (right), Leiden, 1982

Bobrow: Just to fill that in, Peter Pearson was in Leiden having gone from Oxford when the MRC Population Genetics Research Unit was closed.²⁶

Ferguson-Smith: The wonderful thing about these probes was that Peter Pearson, Bert and others made them available to everybody. They were sent out to all the departments who were working in the field and this was a tremendous advance. It cut out competition and made tremendous progress possible for Duchenne and many other X-linked conditions. People like Kay Davies,²⁷ our group and other people could use these probes in family studies, in mapping and in positional cloning.

Bobrow: Absolutely central point.

Dr John Old: I'd like to follow up on Andrew's comments and go back to when I started. I did a PhD on transfer RNA in Liverpool from 1971 to 1974 and while I was doing my PhD we had a departmental seminar from someone

²⁶ This unit was founded in 1958 and closed in 1974. See Landsborough Thomson (1987), page 364.

²⁷ See her biography on pages 101–2. See also an interview with Professor Dame Kay Davies by Professor Peter Harper at <http://www.genmedhist.info/interviews/kay-davies-interview> (visited 25 June 2013).



Figure 8: Dr John Old

called Ed Ziff.²⁸ He was from Sanger's lab and it was all about the wonders of RNA sequencing and someone asked this pertinent question: 'Would DNA ever be sequenced?' And he stood up and said, 'No, it's too complicated; we don't have a handle on how to break it up like we do with RNA', and everyone went away thinking RNA is the future. At that point Professor Weatherall was moving to Oxford and he wanted someone to work on RNA and thalassaemia patients and he offered me a post-doctoral position. So I moved to Oxford and started to prepare RNA from globin and I'd like to give Scotland a reference here, Malcolm, because one of the first things I had to do was to travel up to the Beatson Institute in Glasgow on a commuter basis, to Bob Williamson's lab, to prepare reverse transcriptase, which was the key in those days for converting messenger RNA into cDNA. You couldn't buy it: you had to spend two weeks making it with a long, complicated protein purification process. If you went up to Williamson's lab and participated you could get your hands on a portion of reverse transcriptase and make cDNA. Then you could do lots of wonderful hybridization studies.²⁹ Back in Oxford the technique was to find a thalassaemic patient who made only haemoglobin F and there was one in Stoke Mandeville Hospital who was a compound heterozygote, a beta zero/delta beta zero.³⁰ This

²⁸ Old (1974). Ed Ziff worked in Frederick Sanger's laboratory from 1973 to 1978; <http://www.med.nyu.edu/ziff/lab/Ziff/lab/Welcome.html> (visited 14 May 2013).

²⁹ See, for example, Old *et al.* (1976).

³⁰ Ottolenghi *et al.* (1975).

patient made only alpha globin messenger RNA (mRNA) and gamma globin messenger RNA, so basically if you took normal mRNA and made cDNA out of it you could back-hybridize this to mRNA from this patient. You would get double-stranded alpha and single-stranded beta and you could separate those on an hydroxyapatite column by chromatography and that gave you pure alpha, beta and then gamma cDNA probes. That really was the start, I think, of molecular genetics with purified probes: all because the red cell is unique in that most of the mRNA is just one of two species. You can't do that with other cells because you get hundreds and thousands of cDNAs. So that gave us a handle and then Southern blotting came along and we could start to use these probes with Southern blotting. Then, as Andrew said, cloning was developed, so instead of purified cDNA probes, people put clones into plasmids and purified them to 100 per cent and started to use those. Really, this technique was down to Bob Williamson's lab. He later moved to St Mary's in London and then to Melbourne. Bob was the driving force on that molecular side of things.

Bobrow: That was a very good background. I think we should go straight to the globin story before everyone's talked globin out before we get to you, David.

Professor Sir David Weatherall: There was quite a lot done before the 1970s. As I am sure most of you know, the major haemoglobin disorder, sickle cell anaemia, was first recognized just after Garrod's great lecture.³¹ Thalassaemia was first described in 1925.³² The paper that everybody quotes as the beginning of molecular medicine was Pauling's first description of the structure of sickle haemoglobin.³³ He was on an overnight train with Bill Castle, the Boston haematologist, who told him that there was something unusual about the behaviour of sickle cells in bi-refringent light. This suggested to Pauling that there might be a structural change in sickle haemoglobin. At that time, moving boundary electrophoresis had just been invented so he went back to Caltech, built a machine and, with his colleagues, found that sickle haemoglobin moved in an electric field at a different rate to normal adult haemoglobin. The famous paper appeared in 1949: *Sickle Cell Anemia, a Molecular Disease*. I think that most people do not know that Pauling retracted this paper within three months

³¹ Sir Archibald Edward Garrod (1857–1936) delivered a Croonian lecture at the Royal College of Physicians, London, in 1908, published as Garrod (1909). See also Weatherall (1992).

³² Cooley and Lee (1925). See also Weatherall (2010a).

³³ For Pauling, see note 11 and Dunitz (1997).



Figure 9: Professor Sir David Weatherall

of its publication.³⁴ What he had done was to compare mixtures of the amino acid composition of sickle and normal haemoglobin but could not find any difference.³⁵ The picture then moves to the UK. In 1951 Max Perutz produced his first X-ray pictures of haemoglobin with its pairs of alpha and beta chains.³⁶ Francis Crick and Max suggested to a young post-doc, Vernon Ingram, because somebody had left some sickle cell blood in their laboratory by mistake, that it might be worth trying to determine its structure. Ingram tackled this problem using two-dimensional electrophoresis and chromatography, or protein fingerprinting as it was called, and found a single amino acid substitution difference between the two haemoglobins.³⁷ This was a very under-estimated

³⁴ See the National Academy of Sciences (1950); Eaton (2003) and Weatherall (2010b).

³⁵ Sir David Weatherall wrote: 'In retrospect it seems likely that his technology was just not sensitive enough because his first interpretation soon turned out to be correct.' Note on draft transcript, 26 March 2013.

³⁶ Perutz (1951).

³⁷ Ingram (1957). Sir David further commented: 'In 1981 our group discovered two hypervariable regions flanking the alpha globin genes. The 5' flanking region was later sequenced and it was found to consist of a tandemly repeated 36bp sequence. This sequence was also published in the first edition of my book *The New Genetics and Clinical Practice*. Alec Jeffreys told me it was after seeing this sequence and another hypervariable sequence published by an American team that he set off to see if there were related sequences in other parts of the human genome, work which led to the remarkable era of DNA fingerprinting. Later our team, also using this genetic marker, found that the gene for polycystic disease of the kidney lay close to the alpha globin genes on chromosome 16.' Edited from an email to Ms Emma Jones, 8 April 2013. See Higgs *et al.* (1981); Goodbourn *et al.* (1983) and Weatherall (1982).

paper because it took the concept of one-gene-one-enzyme to one-gene-one-peptide chain and, incidentally, provided some of the first intimations of the nature of the genetic code. A few years earlier, two Italians reported patients who had inherited the sickle cell gene from one parent and thalassaemia from the other, a condition called sickle cell thalassaemia. It was later found that patients of this type had much less haemoglobin A than S.³⁸ In the early 1950s some other unusual haemoglobin variants were found in patients with different forms of thalassaemia, some of which consisted of four beta chains, others of four gamma chains of fetal haemoglobin, suggesting that they might reflect defective alpha chain production. These and related observations were put together by Vernon Ingram and Anthony Stretton in 1959 in a theoretical paper in *Nature*, which suggested that there were two forms of thalassaemia, alpha and beta thalassaemia.³⁹

When I moved into the field in the early 1960s I realised that it would not move much further unless it was possible to actually measure the rates of production of the alpha and beta globin chains. I went as a post-doc to Johns Hopkins Hospital, Baltimore [from 1960 to 1965], and spent a year or more trying to measure haemoglobin synthesis *in vitro* and obtained linear synthesis over short periods because unless you were studying protein synthesis in this way, you may be looking at all sorts of artefacts. After a year or so I found a way of doing this.⁴⁰ By chance I ran into John Clegg at this time – who was working in the Biophysics Department at Hopkins – and we discussed our research problems: I could not separate alpha chains and beta chains and he was having an equally difficult time trying to define the synthesis of insulin. During our conversations he remembered, from his thesis work in Cambridge, that he had been able to separate fibrinogen chains in 8 molar urea; the secret being to add mercaptoethanol to prevent their aggregation. This worked a dream with my labelled globin samples and we were able to show that the anaemia of thalassaemia is not so much due to defective haemoglobin production but is the result of unbalanced globin chain synthesis, the damage was done by the

³⁸ Professor Sir David Weatherall wrote: ‘Since the sickle mutation was in the β globin chain, this suggested that this form of thalassaemia might be due to a reduced amount of haemoglobin A, or β chain, production.’ Note on draft manuscript, 26 March 2013.

³⁹ Ingram and Stretton (1959).

⁴⁰ Professor Sir David Weatherall added: ‘I obtained unequal labelling of the globin chains from patients with thalassaemia but the methods for separating them were not quantitative.’ Note on draft transcript, 26 March 2013.

chains that are produced in excess.⁴¹ The nice outcome of all this was that, using that method – and Bernadette will talk about this later, because she used it with her American colleagues – it became possible to carry out prenatal detection of thalassaemia by fetal blood sampling. By 1990 there had been close on 14,000 prenatal diagnoses carried out globally using the globin synthesis technique.⁴² John (Old) has already mentioned some of the molecular research tools that were developed in the early 1960s and 1970s, but before direct DNA analysis was possible we were able to characterize the molecular basis for at least two forms of thalassaemia. One was the tiny amount of variant alpha chain that was found in a family from Constant Spring, Jamaica.⁴³ To cut a long story short, after we purified this fraction, we found that it was an alpha chain variant due to a mutation in the alpha globin gene chain termination codon. Thus this variant had an elongated alpha chain due to translation of mRNA which was not normally translated.⁴⁴ This was rather nice because the group in Cambridge was sequencing alpha globin mRNA at the time, and we were able to give them the sequence they were going to find in advance, from the amino acid composition of the extended alpha chain variant. In the early 1970s we had found that babies who were stillborn with very severe alpha thalassaemia synthesized no alpha chains at all, raising the question of whether the alpha globin genes might be deleted. As John Old has told us, it became possible round about that time to synthesize complementary DNA, cDNA, on an alpha mRNA template.⁴⁵ We did not know how to carry out this type of hybridization, so we approached John Paul's group in Glasgow and suggested to him that if we could get material from one of these babies, and prove that the baby was not making alpha chains, and make cDNA, we could test the hypothesis.⁴⁶ He agreed and put two of his

⁴¹ Weatherall *et al.* (1965).

⁴² Alter (1990).

⁴³ Professor Sir David Weatherall wrote: 'A family was referred to us by Paul Milner from Jamaica with a relatively severe form of α thalassaemia in which a tiny amount of variant haemoglobin was present which was later called haemoglobin Constant Spring after the name of the suburb of Kingston in which the family lived.' Note on draft transcript, 26 March 2013.

⁴⁴ Professor Sir David Weatherall elaborated: 'Hence this variant was produced at a markedly reduced rate and caused the phenotype of α thalassaemia.' Note on draft transcript, 26 March 2013.

⁴⁵ Professor Sir David Weatherall wrote: 'And so we thought it might be possible to use the cDNA probes of this type to see if the α globin genes were present or absent in these babies.' Note on draft transcript, 26 March 2013.

⁴⁶ Dr John Paul (1922–1994) was Founding Director of the Beatson Institute for Cancer Research, Glasgow. For an obituary, see Freshney (1994).

post-docs, Bob Williamson and Sergio Ottolenghi, on the project.⁴⁷ Using this approach, in 1974, we found that these babies had complete deletion of both their alpha globin genes.⁴⁸ In the *Nature* paper that followed this work we saw, much to our surprise, and annoyance, a similar paper with an identical finding from Y W Kan's group.⁴⁹ Like us, Kan did not know how to carry out this type of hybridization but he had gone for advice to Harold Varmus, in California, who was using this technique.⁵⁰ They had carried out an identical experiment to us and got exactly the same result! So by the mid-1970s at least two forms of alpha thalassaemias had been defined at the molecular level. In the late 1970s the application of Southern blotting together with gene cloning allowed the further definition of the molecular basis of the alpha and beta thalassaemias.⁵¹ There was the big problem of 'everybody's going to be working on the same damn mutations, with a lot of wasted work'. One of the major problems that arose was the considerable amount of work that was required for cloning the globin genes and many groups were finding the same molecular defect after all this work. This problem was solved by several groups, who found that the globin genes were highly variable in their structure and that different haplotypes were linked to different mutations. So already by the early 1980s, a large number of molecular forms of thalassaemia had been identified and I think John (Old) of our group, together with Bernadette's group were probably the first to describe prenatal diagnosis of beta thalassaemia using chorionic villus sampling (CVS) for prenatal diagnosis.⁵² So that provides the background to the story of the period that we are discussing. Just one addition: in the early days of the haemoglobin field, we were able to start to understand the remarkable phenotypic heterogeneity of sickle cell anaemia and the different forms of

⁴⁷ Sergio Ottolenghi was based at the Beatson Institute for Cancer Research, Glasgow, Scotland (1973–1974) and is now Professor of Molecular Genetics at the University of Milano-Bicocca, Milan, Italy.

⁴⁸ Ottolenghi *et al.* (1974).

⁴⁹ Taylor *et al.* (1974).

⁵⁰ Dr Harold Varmus was Lecturer in the Department of Microbiology and Immunology (1970–1979), University of California, San Francisco, a Nobel Laureate in 1989 and Director of the National Institutes of Health, USA, from 1993 to 1996; <http://profiles.nlm.nih.gov/ps/retrieve/Narrative/MV/p-nid/184> (visited 30 May 2013).

⁵¹ See note 15.

⁵² See note 61 and pages 21–7. In addition to the account of how CVS developed in the following pages, a previous Witness Seminar on genetic testing held in 2001 also addressed this topic; see Christie and Tansey (eds) (2003), pages 43–9.

thalassaemia. In other words, we were able to ask the question: ‘You have the same mutation; why is the phenotype so different?’ I will not bore you with the findings of these studies now but I think it is still likely that these diseases are much better understood than any other monogenic diseases in terms of their phenotypic heterogeneity.⁵³

Bobrow: Fascinating.

Old: Shall I just talk about the service development? I think the thing to remember is, it was very exciting times in those days. From the moment you could Southern blot and you had these pure probes, you could start to make restriction enzyme maps of the globin gene clusters, mainly the beta globin gene cluster. There were half a dozen groups worldwide all competing with each other to produce maps and each had a supply of patient material as well, sort of mutant maps, especially the deletional types of thalassaemia, which were the most revealing types of mutations.⁵⁴ You kept these maps to yourself a bit. Then in 1978, Bob Williamson – I think he was the prime mover in this – organized a two-week conference in Crete at a monastery in Kolimbari, and managed to get virtually everyone from these labs worldwide to attend this conference (Appendix 1). Being a monastery, the nearest place was Chania about 15 miles away, and it was on the coast. There were one or two little tavernas nearby so we were very isolated and it was perfect for discussing research and it was probably the best conference I’ve ever been to because we all had our own maps, we all swapped data and it was so inspiring to see all this data put together. It made me want to go home and really work on this. Y W Kan was at this meeting and for 13 days he sat on that Hpa-1 data; he didn’t reveal it. We all revealed our maps: there were polymorphisms that we’d discovered but they didn’t exist in linkage disequilibrium so they were just different maps. On the very last day Kan produced this data about the Hpa-1 polymorphism being linked to the sickle gene in West Africans and it just blew everyone away. He was a showman. I’m sure he wouldn’t mind me calling him that because he loved to present data that way but it was a most impressive piece of data.⁵⁵ As well as that paper in 1978,

⁵³ See Weatherall (1965).

⁵⁴ Dr John Old wrote: ‘The main groups were: Orkin in Boston (Orkin (1978)), Kan in San Francisco (Kan and Dozy (1978a)), Bank in New York (Mears *et al.* (1978)), Maniatis in Pasadena (Lawn *et al.* (1978)), Williamson in London (Flavell *et al.* 1978)), B Forget in New Haven (Tuan *et al.* (1979)) and D Weatherall in Oxford (Higgs *et al.* (1979)).’ Edited from a note on draft transcript, 2 August 2013.

⁵⁵ In the Witness Seminar on genetic testing, Professor Sir David Weatherall recalled: ‘It was something of a difficult talk because the speaker, Yuet Wei Kan, had left all his slides on the aeroplane and had to *ad lib* as he went along.’ Quotation from Christie and Tansey (eds) (2003), page 32.

he also published a paper using the Hpa-1 polymorphism for the very first prenatal diagnosis of sickle cell using amniotic fluid DNA, so that really kick-started the idea that you could do prenatal diagnosis with amniotic fluid DNA.⁵⁶ In the same year Stuart Orkin's group published a paper showing you could do alpha thalassaemia, alpha-0 as we know now, where you have all the genes deleted, and also delta beta thalassaemia, which is again a gene deletion.⁵⁷ So by 1978 three different types of haemoglobinopathy had been diagnosed prenatally. The next step was in 1980. Again it was Y W Kan's group and they published the first prenatal diagnosis of beta thalassaemia and this was a link between the BamHI polymorphism and the beta thalassaemia mutation that is common in Sardinia, the codon 39 mutation.⁵⁸ By 1980, all the different haemoglobinopathies could be prenatally diagnosed. Then Kan's group again, in 1981, showed a different method and this was the direct detection of mutation by a restriction enzyme.⁵⁹ Up to now it had been polymorphisms but Kan showed that the enzyme DdeI could recognize the sickle cell site by either cutting or not cutting the DNA. The problem with DdeI, was that it produced very small fragments, which were very hard to see on a Southern blot because they were maybe 30 to 40 bases long. But in 1982 Stuart Orkin's group found and published the enzyme MstII which was much better; it gave much larger fragments – it was really easy to Southern blot.⁶⁰ Our group published the first chorionic villus DNA diagnosis in 1982 and this was with Bernadette and the group at University College Hospital.⁶¹ In just six years, or less, we'd moved from no prenatal diagnosis with DNA, through amniotic fluid DNA diagnosis by linkage of RFLPs, and then direct mutation detection through to first trimester CVS diagnosis.

Bobrow: Great paradigm.

Professor Bernadette Modell: I'm glad you mentioned the meeting in Crete because what we're moving on to now is the clinical application of the molecular methods that we've been talking about. From the clinician's angle, the clinical application of any method is a multidisciplinary activity. I'd also like to

⁵⁶ Kan and Dozy (1978b).

⁵⁷ Orkin *et al.* (1978).

⁵⁸ Kan *et al.* (1980).

⁵⁹ Chang and Kan (1981).

⁶⁰ Orkin *et al.* (1982).

⁶¹ Old *et al.* (1982).



Figure 10: Professor Bernadette Modell

emphasize the importance of meetings because when you're a clinician, you're not following all the basic science, but if you go to the right meeting and you meet the right person – who is longing to apply that science to help people – and you start talking to them, then you pick up on what the possibilities might be. So if you don't mind me winding back to go through a process of development, we have to go back to 1974/5 when there was a meeting of the Cooley's Anemia Foundation in the United States – a patients' group that supported scientific meetings with an emphasis on the clinical applications of science.⁶² I attended this meeting, and David (Weatherall) was there, and Y W Kan produced a very important paper.⁶³ Now, we're talking about the early 1970s when prenatal diagnosis was beginning to come in for neural tube defects, for Down's syndrome and the paediatricians and the obstetricians were beginning to see that this really had a future.⁶⁴ But I felt frustrated because, though I was

⁶² Founded in the 1950s, in the USA, by Frank Ficarra – a parent of two children diagnosed with thalassaemia major – Cooley's Anemia Foundation funds research into treatments and potential cures for the disorder; <http://www.thalassemia.org/> (visited 20 June 2013).

⁶³ Mr Craig Butler, of Cooley's Anemia Foundation, wrote: 'Yuet Wai Kan presented on "Intrauterine Diagnosis of Thalassemia" at the Third Conference on Cooley's Anemia, presented by the New York Academy of Sciences and the Cooley's Anemia Foundation on April 9 to 10, 1973.' Email to Ms Emma Jones, 17 May 2013.

⁶⁴ See note 18.

always interested in the application of genetics in medicine, and as a young paediatrician I had picked up on the haemoglobin disorders as the most common, really common, disorders. I was also interested in culture, and we had a growing multi-ethnic society. As I had a family and couldn't travel very much I thought, 'How nice. If I specialize in this I'll see people from lots of different cultures and I can learn about culture as well as haemoglobin.' I ended up running a thalassaemia clinic at University College Hospital where we had people of diverse backgrounds. So I was specializing in the clinical management of thalassaemia and what happened within a month, a few months of my having set up this clinic, was that a rather rapidly growing number of patients attended our own hospital or were referred to us from adjacent hospitals. The struggle for independence in Cyprus from 1957 to 1960⁶⁵ caused a large number – 10 per cent – of the entire Cypriot population to migrate to the UK because of civil strife and economic depression.⁶⁶ Most came to North London in the intake area of my hospital (University College), and adjacent hospitals, and so we started seeing thalassaemia major.⁶⁷ First of all, using the Hardy–Weinberg statistical technique, I counted up how many births there were and how many new cases there were, and worked out that at least 14 per cent of these people carried beta thalassaemia, which was a lot.⁶⁸ It turned out to be 17 per cent in the end.⁶⁹ So we had a population at very high risk, and patients started cropping up in all the hospitals round about, so I became a sort of referral centre. I very quickly found out that if a woman who had had a child with thalassaemia major became pregnant, they rang me up in a panic and asked me to arrange a termination because they were so afraid of having another child with this hopeless prognosis and a very punishing treatment of monthly blood

⁶⁵ See, for example, Anon. (1957) and Anon. (1960). In 1974 the island was *de facto* partitioned between Greece and Turkey. See also Greater London Authority (2009), in particular pages 7, 9 and 11.

⁶⁶ For more context from Modell on Cypriot migrants to the UK and thalassaemia statistics in their population, its presence in other ethnic groups in the UK and the effects of genetic counselling on birthrates of babies with thalassaemia major, see Modell and Berdoukas (1984); chapter 4, Thalassaemia in Britain; pages 78–9, 81–2.

⁶⁷ Professor Bernadette Modell elaborated: 'Cypriots first came to Camden by chain migration, then to Islington, and moved further north as they got more established and had families. Green Lanes in Haringey was favourite, near North Middlesex Hospital.' Note on draft transcript, 9 August 2013.

⁶⁸ Modell *et al.* (1972).

⁶⁹ Gill and Modell (1998), page 761.

transfusions. It was about this time that I went to the Cooley's Anemia meeting, and heard Y W Kan's paper.⁷⁰ Why was I frustrated? I was frustrated because these people wanted prenatal diagnosis and could we give it to them? No, because thalassaemia and sickle cell are both disorders of the beta globin gene, which only affects adult haemoglobin, whereas fetuses have fetal haemoglobin, so even if you could develop a technique for getting fetal blood, which wasn't available at the time, you wouldn't be able to make the diagnosis using conventional methods. At the Cooley's Anemia meeting Y W Kan presented a paper showing that in fact the early fetus did have a certain proportion, less than 10 per cent of haemoglobin A, and if you used radioactive labelling, you picked up synthesis rather than quantity, and you could detect haemoglobin A from about 11 to 12 weeks onwards. This meant that it would be possible to do prenatal diagnosis if you could get sensitive enough laboratory techniques, and if you could develop an obstetric technique for getting fetal blood on which to make the diagnosis. We felt this was so important and I ended up coming away from that meeting having established a link with David Nathan and Blanche Alter, in Boston.⁷¹ They had the same vision as us, but they could not proceed because legislation in Massachusetts meant that you could not do experimental work on the products of an abortion. So they couldn't develop it, whereas here we were in London, regularly arranging for highly at-risk women to have terminations of their pregnancies without any restriction on access to, or use of, the fetal material. So I started collecting material from terminations and sending it to my colleagues in the United States for analysis. Now, we had to be able to distinguish normal and heterozygotes – that was the crucial thing – and homozygotes who, in principle, shouldn't be making any or very little adult haemoglobin. It took quite a lot of work; you've all done this kind of work and know that the most demanding part of it can be collecting the material. At this time, I had patients coming to me, young women with one child with thalassaemia, saying they wanted to be sterilized, and I said, 'No, under no circumstances because it looks as if we might be able to do prenatal diagnosis.

⁷⁰ See note 63.

⁷¹ Dr David Nathan was Chief of Hematology at the Children's Hospital Boston (1967–1984) and is now President Emeritus of the Dana-Farber Cancer Institute, Boston. See http://doctors.dana-farber.org/directory/profile.asp?pict_id=0000299 and http://www.childrenshospital.org/cfapps/research/data_admin/Site309/mainpageS309P0.html. Dr Blanche Alter undertook a fellowship at Boston Children's Hospital in pediatric hematology/oncology and worked in David Nathan's laboratory. She is now a Senior Clinician at the National Cancer Institute, USA; <http://dceg.cancer.gov/about/staff-directory/biographies/A-J/alter-blanche> (all websites visited 24 June 2013).

Get your contraception organized.’ So all my patients’ mothers knew that this was in the wind: one of them was a Pakistani paediatric haematologist with a child who had thalassaemia major. She came in one day and asked, ‘How are you getting on?’ And I said, ‘It’s getting very exciting. Would you like to come into the lab and see?’ So I showed her results for five cases: we’d got one normal, three that looked like heterozygotes, one that looked like a homozygote, so it looked as if we could do it. She said, ‘Oh, that’s very interesting’, and she went away. We carried on. Three months later she rang up and said, ‘I’m pregnant. I want you to try and do a prenatal diagnosis because the worst you can do is cause a miscarriage, and if you won’t do it I’m going to have to terminate this pregnancy.’ I said, ‘But we haven’t got a technique for getting fetal blood.’ So I rang Blanche Alter in the United States and said, ‘A terrible thing has happened’, and I told her what had happened, and she started laughing. I said, ‘It’s not funny.’ She said, ‘I know, the same thing happened to us yesterday.’ The point I’m making here is that the patients really pushed the pace. I said to Blanche, ‘What are you going to do?’ and she responded, ‘Well, we’re going to try.’ In fact they had a couple of obstetricians who had been trying to develop techniques for fetal blood sampling with rather promising results. So I went to our Professor of Obstetrics, who had a background in prenatal diagnosis for Rhesus haemolytic disease – I called him Feather Fingers Fairweather – Professor Denys Fairweather, who is a Scot and it was a typical Scottish interview.⁷² I didn’t know him very well at the time but I stood in front of his desk and explained what had happened. There was a three-minute silence which he broke: ‘Alright, why don’t we try?’ So we tried and the end result was that we were hustle-bustled into actually having to provide a prenatal diagnosis service for thalassaemia. When the news got about, people started getting on planes in Cyprus, Italy and Greece to come for the service. We were under no illusion whatsoever that this was a service that was needed. But the experience was awful because we were only seeing patients at 25 per cent risk, which meant that we had 25 per cent affected fetuses, and 25 per cent of those women terminated that pregnancy, and they came at 18 weeks and they terminated at 20 weeks. As part of our clinical responsibility, we accompanied them; sat with them through the termination; showed them

⁷² Professor Bernadette Modell elaborated: ‘I became extremely fond of Denys, who was a wonderful operator and is a kind man. I was asked to give a talk at his Festschrift. In it, I described the development of our collaboration approximately as follows: I had said to Humphrey Ward – the obstetrician with whom we later developed CVS – that I found Professor Fairweather somewhat scary. He replied, “Oh don’t worry. He’s a Scot. The first three years are the worst.” The audience collapsed as they all knew exactly what was meant.’ Note on draft transcript, 9 August 2013.

the baby and discussed the baby with them at the end.⁷³ It was the same for all prenatal diagnosis at this time. I think it's important to emphasize and record that the experience of genetics for these women at that time was with techniques for prenatal diagnosis, which were at the absolute borderline of acceptability. Another important meeting was the one you have spoken about in Crete.⁷⁴ But before that, David (Weatherall) organized another meeting in Oxford where he brought Bob Williamson. When you met Bob you began to understand what it was all about. By the time we had the meeting in Crete, I was really getting a grip on what molecular biology could do and was thinking, 'Well, what can this add?' We've got a technique for prenatal diagnosis that actually is protein-based. It looks at the end product and on the whole it gives you a good diagnosis, though the cut-off is a bit shaky. It was clear to us that if the new molecular techniques could offer us the possibility of first trimester prenatal diagnosis that would be a major advance. So, having had the experience of developing one obstetric technique – fetal blood sampling – we were able to move on to develop CVS.⁷⁵ We approached women who were having social abortions, and they agreed for us to take samples during the procedure. Those samples were sent to John Old in David's laboratory to make sure that you could get DNA out, and we started collaborating with Bob Williamson's group, sending them material to do the diagnosis in parallel with us, so that they could compare their DNA

⁷³ Professor Bernadette Modell wrote: 'This was in the early 1980s, when it was becoming recognized that stillbirth was a bereavement and should be handled as such. Previously it had been customary in cases of stillbirth to try to protect the mother by hiding the baby and essentially trying to pretend it had never happened. Therefore, obstetricians and midwives began to show the dead baby to the mother and accompany her through the bereavement, including offering funeral and burial services. We agreed with Professor Fairweather that late termination of a wanted pregnancy fell into the same category, discussed it with the midwives, and used the same approach from the beginning of our prenatal diagnosis service. I was the person principally involved. It was, of course, very emotional, but from the beginning we understood it was the right thing to do. The mothers really appreciated the opportunity to greet and say goodbye to the baby. We were privileged to share these deep moments of truth with our patients – and it also helped to give us confidence in the service we were providing. This was a new concept at the end of the 1970s: it is standard practice now. Some mothers want photos. Some Church of England chaplains (and perhaps others) also offer a small service for the baby. I remember particularly one Cypriot uncle, resident in the UK, who accompanied his young niece who had come alone from Cyprus for PND (prenatal diagnosis) – when we discussed this he was shocked at first, but then said "Oh, I see, at least she will know she was a mother."' Note on draft transcript, 9 August 2013.

⁷⁴ See page 20.

⁷⁵ For another account of how chorionic villus sampling developed, from Professor Bernadette Modell and other Witness Seminar contributors, see Christie and Tansey (eds) (2003); pages 46, 47–9 and 50–1.

results with our protein-based prenatal diagnosis. In fact, they found that they could make the diagnosis using DNA.⁷⁶ Can I say one final thing, one very final thing, about the patients?

Bobrow: We have to move on. Sorry to hassle you but you understand why.

Modell: Yes, I understand. When we started using first trimester CVS for prenatal diagnosis, we had patients who had been through the old procedure. When they went through the new procedure we felt so gratified because they said, ‘It’s a miracle! The baby’s only “so big” and we already know the answer’, ‘so big’ being an inch. We felt wonderful; then, as time passed, we started getting patients who hadn’t been through the old procedure and they sat there and they looked at us just like the other ones used to do and said, ‘This is awful. Can’t you do anything better than this?’

Bobrow: That is a very important message. The links with the developing capabilities in prenatal diagnosis have also come out very clearly, as has the fact that the globin story is an absolute paradigm of how the science of disease genetics developed.⁷⁷ There is one question that I would like to put, which is whether the model for clinical delivery, as opposed to scientific discovery, presented in a way that turned out not to be the way in which clinical genetics services as a whole developed? I wondered whether you thought that, was there any special reason for that or do you have any reflections? Would you have preferred, from the position as a physician doing genetics, all of genetics to have stayed within mainstream departments of medicine and never to have run out into a separate medical and laboratory specialty?

Weatherall: Well it’s very interesting you say that. I’ve been cogitating on this question recently. The question you’re asking really is: Why did the haemoglobin field drift away from the mainstream of medical genetics?

Bobrow: Well, the other way around, I would put it. Let’s not quibble.

Weatherall: No, let’s not quibble about that. I just did not want to start with the inferior part of the field first. [Laughter] I think the only way I can put this together is to consider the way clinical genetics as a specialty developed after

⁷⁶ Little *et al.* (1980).

⁷⁷ Professor Martin Bobrow wrote: ‘As Weatherall says in the next paragraph, the intensive investigation of the globin genes meant that many broad principles were learned there long before the rest of the genetics field had caught up.’ Note on draft transcript, 31 July 2013.

World War II.⁷⁸ There really was nothing before that. It started in places like Baltimore and the west coast of the USA and one or two centres here in the UK. It was natural for those departments to focus on local diseases, as it were, chromosomal abnormalities in particular, and standard monogenic diseases. I suspect that what happened was that the haemoglobin disorders tended to drift into haematology departments and there was a beginning of the separation. This is the case if you look at the literature over the period, for example in Paul Polani's Royal College of Physicians lecture on genetics in 1988, there is a whole list of recessive diseases yet the haemoglobin disorders are not even mentioned.⁷⁹ In fact, they are not mentioned at all in this extensive lecture. Even as early as that the two fields had begun to drift apart. I think it is a great pity because, examining the current situation, I think there are so many lessons that both parties could learn from each other. We're not talking about genome-wide association studies here but these issues are particularly important in the field of phenotypic diversity. I well remember that when those wretched mice were developed with the cystic fibrosis mutation and a modifier gene was discovered, the message that 'monogenic disease is not as simple as all that' was paraded all over the literature, including *Nature*.⁸⁰ Yet we had known in the haemoglobin field for the previous 20 years that this was the case. I think you will find, in the haemoglobin field we still know a lot more about the genetic, environmental and adaptive factors that modify phenotypes of monogenic disease than any other conditions of this type. That is how it all happened. It is a shame it happened and I hope that there will be some kind of coming together again.

Bobrow: I have to say it's exactly my view but we aren't really dealing today with the whole history of cytogenetics, which also drove the clinical genetics agenda very strongly at around that time (late 1960s to early 1970s), but just differently – they were just ships that passed in the night.⁸¹ That was a really helpful discussion of a group of diseases but they are a pretty unusual group of diseases.

⁷⁸ Professor Malcolm Ferguson-Smith wrote: 'Arguably, clinical genetics did not take off as an effective practical service for patients before 1967 when prenatal diagnosis became an option. Prior to that, genetic counselling had little to offer and was mostly unavailable.' Note on draft transcript, 1 June 2013. See also Professor Peter Harper's comments in Harper *et al.* (eds) (2010), pages 5–7, and Professor Rodney Harris' comments in Christie and Tansey (2003), pages 64–5.

⁷⁹ Polani (1990).

⁸⁰ Ratcliff *et al.* (1993).

⁸¹ For histories of cytogenetics see Ferguson-Smith (1993) and Harper (2006).

Weatherall: What do you mean by unusual?

Bobrow: Unusual in the depth of understanding and the fantastic talent of the people who work on them. [Laughter]

Ferguson-Smith: There were links here with cytogenetics and mapping the globin genes. Although we knew which chromosomes they were on, from work on somatic cells, the actual position on the chromosome was determined by *in situ* hybridization using cDNA probes. This was done by Sue Malcolm, who worked in my lab on an MRC grant that Bob Williamson and I had together.⁸² So globins came into the *in situ* work as well and spurred on the development of FISH (fluorescent *in situ* hybridization).

Bobrow: Excellent, that ties that story together as well. Very satisfying; thank you for reminding me Malcolm.

Professor John Yates: Well, I struggle a bit to know where one starts with such a large topic but I'll start with how I got into this whole game. I was training as a paediatrician when I got interested in genetics and so I spent a year with Alan Emery in Edinburgh learning some medical genetics.⁸³ Then, in 1982, I went to work with Malcolm Ferguson-Smith in Glasgow where there was a very strong interest in gene mapping. Two years previously Botstein and colleagues had published their famous paper describing how restriction fragment length polymorphisms could be used to map genes.⁸⁴ I think it's easy to forget how feeble the resources were to map human disease genes at that time; there were just a handful of blood groups and a few protein polymorphisms with very low heterozygosity. The effect of that paper, certainly in Glasgow, was quite dramatic because Malcolm had a very well set up laboratory with experienced technical staff who could type all the blood groups, and protein polymorphisms, and that was rapidly being shut down when I arrived in 1982, and these people had to retrain to type RFLPs. Although that was a major advance in terms of giving us a handle for gene mapping, again it's easy to forget just how rudimentary even the RFLPs were at that time and indeed the difficulty of typing RFLPs, certainly in my hands, in the lab. Southern blot analysis was problematic; you

⁸² See Professor Sue Malcolm's biography on page 106 and Malcolm *et al.* (1977).

⁸³ In 1964 Professor Alan Emery founded the first medical genetics clinic in the UK outside London, in Manchester. He became Professor of Human Genetics at the University of Edinburgh in 1968. See Professor Peter Harper's interview with him at <http://www.genmedhist.info/interviews/Emery%20Alan> (visited 31 May 2013).

⁸⁴ Botstein *et al.* (1980).

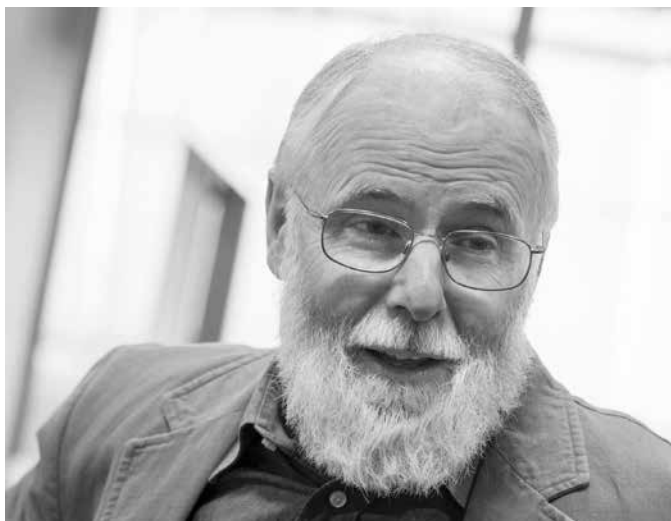


Figure 11: Professor John Yates

had to get the chemical buffer exactly right or the background was terrible. It could take you up to two weeks to get a result and if the wretched nitrocellulose filter fell to bits, as they often did, you'd find yourself trying to reconstruct it like a jigsaw to stand a reasonable chance of getting an autoradiograph at the end. If you were lucky, you'd genotype perhaps a dozen subjects – it was hard work. I rapidly got recruited to this activity, partly because before doing medicine I had done some maths at university and so I was asked to try and sort out the linkage data, which I found quite a struggle. My recollection of that time was first of all trying to understand what linkage analysis was all about and then getting my head around the complicated computer programmes, and then trying to get enough computing power to actually do the analysis, which, in Glasgow at that time, required the use of the university mainframe computer. If I wanted to run a multi-factor analysis, I had to negotiate the use of this machine for the weekend, because its power was so feeble. Malcolm's interest, of course, was in the X and Y chromosomes and sex determination and, in particular, the tip of the short arm of the X chromosome and trying to understand the phenomenon of X chromosome inactivation.⁸⁵ The first disease I worked on was X-linked ichthyosis because the steroid sulphatase gene associated with that condition escapes X inactivation and was known to be on the short arm of the X chromosome. Much of my time for the first year or so in Glasgow was spent chasing around all over the country trying

⁸⁵ For his early work see, for example, Ferguson-Smith (1965).

to find families with this skin condition and doing linkage studies.⁸⁶ The X chromosome is certainly my favourite chromosome because linkage analysis on it is so much easier than on the autosomes and not only that, but of course X-linked inheritance is usually obvious from a family tree and so diseases and traits are much more easily assigned to the X chromosome than the autosomes. When I started working on the X chromosome, following the Human Gene Mapping Workshop in Oslo in 1981, there were over 100 genes assigned to the X chromosome, which was well in excess of any of the autosomes.⁸⁷ Although we knew a lot of diseases that were on the X chromosome, the map of the X chromosome was rudimentary.⁸⁸ Effectively there was a linkage group on the tip of the short arm dependent on the Xg blood group, and a linkage group on the tip of the long arm dependent on colour blindness and G6PD. But rapid progress was made with the use of RFLPs and at the same time as the genetic map was being developed, there was also steady progress being made with physical mapping using, first of all, yeast artificial chromosome clones and pulsed field gel electrophoresis and then other techniques. Spectacular progress was achieved by extensive international collaboration – that was the key – with the sharing of resources and information. That collaboration was driven by the international Human Gene Mapping Workshops that were held through the 1970s and the 1980s – also in 1990/1.⁸⁹ And for those of us who were interested in the X chromosome, of course, there were chromosome-specific workshops. For me the key workshops on the X were held in St Louis in 1993, Heidelberg in 1994, Banff in 1995 and, finally, Cambridge in 1996.⁹⁰ There was extensive

⁸⁶ Yates *et al.* (1987).

⁸⁷ The Sixth International Workshop on Human Gene Mapping took place at the University of Oslo, 29 June to 3 July 1981. See Berg (1982).

⁸⁸ See, for example, Miller and Siniscalco (1982).

⁸⁹ The First International Workshop on Human Gene Mapping was held at Yale University, New Haven (1973). See Ruddle *et al.* (eds) (1974) for the published report and papers from the workshop. Subsequent Human Gene Mapping Workshops (HGMW) took place in Rotterdam (1974); Baltimore (1975); Winnipeg (1977); Edinburgh (1979); Oslo (1981); Los Angeles (1983); Helsinki (1985); Paris (1987); interim meeting New Haven (1988); New Haven (1989); Oxford (1990); London (1991). Full reports and papers from each HGMW are published in the journal *Cytogenetics and Cell Genetics*. See also note 4.

⁹⁰ International Workshops on the Human X Chromosome are all documented in *Cytogenetics and Cell Genetics*. For St Louis see Schlessinger *et al.* (eds) (1993); for Heidelberg see Willard *et al.* (eds) (1994); for Banff see Nelson *et al.* (eds) (1995). For Cambridge, 1996, Professor John Yates confirmed that a report was not published. See correspondence deposited with the archives of this meeting in the Wellcome Library at GC/253.

collaboration, albeit with some healthy competition as well, and there was some great teamwork between clinicians and scientists, which was also key to the progress that was made. Clinicians were recruiting and evaluating families for genetic studies but were also spotting unusual patients, who sometimes were the key to isolating particular disease genes. Of course, the families also played an important role in taking part in the studies by raising significant amounts of funding through their patient organizations – much of my research over those years [in the 1990s] was funded by patient organizations.⁹¹ What about Duchenne? I think no disease better exemplifies the success of this sort of collaboration than Duchenne muscular dystrophy (DMD). The cloning of the Duchenne gene is well documented; I'm not going to try and go through that in any detail at all, and in any event there are other people here who are much better qualified to talk about that than I am.⁹² But the positional cloning of the Duchenne gene depended on all the factors that I've already mentioned. There were invaluable contributions from clinicians identifying, for example, girls affected by Duchenne due to X autosome translocations who were crucial to the cloning of the gene, and the identification of the key patient, BB, who had a huge deletion that not only caused DMD but also chronic granulomatous disease, retinitis pigmentosa and the McLeod phenotype. These meetings also enabled the recruitment of large numbers of Duchenne patients and families in many centres right across the world. There was outstanding work done by all the scientists who were involved in this activity. With regard to international collaboration, just to take one example, when Lou Kunkel's lab identified the pERT-87 probes that could detect deletions in some Duchenne boys,⁹³ these were made widely available for researchers right around the world and led to data being collected on well over a thousand cases in quite a short period of time, which was a tremendous achievement. These discoveries were very rapidly implemented clinically. If we think of the beginning of the 1980s, determining

⁹¹ For research funded by the Muscular Dystrophy Group of Great Britain, see Yates *et al.* (1993) and by the Tuberous Sclerosis Association (UK) and National Tuberous Sclerosis Association (USA), see Green *et al.* (1994).

⁹² Professor Bert Bakker wrote: 'The most important events in this were the BB deletion detected by Uta Francke *et al.*, the probe 754 cloned by Hofker *et al.* (our Leiden group), p754 was located within the BB-deletion, and the work by Kunkel *et al.* to isolate more clones from the BB-deletion which enabled Monaco *et al.* to clone the DMD gene.' Note on draft transcript, 18 July 2013. See Francke *et al.* (1985); Hofker *et al.* (1985); Kunkel *et al.* (1986) and Monaco *et al.* (1986). See also Davies *et al.* (1983) and Bakker (1989), in particular pages 17–30.

⁹³ Kunkel *et al.* (1986).



Figure 12: Dr Rob Elles

carrier status for Duchenne relied on pedigree analysis and a measurement of serum creatine kinase levels, but once the gene had been mapped, linkage data was also taken into account.⁹⁴ Still, the results often left families with great uncertainty. Advising a woman who was contemplating starting a family that she had a 20 per cent risk of being a carrier and therefore a five per cent chance of having an affected child was not really terribly helpful. All that changed dramatically for two thirds of families when it became possible to identify a deletion in the Duchenne gene.⁹⁵ Carrier detection immediately became more straightforward and reliable; prenatal diagnosis was an option. I think it's fair to say that many diagnostic laboratories cut their teeth on the molecular genetics of DMD.

Dr Rob Elles: I worked in Bob Williamson's lab in St Mary's Hospital, in Paddington, as a technician from 1977 to 1983 and for most of that time I was associated with Kay Davies' group. Her group started to work on the X chromosome I guess about 1978 or 1979. At that time, as Bert has already described, we needed to pick out clones that were extracted from whole human DNA cut with a restriction enzyme. Of course, if you took the whole genome, then finding a probe that was relevant, for example for the X chromosome, was a pretty inefficient process – although Bert did it magnificently.⁹⁶ So there was a lot

⁹⁴ Harper *et al.* (1983).

⁹⁵ See, for example, Monaco *et al.* (1985).

⁹⁶ Hofker *et al.* (1985).

of effort to try and purify fractions of the genome in order to make that process more efficient and there were some weird and wonderful machines that were used.⁹⁷ I remember a huge slab of agarose in a cylinder and there was an attempt to electrophorese the material out and collect fractions and then clone that – I don't think that was ever very successful.⁹⁸ But one approach which was successful in Kay Davies' group was a collaboration with Bryan Young from Glasgow, which involved Fluorescence Activated Cell Sorting (FACS) of chromosomes.⁹⁹ They took a cell line that had four copies of the X chromosome, again to enrich for the X chromosome, successfully FACSed that material, collected fractions and then cloned the material into a bacteriophage vector, lambda G2WES.¹⁰⁰ There was a bit of a production line going on in the laboratory: there was a doctoral worker who was responsible for the ligations and then the ligations went into the transfections, and my job was to plate out clones and to be the curator of the cloned library. Once we had clones, we picked them out into grids and our first method of identifying whether we might have a single copy probe was to hybridize blots on nitrocellulose filters taken from those plates, with whole human DNA. Those clones that did not light up on the autoradiograph were candidates as being single copy clones, and in fact I've got an artefact here that is one of the plates which is gridded out.¹⁰¹ At that time [in 1982 to 1983], we worked with Marcus Pembrey's group in Great Ormond Street and there was

⁹⁷ See, for example, Carreira *et al.* (1980).

⁹⁸ Dr Rob Elles elaborated: 'We also trialled but did not persist with a centrifugal method that involved pumping a mixture of DNA restriction fragments through a coil containing a two-phase organic system.' Note on draft transcript, 14 August 2013. See Elles and Sutherland (1980).

⁹⁹ Professor Bryan Young was a Research Fellow at the Beatson Institute, Glasgow, from 1972 to 1984. See <http://www.bci.qmul.ac.uk/index.php/staff/item/bryan-young.html> (visited 1 July 2013)

¹⁰⁰ Davies *et al.* (1981).

¹⁰¹ Dr Rob Elles brought a sample of one plate on a transparency to the meeting, but we were unable to reproduce this successfully as a printed image. He further explained: 'The clones were grown on a Petri dish in a grid pattern and screened with a probe labelled with a radioisotope that was specific for the highly repeated sequences that are widely scattered in the genome. A dark signal represented a clone that contained repetitive DNA and was not useful as a bio-marker. Some clones did not darken the film and these were candidate markers to help map inherited diseases such as Duchenne muscular dystrophy carried on the X chromosome. The clone in the C8 position was shown to be close to the DMD gene and was one of the first biomarkers to be applied in tracking the DMD gene through families.' Email to Mr Adam Wilkinson, 26 February 2013. A digital copy of this sample can be viewed on the History of Modern Biomedicine Research Group's website, and one will also be deposited with the records of this meeting in the Wellcome Library at GC/253.

a kind of ‘proof of concept’ paper that we published with his group about how this particular RFLP might be used as a linked marker for carrier detection and prenatal diagnosis.¹⁰² We showed that, in a woman heterozygous for RC8, male fetal material would only inherit one allele clean from the second allele that the woman carried, and so it demonstrated that chorionic villus biopsy diagnosis was possible and could be free from maternal contamination. So that work went on at St Mary’s and my own personal story is that I was quite interested in the clinical application of these technologies and actively looked to move from the research environment into the clinical environment. Bob Williamson was always very helpful about moving his people on in their careers and said, ‘Well, either go to Cardiff or Manchester’ and I would have been very happy to go to Cardiff but in fact I went to Manchester, where I had family links, in 1983. One of the things that astonished me in moving from a research environment into that clinical environment was the efficiency with which the clinical department could gather samples from families with experience of DMD. It was very far-sighted of that clinical community to start to develop voluntary family registers in advance of these technologies being available because that really drove the clinical application of these technologies. We worked with Andrew (Read), and we were quite quickly able to establish a series of families from the North West and started to demonstrate in a real clinical environment the application of these technologies.¹⁰³

¹⁰² See Pembrey *et al.* (1984). Professor Marcus Pembrey was Consultant Clinical Geneticist at the Hospital for Sick Children, Great Ormond Street from 1979 to 1998. See also his biography on page 109. Professor Marcus Pembrey commented: ‘I would like to emphasise the key role of Bob Williamson’s lab and Kay Davies’ X chromosome library. Kathy Harper was a laboratory technician I met during my haemoglobinopathy work in Saudi Arabia and Bob agreed to let her train in his lab as part of a grant I had to investigate Fragile X. When the DX13 probe proved not to be linked to Fragile X, Robin Winter suggested we look at the haemophilia A families he had collected with Ted Tuddenham. DX13 was closely linked and we immediately applied it clinically for carrier testing and prenatal diagnosis (or exclusion) with Kathy Harper doing much of the service work until Sue Malcolm and Helen Middleton-Price arrived. It was very stimulating in the early 80s – we learnt as we went along. I remember how the ability to “exclude” a male fetus being affected, even though we could not determine the mother’s carrier status, dawned on us (actually I think it dawned on John Burn, who was training with us) during a clinical meeting. I also remember introducing the term “gene tracking” (wrote it in my diary) to avoid the clumsy “by linkage analysis”, to see if it would fly – it lasted a few years and even got into Strachan and Read (1996).’ Note on proof transcript, 1 November 2011. See Harper *et al.* (1984) and Winter *et al.* (1985).

¹⁰³ Read *et al.* (1986). For the records of the North West of England’s Regional Genetic Register, based at St Mary’s Hospital, Manchester, see the papers of Rodney Harris, archival reference GB 133 ROH, located at The John Rylands University Library, University of Manchester.

Bakker: I will go back a little bit to how I came to switch from pure research into the clinical setting. Around 1981 we had these RFLP-detecting clones, a whole set of 20 to 30 clones we had made that were unique and displayed polymorphisms all over different places in the human genome and we had to localize them to different chromosomes with somatic cell hybrids. One was on the X chromosome. Peter [Pearson] went to the HGM (Human Gene Mapping) Workshop in Oslo and showed all these polymorphisms. Then he went to the human genetics conference in Israel and there he met, on the airplane, a guy from a patient organization in the Netherlands and he was Ysbrand Poortman, who was interested on behalf of the families with DMD.¹⁰⁴ He told Peter, ‘If you have a DNA probe on the X chromosome, you could work on DMD.’ So Peter came back in 1981 to Leiden and he said, ‘We are going to work on Duchenne muscular dystrophy.’ I was doing research, finding polymorphic clones and putting them on the human genome map. He hired a clinician, a clinical geneticist in training – clinical genetics was not yet a specialty at that time. This guy, Henk Venema, went out to the families to get DNA samples in for linkage analysis of the Duchenne gene. In the meanwhile we had had contact with Bob Williamson’s group (St Mary’s Hospital) to exchange their probe RC8 with our L1.28 and together we could do carrier detection by linkage.¹⁰⁵ In a small number of the families we showed carrier detection was possible. At that time, there was a PhD student in our lab, Marten Hofker, who made more of these polymorphic probes, one being probe 754, which later turned out to be located within the deletion of the BB patient, described by Uta Francke.¹⁰⁶ By using more of these probes we could improve the linkage analysis and get very high informativity over the whole region and perform carrier detection in most of the families. Also, in 1984, the first prenatal diagnosis worldwide for DMD took place.¹⁰⁷ Prenatal diagnostics was going into the clinic and we had to choose either research or diagnostics. Gert-Jan van Ommen, who had started in Leiden in 1983 said, ‘I will go with research and try to find the gene defect in DMD.’¹⁰⁸ I said, ‘Okay, I will do the DNA diagnostics side, setting up the DNA diagnostics

¹⁰⁴ See note 87 for Oslo meeting. The Sixth International Congress of Human Genetics took place in Jerusalem from 13 to 18 September 1981. See Bonn -Tamir (ed.) (1982).

¹⁰⁵ Davies *et al.* (1983).

¹⁰⁶ See note 92.

¹⁰⁷ Bakker *et al.* (1985).

¹⁰⁸ Subsequently, Professor Gert-Jan van Ommen was Head of the Department of Human Genetics, Leiden University Medical Center; <http://rd-neuromics.eu/contact/gert-jan-van-ommen/> (visited 11 September 2013).

lab.’ At the same time, requests came through for Huntington’s, for haemophilia, so around 1984/85 we started up the whole DNA diagnostic clinical setting. But at that time it was not yet financed. The finance for the clinical work came only later. The first money we got from the Dutch Medical Research Council and Dutch Prevention Funds was to stimulate the development of techniques for diagnosis and therapy. With this research funding, we showed that prenatal diagnosis was possible, and then we asked the health insurance companies to give money for genetic tests. Now, I have to go a little back in time to explain how the clinical setting arose because genetic counselling started in the Netherlands in the 1980s.¹⁰⁹ So the rise of clinical genetics was actually from different disciplines, from haematology, from ophthalmology and all different areas where genetic diseases were apparent. At a certain point the acting clinical geneticists or the paediatricians came together and said, ‘Okay, we should form clinical genetics centres funded by the government.’ It was in 1977, I think, this plan was already discussed by Hans Galjaard in the Health Council Committee.¹¹⁰ In 1980 clinical genetics centres started; eight all aligned to university medical centres with funding for genetic counselling, cytogenetics and prenatal diagnosis, or prenatal diagnosis for what was possible at that time: haemophilia and the three haemoglobinopathies. There was lots of cytogenetics in clinical genetics at that time. The people involved were, of course, Hans Galjaard from Rotterdam, who really drove things to get the funding and Professors Anders and Geerts and other people in the Netherlands helped; also Peter Pearson for the cytogenetics.¹¹¹ And then the eight centres were set up, but the committee was demanding that it would be a foundation outside of, but aligned to, the university medical centres and specialized because they were afraid that the money that they put into clinical genetics would diffuse into the academic centres. This was the foundation of clinical genetics services and these services had

¹⁰⁹ Professor Bert Bakker wrote: ‘Genetic counselling in the Netherlands was set up between 1979 and 1983 as individual foundations aligned to each of the eight university hospitals. The driving force behind the start and later the recognition of clinical genetics as a medical profession was Professor Hans Galjaard from Rotterdam.’ Note on draft transcript, 18 July 2013.

¹¹⁰ The Health Council of the Netherlands, in the organization’s own definition, ‘is an independent scientific advisory body. It is our task to provide the government and parliament with advice in the field of public health and health/healthcare research’. Quoted from the Council’s website; <http://www.gezondheidsraad.nl/en> (visited 25 June 2013).

¹¹¹ In the Netherlands, Professor Hans Galjaard initiated medical genetics research at Erasmus University Rotterdam; see <http://www.genmedhist.info/interviews/hans-galjaard-interview> (visited 30 May 2013); G J Anders was Professor of Antropogenetica at the Department of Human Genetics, State University of Groningen from 1965 to the early 1970s. S J Geerts was Professor of Antropogenetica at the Department of Human Genetics from 1965 until the early 1970s at the Radboud University, Nijmegen Medical Centre.

cytogenetics and counselling and, of course, biochemical genetics which was, at that time in Rotterdam, very strong. Later, in 1985, when we had these DNA probes ready, DNA diagnosis could come in. In 1988 we asked the government to fund the DNA-diagnostics as well. Each of the eight centres was asked: ‘Who is doing diagnosis for what?’ In Leiden we did Duchenne, haemophilia and Huntington’s; in Groningen it was retinoblastoma and SMA (spinal muscular atrophy); in Nijmegen it was myotonic dystrophy (MD); and in Rotterdam, Fragile X and CF (cystic fibrosis). We got a lump sum for each of the four laboratories, so these four centres started. The other four centres didn’t yet have DNA techniques running. With this lump sum of money we could show that it worked and, after a couple of years, and a health technology assessment in 1988, it was officially funded.

Bobrow: Actually, that was not a dissimilar model for service provision in the UK but different in a few important respects that we might come back to later.

Harper: Just before we leave the X chromosome, I’d like to reinforce some of the things that people have already said about Bob Williamson and also Kay Davies, who together really were such a powerful combination at that time. Bob’s enthusiasm and the collaborations he created were quite outstanding and, even more so, the number of people that he trained in some way or another who went on to form very distinguished careers themselves elsewhere, including Gill Bates, Keith Johnson and Brandon Wainwright, among many others. It’s an extraordinary list.¹¹² We were very fortunate in Cardiff to start collaborating more or less as soon as Bob had come down from Glasgow to London [in 1976]. Bob was just starting to think about Duchenne, perhaps largely as a proof of principle, as Rob said, and realized that we had very large numbers of well-worked-on families, which we’d done quite a bit with in terms of linkage analysis and broad family analysis and which were, so to speak, there to be studied. So that was the beginning of our collaboration – firstly Kay coming back from France where she’d been and I remember the great changes in the lab that she brought to London.¹¹³ She very rapidly moved from cystic fibrosis to the X chromosome. I remember her going to Bryan Young for chromosome sorting and the excitement that came out from those first probes. I remember in particular when the RC8 probe came out and we were looking at a sample in a Duchenne presumed heterozygote and there

¹¹² For further details on Professor Bob Williamson’s influence on the careers of others, see Professor Peter Harper’s interview with him at <http://www.genmedhist.info/interviews/Interviews%20web> (visited 25 June 2013).

¹¹³ See note 27 for details of an interview with Professor Dame Kay Davies by Professor Peter Harper in which she discusses her time in Paris.

were two bands.¹¹⁴ I said to Kay and Bob, ‘Look! You can absolutely, definitely see two bands; this person’s a definite heterozygote.’ They looked a bit blankly at me and said, ‘Well, yes, of course, you see two bands: it’s DNA.’ What they hadn’t realized from the point of view of clinicians working with X-linked diseases, is how frustrating and difficult it had been until then, that every phenotypic or biochemical test you did on heterozygous females had a quite sizeable margin of error due to X-inactivation; there were people who you just couldn’t pick up.¹¹⁵ Having DNA probes just removed that uncertainty at a stroke. I remember also that Bob had a fairly naive idea about how rapidly you could progress and after we’d looked at the first family he turned to me and said: ‘Do you mean to say we need more than one family to prove linkage in Duchenne?’ I had to let him down gently and said, ‘Well, 25 families might do it.’ At the same time, we got a bit of discouragement because we went to a meeting of the Muscular Dystrophy Group of Great Britain [and Northern Ireland] and were presenting some of our data – not the linkage then – when John Edwards got up and proved mathematically that it was quite definitely impossible to find the Duchenne gene by linkage and we looked rather sheepish, because we already had some suggestion of linkage by then, and said nothing.¹¹⁶ But John convinced the whole panel there that it was definitely impossible and probably not worth funding, although I don’t think he actually said that. Then at the same time, in the early 1980s in Cardiff, we were also working on the Becker late onset, X-linked dystrophy. Received wisdom had said that the gene was located at the other end of the X chromosome. My colleague Helen Kingston showed very rapidly that it wasn’t and it was indeed likely to be allelic to Duchenne.¹¹⁷ At that time we had a site visit from the Muscular

¹¹⁴ Davies (1985). For details of the X chromosome library see, in particular, pages 243–4, and for the RC8 and other Duchenne muscular dystrophy-related probes, see page 245.

¹¹⁵ Professor Peter Harper elaborated: ‘Because one of the two X chromosomes in the cells of a female is randomly inactivated, there will be some Duchenne carriers that have most cells with the abnormal X chromosome inactivated, making conventional tests give a normal result. Conversely, a few heterozygotes will have most of their normal X chromosomes inactivated and may have symptoms. This had been a long-standing, general problem for carrier detection of X-linked disorders – hence my excitement at seeing an unambiguous result for the DNA of Duchenne heterozygotes.’ Note on draft transcript, 23 August 2013.

¹¹⁶ John Edwards (1928–2007) was Professor of Human Genetics at the University of Birmingham (1971–1979) and Chair of Genetics at University of Oxford, Keble College (1979–1995). His archival papers, which have been catalogued by the Genetics and Medicine Historical Network project at Cardiff University, are available for public consultation at the Cadbury Research Library: Special Collections, University of Birmingham, at reference US99.

¹¹⁷ Kingston *et al.* (1983). During this period Dr Helen Kingston was a Clinical Research Fellow and trainee in medical genetics at Cardiff University.



Figure 13: Dr Helen Middleton-Price

Dystrophy Group [of Great Britain and Northern Ireland]¹¹⁸ and I showed them rather proudly our Becker family records and they were very indignant and said, ‘What do you mean? We funded you to work on Duchenne. Why are you using our money to work on a completely different disease?’ Well, it turned out okay in the end.¹¹⁹ But those early days were, well, they were very exciting, but it was just a unique time and Bob’s contribution – I’m sorry he has to be in Australia rather than here so he can’t tell it himself – was huge.

Dr Helen Middleton-Price: I’d like to talk a little bit on behalf of Marcus Pembrey and Sue Malcolm who can’t be here today.¹²⁰ I joined Sue Malcolm’s lab in the department of Marcus Pembrey at the Institute of Child Health, Great Ormond Street in 1985. I was a research assistant doing my PhD at the time but, of course, we all sat in the same lab cheek-by-jowl with the new Special Medical Development lab, which started in May 1985.¹²¹ One of the great things about working with Marcus and with Sue was their capacity for collaboration and the way that enabled us to develop the techniques that we started to use in the lab. In

¹¹⁸ This organization is now called the Muscular Dystrophy Campaign; see <http://www.muscular-dystrophy.org/about/history> (visited 29 May 2013).

¹¹⁹ Professor Peter Harper clarified that the Becker and Duchenne genes ‘proved to be alleles, both at Xp21’. Note on draft transcript, 23 August 2013. See Murray *et al.* (1982) and also Davies *et al.* (1983).

¹²⁰ For Professor Marcus Pembrey see note 102 and for Professor Sue Malcolm see note 82.

¹²¹ Middleton-Price (1989).

particular, I remember the work of Judith Goodship with the immunologists and the late Roland Levinsky, and his department's work on the development of carrier detection and prenatal diagnosis for the very rare paediatric immunodeficiencies, in particular X-linked agammaglobulinaemia (XLA) and severe-combined immunodeficiency (SCID).¹²² We had to work very closely with the clinical and research departments to develop linked probes for these conditions and also to develop carrier detection methods using X chromosome inactivation studies in B cells for XLA, and in T cells for X-linked SCID.¹²³ I think that the outward-facing, collaborative capacity also created an enormous number of opportunities in ICH and Great Ormond Street too.

Read: Just in passing, I was interested in Peter's anecdote about John Edwards 'proving' that linkage in Duchenne was impossible because I had an extremely similar experience about CF where he proved to me that that was 'impossible'. I pointed out to him that you could actually establish phase from the grandparents and this was clearly something he had somehow overlooked. At that moment I had this embarrassing situation where he believed that I was one of the very few people apart from himself and Newton Morton who understood linkage and, of course, this led to me going about the whole time believing that I was a fraud about to be unmasked.¹²⁴ [Laughter] Also, with regard to what you (David) were asking before about the difference between the haemoglobinopathies and the other diseases,¹²⁵ maybe part of it is that they were recessive conditions and you didn't get the big, extended families. Certainly in Manchester, the model on which we were working all the time was one in which the risk extended

¹²² Professor Judith Goodship was based at the Mothercare Department of Paediatric Genetics, Institute of Child Health, Great Ormond Street Hospital for Children, University of London, as a Lecturer in Clinical Genetics/Honorary Registrar in Clinical Genetics (1985–1988) and is now Professor of Medical Genetics at Newcastle University. Details confirmed in an email from Dr Helen Middleton-Price to Ms Emma Jones, 20 August 2013. Professor Roland Levinsky (1943–2007) was Hugh Greenwood Professor of Immunology at the Institute of Child Health, University College London (1985–2002).

¹²³ See Lau *et al.* (1988); Goodship *et al.* (1988) and Goodship *et al.* (1989). Prior to these research developments, Professor Marcus Pembrey noted that the Department of Paediatric Genetics was 'the first to publish a useful probe for haemophilia A, with a series on clinical use including prenatal diagnosis'. Email to Ms Emma Jones, 28 October 2013. See Harper *et al.* (1984) and Winter *et al.* (1985).

¹²⁴ Newton Morton is Senior Professorial Fellow in Human Genetics at the University of Southampton, formerly Director of the Cancer Research Campaign Research Group in Genetic Epidemiology at Southampton, from 1987, and Director of the Population Genetics Laboratory at the University of Hawaii (until 1985). See <http://www.genmedhist.info/interviews/Morton> (visited 1 October 2013).

¹²⁵ See page 28.

beyond the nuclear family. We had a genetic register that we'd set up in 1980, inspired by a register that Alan Emery had in Edinburgh called *RAPID* (Register for Ascertainment and Prevention of Inherited Disease).¹²⁶ I think *RAPID* was more of an epidemiological tool, whereas ours was very much a management tool.¹²⁷ We established this register for Duchenne, for Huntington's and for adult polycystic kidney disease.¹²⁸ We saw that as a very central tool for our ability to deliver a service to these families. When we started on the early Duchenne stuff, after I had been to Bert Bakker and Peter Pearson's course in Leiden, we set up 'DNA corner' and then we were able to bring Rob (Elles) in, who could actually make these things work.¹²⁹ He brought the RC8 probe and Peter and Bert generously gave us L1.28, with which we worked through our families. That

¹²⁶ Emery *et al.* (1974).

¹²⁷ Dr Rosalind Skinner commented: '...*RAPID* was really more than an epidemiological tool. It was used to facilitate patient and family management.' Note on draft transcript, 24 April 2013. *RAPID* was the first computerized genetic register to be created with the intention of preventing 'a greater proportion of cases of serious unifactorial disorders', through ascertaining individuals who could benefit from genetics advice. Quote from Emery *et al.* (1974), page 145.

¹²⁸ For adult polycystic kidney disease, see Elles *et al.* (1994).

¹²⁹ For the University of Leiden course, see note 24. Professor Andrew Read elaborated: 'Initially we had about two metres of bench in a corner of the cytogenetics lab. Personnel were myself and Jonathan Waters, who was a member of the cytogenetics lab staff – I suppose he must have been allowed to spend time on the DNA work. There were no salaries specifically for DNA work until Rob Elles arrived on our first grant, a Locally Organised Research grant by the local NHS to Rodney Harris – I can't remember whether or not I was a co-applicant. As for what we were doing, it was mainly learning how to extract DNA from blood (our own, or volunteers among lab staff), digest with restriction enzymes and run gels. Also developing some infrastructure – I wrote programmes to set up and maintain databases of samples, tests and results, and we started the DNA archive (sample 82/0001 was my DNA). We didn't attempt Southern blotting until Rob came, although I had had a go at it in Leiden – it would have meant tooling up for P-32 radioactive work, which would have been a big development. A couple of years previously, I had introduced the acetylcholinesterase test into the lab – a method of testing amniotic fluid for fetal neural tube defects, as a supplement to measuring alpha-fetoprotein. My main work pre-DNA was on neural tube defects; but also I knew I had to up the biochemical expertise in the lab in anticipation of the work becoming more molecular, and this test, using polyacrylamide gel electrophoresis, was a step in that direction. So we had electrophoresis rigs and I can't remember whether we borrowed or bought one for the DNA. I suspect initially we were using polyacrylamide gels – I remember eventually the hospital workshop made some tanks for us for running horizontal submerged agarose gels. They didn't work very well, so we bought commercial ones. We could check the quality of the whole procedure because DNA digested with HindIII (I think) enzyme gave some discrete male-specific bands derived from the Y chromosome, which you could see directly on the gel by UV fluorescence. As for equipment, we must have had a gel rig, some general biochemical stuff like pipettes, a water bath, probably a pH meter. We must also have had a UV light in the cytogenetics darkroom for looking at our gels, but nothing very much at first.' Note on draft transcript, 4 July 2013.

first cycle using RC8 and L1.28, I think we worked up something like 50 families and there was only one single individual where we were able to make a clinically significant change to their risk because it was a combination of the relatively low informativeness of both of those probes and the relatively high recombination rate of about 20 per cent for each probe.¹³⁰ So, although in principle they looked wonderful, actually they didn't deliver much. But by the time we had found that out we had the probes 99-6 and 754 which were closer with, perhaps, 10 to 15 per cent recombination.¹³¹ Again, they were good to score because you could score both of them on a single *Pst*I digest and that was considerably more helpful. We were just beginning to get quite useful information about our families from those probes, when along came Kunkel's pERT87 probes and, like everybody else, we greatly appreciated the generosity with which he immediately made those available to the whole community.¹³² That was really the point at which our ability to deliver a useful clinical service took off, both the deletions and the polymorphisms you could detect with various probes – 87-1, 87-8 and 87-15 – completely revolutionized our ability to deliver clinically useful results to our patients.¹³³

¹³⁰ Read *et al.* (1986).

¹³¹ Professor Andrew Read wrote: '... we had two probes, 99-6 (*DXS41*) and 754 (*DXS84*) that were closer ... Note that the DXS names, but not the probe names, should strictly speaking be italicised. If, for consistency, you want to do the same for the RC8 and L1.28 probes mentioned above, they are *DXS9*(RC8) and *DXS7*(L1.28).' Email To Ms Emma Jones, 4 October 2013. DXS refers to markers for the locus to which a probe relates on a chromosome.

¹³² See note 95.

¹³³ Professor Andrew Read further commented: 'I had been opportunistically collecting and storing DNA from Register families ever since we had the ability to do so. Then once Rob had RC8 and L1.28 working we started working through the families and would have reported any useful results we got, but there were precious few. It all speeded up a little with 99.6, then again much more so with the pERT probes. But there never was a formal start date for the molecular service. As for the name – well, it was very much an arm of the Genetic Register operation. All my reports were to the Register clinicians and counsellors, so I don't think it had a specific name. It was part of the North West Regional Genetics Service. At that time the department (University and NHS) was called the Department of Medical Genetics. I was always paid by the University and I don't think I ever had an NHS contract – things were more flexible and informal in those days. Eventually I realized that managing the increasing DNA service work was a job I couldn't justify doing on my university pay, and anyhow I wanted to concentrate on research, where I was having fun mapping genes, so Rob took over formal responsibility. That would have been sometime around 1988.' Note on draft transcript, 4 July 2013. Central Manchester University Hospitals NHS Foundation Trust's clinical genetics services are now based at the Manchester Centre for Genomic Medicine; <http://mangen.cubecore.co.uk/about-us.php> (visited 26 June 2013).

Bobrow: It would probably be fair to say the period of history over which people tried to get real clinical utility out of moderately linked probes was mercifully short, because these probes were a pain. Should we tidy up the rest of the genome quickly? That's not meant to be disrespectful of autosomes – it's just because the first action came where nature did her best experiments. Peter, I would like you to kick off on triplet repeats. I thought we should do Huntington's and CF.

Harper: I'm only going to say a few words about these because actually my lab colleagues in Cardiff, Laz Lazarou and Linda Meredith, can cover this a lot better. I suppose there are two trinucleotide repeat disorders which we were especially involved with in Cardiff: Huntington's disease and myotonic dystrophy. Of course, the strange thing was that for the first 20 years of the work, before the molecular side had begun, one had no concept that the basic mechanism would be the same for both and so there were parallel lines of work going on, at first mainly clinical, then gene mapping. The mapping was on two different chromosomes and it was only at the end that the work suddenly came together, when both were found to be trinucleotide disorders. Actually, I think this brings up a general theme of this phase of the work – so long as one was working at the DNA level, one could run several diseases in parallel and the technology was very much the same. Whichever chromosome you were using, you just had a different lot of markers. The moment the mutation came out, though, and you had some clue as to the function of the gene, then everything went to the winds in different directions and it became impossible to run a whole pack of genes through to their function. You had to concentrate just on one or two unless your lab was unbelievably well resourced, which was certainly not the case with us in Cardiff. I also think people have very little concept of the length of time this process took for both myotonic dystrophy and Huntington's and I think it was probably much the same for PKD.¹³⁴ It took about ten years. Now people wouldn't believe you if you said it took ten years to map and isolate a gene; people would not be prepared to invest that amount of time now. It was a huge effort. I don't want to go into the details of the isolation of these genes except to say that one end result, which was hugely important, was that it turned out that one had a single, unique mutation for each of these trinucleotide repeat disorders that could mean a single diagnostic test, not like cystic fibrosis or Duchenne where you have lots and lots of different mutations requiring

¹³⁴ Huntington's Disease Collaborative Research Group (1993).



Figure 14: Professor Patricia Jacobs

different ways of looking for them. These disorders had just one, which meant the test could be used not only in prediction in a known family but in primary diagnosis as well. That was something of general importance.

Professor Pat Jacobs: Just before we leave trinucleotide repeats, which I'm astonished to see we almost have without mentioning the Fragile X, I think that's absolutely unique and we really have to mention it in this context. Fragile X syndrome is the only disease I know that's had both a cytogenetic marker and a molecular mutation. It's enormously added to our knowledge about trinucleotide repeat diseases and, as far as I'm concerned, it's the most fun disease I ever had anything to do with, so I really think we must just at least mention it.

Bobrow: Who were the big players?

Jacobs: Jean-Louis Mandel was the big player.¹³⁵ The group in Hawaii, where I was at the time, did both cytogenetics and a very considerable amount of work trying to understand the way this syndrome was inherited. This curious phenomenon came to be known as Sherman's paradox after Stephanie Sherman

¹³⁵ Jean-Louis Mandel is currently Professor of Human Genetics at the Collège de France (since 2003). From 1982 he led research into genetic diseases including Fragile X syndrome; <http://www.usias.fr/en/jean-louis-mandel/> (visited 27 June 2013).



Figure 15: Mr Laz Lazarou

who did the analysis of what appeared to be an extremely common disease.¹³⁶ It's somehow become less common and I can't quite understand that either. Maybe there were huge numbers of families out there waiting to be diagnosed and then they were all diagnosed because now, as anybody here would know, it's actually quite exciting when you find a new family with Fragile X and it doesn't happen very often. Maybe in our lab, and we do a lot of Fragile X testing, not only for ourselves but for people who send them to us, we get quite excited if we find a new family but very few turn up now.¹³⁷

Mr Laz Lazarou: I think originally what happened was that the family registers were very good in actually pulling together a lot of the Fragile X families, so that we were all prepared at that point when the gene was found to actually do the testing. A lot of them were found via the genetics clinics. I remember the first time I started testing, I was getting a 10 per cent pick-up rate of the individuals I was testing for Fragile X. Now it's dropped to 0.5 per cent. It's because the referrals we're now getting are from paediatricians and they are referring everybody who has developmental delay, no matter what other characteristics

¹³⁶ Sherman *et al.* (1985).

¹³⁷ At the Wessex Regional Genetics Laboratory, of which Professor Jacobs was Director until her retirement in 2001, four tests for Fragile X disorders are conducted to detect mutations of *FMR1* in carriers as well as those who may have the syndrome. Mutations in this gene cause a spectrum of intellectual disabilities. See <http://ukgtn.nhs.uk/find-a-test/search-by-laboratory/laboratory/salisbury-rgc-41/f/> (visited 1 October 2013).



Figure 16: Dr Linda Meredith

they have, dysmorphology of any kind, etc. Consequently your pick-up rate is going to be a lot less, but, because the registers were so well-established and the referrals were primarily from clinical geneticists, who were more clinically selective, we picked up a lot of cases.

Bakker: The Fragile X gene was actually cloned by the groups in the Netherlands and the States, Annemieke Verkerk in Rotterdam.¹³⁸

Dr Linda Meredith: I want to mention a little bit about the work that we did in Cardiff both on Huntington's disease and myotonic dystrophy. From a practical point of view, I remember that to actually perform RFLP analysis was really quite challenging because each stage of analysis that you did could be, shall we say, less than robust, quite time-consuming, and did not always give you the result that you wanted, or that was clinically useful in the end. As Professor Read just mentioned, the RFLPs weren't always that informative in the person who wanted a test done and the family structure sometimes might not allow you to make an accurate prediction.¹³⁹ So the usefulness of the RFLPs was quite

¹³⁸ Professor Pat Jacobs wrote: 'The first paper was by Jean Louis Mandel's group, Heitz *et al.* (1991); followed by a second paper from the same group, Oberlé *et al.* (1991); then, from Australia, Yu *et al.* (1991). Later that year Verkerk *et al.* (1991) was published, which identified a gene that looked to be involved in the Fragile X syndrome. Because of the complexity of the Fragile X gene and the fact that its mutations represented an entirely new type of event in biology, it is impossible to claim priority for any of these four papers.' Email to Ms Emma Jones, 8 August 2013.

¹³⁹ See Professor Andrew Read's comments on page 43.

limited in some ways. Obviously, as more RFLPs were developed we could use those families with recombinants identified to them, replace and relocate the new markers and so the whole thing became a lot easier with the momentum of the extra work that we did. I do recall that we were fortunate enough to get a grant from an American group – I don't know whether you recall this, Peter? When they'd come over, first of all we told them we believed, based on initial linkage studies, that the myotonic gene was on chromosome 4. Then when they came back, it had been located to chromosome 19 and the guy who was in charge of giving the money remembered our first location of the myotonic gene and he gave us a few sticky minutes trying to explain why things had changed. We did explain ourselves quite successfully and we were given the money for locating the gene for myotonic dystrophy.¹⁴⁰

Harper: I can't resist embroidering that anecdote, Linda, because you're absolutely right in what you say, and the evidence that it was on chromosome 4 was incredibly flimsy. This was an application we made with Bob Williamson and I remember it was at the international meeting in Jerusalem where the chromosome 19 location of myotonic dystrophy was proved indirectly because they'd assigned complement C3 to that, and it was already known to be linked to myotonic dystrophy.¹⁴¹ I remember thinking, 'Oh my God, we've just sent off this application to say we're going to map it on chromosome 4 and it's on another chromosome. Now that's the end of our grant.' I rushed into the office when we came back from the meeting and said, 'Has that grant application gone off?', and the girls in the office said, 'Oh, we're terribly sorry, it's been awfully busy here this last week; we haven't quite got round to putting it in the post.' [Laughter] So we fished it out; I remember using Tipp-Ex, which I don't think is in use now, 'tippexing' out '4' and then waiting till it dried and blowing on it and writing in '19', by hand, on the top. As Linda said, we got the grant.

Bobrow: Julian, other autosomal diseases and bringing research up to date a bit?

Professor Julian Sampson: Well, we've already heard quite a bit about the identification, or positional cloning, of genes, particularly in the settings of Huntington's and Fragile X, where large families are the norm. I think you wanted me to mention tuberous sclerosis because here large families actually are unusual; most cases are isolated; two-thirds of cases are isolated, with no family

¹⁴⁰ Shaw *et al.* (1985). The funding body referred to by Dr Meredith was the Denver Fund for Health and Medical Research.

¹⁴¹ See note 104 and also Eiberg *et al.* (1983).



Figure 17: Professor Julian Sampson

history. This imposes limitations on the positional mapping, the refinement that you can get in positional mapping. It was further compounded by the fact that, unlike most of the other diseases we've heard about, our work showed fairly quickly that although a gene for tuberous sclerosis was certainly linked to the ABO blood group in some of these families, in others it was not. So it appeared there were at least two different genes that could cause tuberous sclerosis. We've heard about John Edwards' proclamations of the impossibility of mapping some disease genes.¹⁴² Tuberous sclerosis was actually a third one that he declared to be formally impossible to map, certainly in the northern hemisphere I seem to remember, because of the limited family size and the prevalence of the condition. Again, fortunately, that didn't come to pass.¹⁴³ Certainly the cloning of *TSC2* and *PKDI* was very dependent upon chromosomal rearrangements.¹⁴⁴ In relation to *TSC2* they were particularly important because of the relative lack of good linkage information. We were very fortunate in Cardiff to have a visit from Isabel Cordeiro from Portugal, Lisbon, in 1992. She had been sent to work with us on neurofibromatosis type 1, and her boss, Heloisa Santos, asked her to tell me that she had already identified, several years before, a family with a translocation

¹⁴² See page 39.

¹⁴³ See, for example, Connor *et al.* (1987); Haines *et al.* (1991); Nellist *et al.* (1993) and Cheadle *et al.* (2000).

¹⁴⁴ For the cloning of *TSC2* see the European Chromosome 16 Tuberous Sclerosis Consortium (1993) and for *PKDI* see European Polycystic Kidney Disease Consortium (1994).

in a boy with tuberous sclerosis.¹⁴⁵ Further investigation of that family showed that they also had polycystic kidney disease and this was of great interest because of the co-occurrence sometimes of the polycystic kidney phenotype as part of tuberous sclerosis. That translocation really facilitated identification of both of those genes, largely through the application of another technique that we've heard a little bit about today: pulsed field gel electrophoresis. This enabled the more precise physical mapping of stretches of DNA as opposed to linkage analysis that we've heard a lot about.¹⁴⁶ Our progress in tuberous sclerosis depended on critical clinical observations made by Heloisa in Lisbon.

You wanted me to mention a little bit about the move from linkage analysis into mutation analysis and this was something that I think the diagnostic labs were doing in parallel with the same moves happening in research labs following positional cloning of disease genes. At the start of our discussions this afternoon we heard an awful lot about haemoglobinopathies where, of course, the proteins and the genes were already known although the molecular pathology was not. For most of the Mendelian disorders that were filling the genetics clinics, we recognized the disorders clinically but didn't have the genes and in most cases we had absolutely no idea about the pathophysiology of the disorders. So linkage analysis was a way for researchers to try and get at these disease genes.¹⁴⁷ We heard about RFLPs but progressively more informative groups of markers were identified, the VNTRs (variable number of tandem repeats) and then the microsatellite repeats, which enabled increasing amounts of information to be derived from families.¹⁴⁸ The markers were increasingly densely placed onto genetic maps and transposed onto physical maps. So we began to build up sort of 'mini-genome projects'.¹⁴⁹ Each disease that was being worked on created its own mini-genome project, a little area of the human genome. The genetic markers were taken up rapidly by the diagnostic laboratories for clinical application, but the approach in linkage was usually very dependent on close interaction with the clinical services

¹⁴⁵ See European Polycystic Kidney Disease Consortium (1994), pages 882–6.

¹⁴⁶ Professor Julian Sampson elaborated: 'Where genetic distances are determined but vary in relation to physical distance in different parts of the genome.' Note on draft transcript, 25 October 2013.

¹⁴⁷ For elucidation on linkage analysis in the sphere of cancer genetics, and specifically hereditary non-polyposis colorectal cancer, see, for example, Jones and Tansey (eds) (2013), pages 37–45.

¹⁴⁸ For an explanation of the use of these markers in forensic DNA profiling and genetic linkage analysis, see, for example, Bennett (2000).

¹⁴⁹ van Slegtenhorst *et al.* (1995).

because we needed samples from additional family members. So sometimes you'd need samples from spouses or grandparents to establish phase, for example, and so the clinical and lab services got very used to working with extended families.¹⁵⁰ We've already heard from Andrew that until these markers were really close to the disease gene concerned, they were of limited clinical utility. That changed over a period of a few years. This was really all going on, I guess, during the 1980s and into the early 1990s and during that period many genes were positionally cloned and so things moved to a point of direct mutation analysis.¹⁵¹ We have heard that in Huntington's disease this was very straightforward because the same mutation was present in every, or virtually every, patient. That, of course, wasn't the case with many other disease genes, where hundreds of individual different mutations could underlie the disease. So we really needed ways, once the disease genes had been identified, of scanning across large genes looking for various types of mutation and so we saw the emergence of a lot of different mutation-detecting technologies like single strand conformation polymorphism analysis and denaturing gradient gel electrophoresis, and chemical cleavage of mismatches and so on. These were all very labour-intensive processes. They were manual and very time-consuming and often actually not that sensitive because they frequently couldn't be applied comprehensively, just for logistical reasons to the whole coding sequence of large genes. There was a gradual transition in diagnostics from linkage to the application of these screening modalities, and it wasn't really until sequencing became more practical, and quicker, that this transition was complete. Initially, sequencing was also based on very manual procedures. I can remember using panes of glass that had to be meticulously cleaned and then gels would be poured between two panes of glass held together by bulldog clips, usually leaking out all over the place, and you'd run the gel and develop autoradiographs. The whole thing was really quite bizarre and when these plates broke someone had to go down to the local glazier shop and get another one. It was really a cottage industry. People are giggling because they can remember, you see; it's all true! [Laughter]

Bobrow: Ah, nostalgia! [Laughter]

¹⁵⁰ Professor Julian Sampson wrote: 'In order to determine which genetic marker(s) were associated with a disease gene, linkage analysis usually required the genetic analysis of multiple family members including spouses and members of preceding generations. The laboratories working on these projects would therefore have to work very closely with clinical geneticists and other members of the clinical team to recruit and obtain samples from extended families.' Note on draft transcript, 25 October 2013.

¹⁵¹ See, for example, MacMillan *et al.* (1993).

Sampson: It was the emergence of automated sequencing that enabled the completion of that transition from linkage analysis to mutation detection as the technique we use to diagnose these diseases now.

Bakker: What helped tremendously for the linkage analysis was the CEPH (Centre d'Etude Polymorphisme Humain) pedigrees because we needed to have all these markers sorted out; we needed to have linkage groups.¹⁵² We needed markers, which you could use in searches for disease loci. So having these huge, normal CEPH families and putting probes to these families and finding the segregation in these large pedigrees produced enormous amounts of data. That was all done in a European project run by Nigel Spurr called EUROGEM.¹⁵³ I worked mainly on the map of chromosome 4, and other groups worked on other chromosomes. Sue Povey and John Edwards were involved, and we made a lot of mileage into getting all these maps, and later the meiotic break point maps, to really pinpoint loci and set the basis for the sequencing of the whole human genome.¹⁵⁴ So the CEPH pedigrees and this project, EUROGEM, were tremendously useful. You had genetic markers as well, all the Généthon STR (short tandem repeat) markers, CA repeats, which were very informative.¹⁵⁵ Although they were labour-intensive, because you had to do radioactive PCR, running gels using the same glass plates that Julian Sampson described.¹⁵⁶ This was a lot of work to do all the linkage, but it helped enormously to make the maps.

¹⁵² 'The Centre d'Etude du Polymorphisme Humain (CEPH) is a research laboratory created in 1984 by Professor Jean Dausset.' In 1993 CEPH was renamed the Fondation Jean Dausset. Quotation from organization's website; <http://www.cephb.fr/en/index.php> (visited 27 June 2013).

¹⁵³ Professor Malcolm Ferguson-Smith wrote: 'EUROGEM was part of the EC Human Genome Analysis Programme established and funded in 1990 through a committee in Brussels which Peter Pearson and I chaired over several years. It consisted of two resource centres: CEPH that made and distributed Southern blot membranes and DNA samples for PCR made from 750 members of 60 families; and ICRF, responsible for distributing the DNA probes that recognized polymorphisms. This material was sent for linkage studies to a network of 20 research labs throughout EU member states. Results were presented at HGM Workshops and chromosome-specific workshops before joint publication. The programme encouraged effective collaboration in Europe and made major contributions to the human gene map.' Note on draft transcript, 1 June 2013. See also Ferguson-Smith (1991).

¹⁵⁴ Professor Sue Povey was Deputy Director of the MRC Human Biochemical Genetics Unit (1989–2000) and Haldane Professor of Human Genetics (2000–2007) at University College London; now Professor Emerita of Human Genetics. She was Chair of the HUGO Genome Nomenclature Committee from 1997 to 2007. See also note 4. For John Edwards, see note 116.

¹⁵⁵ See, for example, Gyapay *et al.* (1994).

¹⁵⁶ See previous page.

Middleton-Price: Going back very briefly to Fragile X and I'm looking to Pat because she'll tell me if I'm wrong about this, but I believe it was Marcus Pembrey and Kay Davies who together coined the term 'premutation' in a hypothesis to explain the Sherman paradox,¹⁵⁷ in which a premutation in normal transmitting males and non-manifesting females required transmission through a female meiosis in order to develop into what was called a full mutation, the nomenclature we still use today.¹⁵⁸

Jacobs: You may very well be right. I can't remember exactly who said what because there were a lot of people involved and that's what made it so interesting. When I think of the days, weeks and years I spent thinking and discussing this problem of the Fragile X, it was just the most intriguing thing.¹⁵⁹

Dr Fiona Macdonald: I want to carry on from what Julian was saying. When I started in the lab in 1988, my first disease to work on was familial adenomatous polyposis (FAP) and we did that originally by linkage using Southern blotting which was, as you know, a pain. We then developed some PCR markers. We were greatly supported by having a European FAP network. There were a lot of UK and Dutch labs involved, particularly with the EuroFAP project that then extended into HNPCC (hereditary non-polyposis colorectal cancer) and we were able to share linked markers around.¹⁶⁰ At the time my boss in the department was Maj Hultén and she was a good friend of Professor Meera Khan who was

¹⁵⁷ For Professor Dame Kay Davies see note 27 and for Professor Marcus Pembrey see note 102. Professor Pat Jacobs discusses the Sherman paradox on pages 45–6.

¹⁵⁸ Professor Marcus Pembrey wrote: 'I believe we were the first to use premutation in relation to Fragile X. If I remember correctly, I was unaware of the term's earlier use at the time, but was put right by John Opitz in an editorial accompanying our paper in the *American Journal of Medical Genetics*. This editorial seemed to be largely devoted to explaining why the review process had taken nearly a year, but added that the term delayed mutation or "premutation" had been used earlier in relation to achondroplasia pedigrees. In fact, when our paper came out I was surprised, but happy, to see that John Opitz had added a sentence and his reference at the beginning.' Email to Ms Emma Jones, 4 October 2013. See Opitz (1981); Opitz (1985) and Pembrey *et al.* (1985).

¹⁵⁹ Professor Pat Jacobs wrote: 'But in the end it was Jean-Louis Mandel who found the answer.' Note on draft transcript, 8 March 2013.

¹⁶⁰ For collaborative research on HNPCC in Europe, see Dr Pål Møller's comments in Jones and Tansey (eds) (2013), page 18.



Figure 18: Dr Fiona Macdonald

in Leiden.¹⁶¹ We set up a collaboration with Meera and with Riccardo Fodde and that was primarily to develop mutation detection once the gene had been found.¹⁶² Riccardo was setting up denaturing gradient gel electrophoresis, which he thought was probably the best mutation detection method around at the time if you didn't want to go down the sequencing route. So we did that and we had to set up a register with Carol McKeown as the clinical geneticist.¹⁶³ We had probably 200 to 300 families at the time, so we could do the mutation analysis relatively straightforwardly though, again, we had horrible gels to pour that leaked all the time and which were stuck together with bits of Sellotape. I also went out to the glaziers to buy some glass plates.¹⁶⁴ Things have clearly moved

¹⁶¹ Dr Fiona Macdonald wrote: 'Professor Maj Hultén was Clinical Director of the West Midlands Regional Genetics Laboratory at Birmingham Heartlands Hospital from 1975 to 1997. She became Honorary Professor in Medical Genetics/Reproductive Genetics at the University of Birmingham (1989–1999). Her main research interest was devoted to studying patterns of meiotic recombination in males and females.' Note on draft transcript, 6 September 2013. Professor Meera Khan (d. 1998) worked at the Department of Human Genetics, University of Leiden from 1966; see Pearson (1999).

¹⁶² Riccardo Fodde is now Professor of Experimental Pathology at Erasmus Medical Centre, Rotterdam.

¹⁶³ Dr Carole McKeown was a Consultant Clinical Geneticist for the West Midlands Regional Genetics Service from 1987 to 2012.

¹⁶⁴ See comments by Professor Julian Sampson on page 51 and also Professor Bert Bakker's comments on page 52.

on because now, in our lab, we have the next generation sequencing panel for colorectal cancer with 10 to 15 genes on it, so we can look for all of these genes at the same time in about probably a tenth of the time that it took then.

Middleton-Price: I want to mention one of the experiences I had working in the lab just after the 1989 paper that cloned *CFTR*.¹⁶⁵ We had a family with a child who died of cystic fibrosis and we'd used the *KM19* probes for a linked marker to do several subsequent prenatal diagnoses, each of which showed the fetus to be affected with cystic fibrosis and each was followed by termination. This family got more and more distressed as time went on. It went on over a period of two or three years. Marcus, I remember, was counselling the family and having difficulty explaining that this was a real result and not some sort of artefact. When the gene was cloned, we were able to use allele-specific nucleotides to detect the delta-F508 mutation and we could show within a few weeks of that paper that each of these fetuses, which had been terminated, really was homozygous for the delta-F508 mutation and, therefore, affected.¹⁶⁶ The family was relieved and finally convinced that their potential babies did have cystic fibrosis.

Bobrow: I would hate to leave this section without a brief word on population screening. I wonder if Bernadette can manage to do just a little bit on that just so that we don't pass off without it ever being mentioned? First, though, we're going to have a few words on cancer genetics.

Macdonald: I've talked already about FAP, so all I wanted to add is to explain how it took quite a long time before any of the other cancer genes started to be used routinely.¹⁶⁷ There was a little bit of linkage going on for MEN and VHL at Cambridge [in the 1990s] and we started to do some for HNPCC.¹⁶⁸ Once the breast cancer gene became identified, we all started to do mutation analysis.¹⁶⁹ Quite a lot was going on with Myriad Genetics, which was starting to talk about

¹⁶⁵ *CFTR* (cystic fibrosis transmembrane conductance regulator) is the gene in which mutations cause cystic fibrosis. See Kerem *et al.* (1989) and also Christie and Tansey (eds) (2004), pages 59–62.

¹⁶⁶ McMahon *et al.* (1990).

¹⁶⁷ For cancer gene testing, see also, for example, Jones and Tansey (eds) (2013), pages 69, 72–3, 75–6.

¹⁶⁸ For MEN, see Ponder (1990) and, for VHL, see Maher *et al.* (1992). The HNPCC research did not conclude with a publication; note on draft transcript from Dr Fiona Macdonald, 6 September 2013.

¹⁶⁹ Miki *et al.* (1994).

the patent they owned for that gene.¹⁷⁰ Maybe Rob can mention something about that because he was secretary of the CMGS (Clinical Molecular Genetics Society) at the time and he did quite a lot of talking to the European labs about the patent and discussed it with Myriad.

Elles: Other people might have to fill in the gaps but I remember that there was a cancer genetics group meeting in London in 1998 at which the chief executive or some executive from Myriad stood up and said, ‘What’s gone before has gone before but we’re drawing a line in the sand now, and if it’s not for research use, you owe us money or you have to stop.’¹⁷¹ I’m paraphrasing what he said but it was pretty clear and blunt, as I recall, and everybody kind of rocked back on their heels. I was secretary of the CMGS at the time.¹⁷² We thought it was a serious issue and we also thought that it was a policy issue and so we referred to the Department of Health (DoH). There was a precedent for it because there had also been the story of the Taq polymerase patent and the attempt to restrict the use of polymerase chain reaction (PCR) that had also gone for central negotiation by the DoH.¹⁷³ The CMGS dealt with a unit at the DoH for a couple of years, feeding it information about the scope and level of activity on breast cancer genetics research in the UK and the potential damage, as we saw it, to the development of the field in the UK. I think it’s fair to say that *BRCA* was really quite a driver in terms of the public’s connection to clinical molecular genetics at that time.¹⁷⁴ There was a build-up of pressure from the patients, with Breakthrough Breast Cancer and other cancer patient organizations driving a greater awareness of the potential for this type of testing and its benefits among

¹⁷⁰ See Jones and Tansey (eds) (2013), page 74.

¹⁷¹ Dr Rob Elles wrote: ‘This was the Cancer Family Study Group, forerunner of the Cancer Genetics Group. The meeting was on Tuesday 8 December 1998 at St Thomas’ Hospital, London. Greg Critchfield was the Myriad Executive who spoke.’ Note on draft transcript, 14 August 2013.

¹⁷² Dr Rob Elles was Secretary of the CMGS for two three-year terms between 1988 and 1994.

¹⁷³ *The Probe* newsletter (of the CMGS), autumn 1995 issue, included an article on the royalty fees charged by Hoffman-LaRoche for PCR tests, noting that the corporation waived fees pre-April 1995; pages 3–4. A copy of this newsletter will be deposited with the records of this Witness Seminar at the Wellcome Library under reference GC/253.

¹⁷⁴ See Professor Gareth Evans’ comments on the impact of the identification of cancer genes and referrals to clinical genetics services in the UK in Jones and Tansey (eds) (2013), pages 53–4.

the public.¹⁷⁵ All of that fed into a policy within the DoH. Anyway, to cut a long story short, the upshot was that we got the message – maybe not quite overtly – that it was okay to carry on, and we did. However, I think the patent issue did put a ‘planning blight’ on the field for a couple of years. I think it’s true to say that *BRCA* service efforts, others may also comment, were very fragmented for a while: the field was poorly funded and we didn’t do very well. In part, that led to the development of pressure because there were huge backlogs of patients waiting to be tested.¹⁷⁶ It was only really, we’re rolling forward a little bit, with the genetics White Paper that there was an overt decision to invest in this field and even to set us quite stringent targets to clear our *BRCA* backlogs.¹⁷⁷ So the UK came out with a position on the patenting issue, I think.

Bakker: On the European level, a lot has happened because the *BRCA1* patent was also enforced by Myriad Genetics in all other countries, in the Netherlands, in Belgium, etc.¹⁷⁸ The guys from Myriad came and visited the lab and said, ‘Okay, you should go for licensing’. We didn’t want to do that because we were already performing pre-symptomatic tests based on an earlier paper that had been published, and the patent was on a later gene sequence, before their patent came into force and that point was also argued. Together with the clinical genetics centres in Netherlands and in Belgium, we put money aside and hired an attorney on patent rights and he successfully revoked the patent: Myriad now only has the patent on the Ashkenazi Jewish mutation.¹⁷⁹ To come back to

¹⁷⁵ The charity Breakthrough Breast Cancer was founded in 1989 to create the UK’s first dedicated breast cancer research centre. It presently funds approximately 25 per cent of breast cancer research in the UK; <http://www.breakthrough.org.uk/about-us/our-work/our-story> (visited 28 June 2013). For recent international media coverage of genetic testing issues for *BRCA1* and *BRCA2*, see also Hurley (2013).

¹⁷⁶ Dr Rob Elles wrote: ‘By 2001 there were substantial backlogs of *BRCA* patient samples awaiting testing in all areas of England. All services bid against £18m lab modernisation funding from the 2003 White Paper in 2004 and rationalised their capability in *BRCA* testing. From 2005 to 2006 all services were required to report their progress on clearing *BRCA* backlogs to the Genetic Commissioning Advisory Group. This was the only service area for which we were asked to provide this data. In 2006 and 2007 we and other services were asked to provide an audit of performance against *BRCA* reporting time targets for Breakthrough Breast Cancer, so the pressure came from patients and the DoH in my opinion.’ Note on draft transcript, 14 August 2013.

¹⁷⁷ Department of Health (2003).

¹⁷⁸ See, for example, Matthijs and Halley (2002).

¹⁷⁹ The Myriad patent for *BRCA2* that specifically related to people who are Ashkenazi Jewish, or their descendants, is for the mutation 6174delT associated with breast-ovarian cancer. See, for example, Gold and Carbone (2010).

the PCR patent, at a certain moment the company PerkinElmer had bought the patent from [Kary] Mullis and they wanted to enforce this patent on the laboratories that were using PCR for diagnostic services.¹⁸⁰

At that time my position was that we had paid royalties when we bought the enzyme. Buying the enzyme pays for everything in there and with the diagnostic service we don't earn money because it's closed patient care, so we are not going to pay for that and if you want you can come and sue us, but then you would have to sue all the laboratories which were performing these tests. So they never did that. Then they sold the patent to Roche and again the circus started and Roche came to ask for royalties.¹⁸¹ We said the same, just moved it up to the Ministry of Health and said, 'Okay, we are not going to pay to do it. Come and sue us.' And they never did.

Bobrow: And there was, I can't remember his name, Jacques –

Bakker: In Belgium it was Gert Matthijs.

Bobrow: That's right; it was Gert Matthijs who devoted years of his life to leading this effort.

Bakker: He led this consortium that we had with all the clinical genetics centres in Belgium and Netherlands to get the patent revoked. Gert Matthijs was the spokesman and he had an article in the *European Journal of Human Genetics* on that.¹⁸²

Bobrow: He deserves much thanks. Let me just note in passing that one of the things that is now self-evident, but to me was quite surprising at the time, is that out of this very large morass of what could have been coincidental accumulations of breast cancer, a very common disease in families, people actually in the end managed to drag out a monogenic set of conditions. To my recollection it was not self-evident at the time that these aggregations represented anything other

¹⁸⁰ Dr Kary Banks Mullis (b. 1944) developed the process of polymerase chain reaction in 1983, for which he was awarded the Nobel Prize for chemistry in 1993. For a full biography, see <http://www.karymullis.com/biography.shtml> (visited 7 October 2013).

¹⁸¹ '[In 1991] Hoffman-LaRoche Inc. acquires worldwide rights and patents to PCR.' Quoted from *Timeline of PCR and Roche* at <http://molecular.roche.com/About/pcr/Pages/PCRTimeline.aspx> (visited 28 June 2013).

¹⁸² Professor Gert Matthijs is Head of the Laboratory for Molecular Diagnosis, Center for Human Genetics, University Hospital Leuven, Belgium. For the work of the consortium see, for example, Aymé *et al.* (2008).



Figure 19: Professor Malcolm Ferguson-Smith

than chance aggregations. It was quite a lot of hard work to make that step. Let's go to molecular cytogenetics and I was hoping that Malcolm might have something to lead off on.

Ferguson-Smith: First, an observation that, of course, molecular cytogenetics emerged 43 years ago, so there's quite a long period to cover.¹⁸³ It started in 1970 with Mary Lou Pardue and Joe Gall and their work with major mouse satellite DNA, which they obtained by ultra-centrifugation; they labelled this DNA with tritiated thymidine and showed by autoradiography that all the hybridization signals on metaphases occurred at the centromeric regions of the mouse chromosomes.¹⁸⁴ At the same time, they observed that these mouse chromosomes, after this denaturation treatment and stained with Giemsa, showed a dark band over the region of satellite DNA. This was the start of C-banding and all the rest of the C-banding methods, including trypsin banding, emerged from that experiment with the exception of Q-banding, which Caspersson, with Lore Zech, independently discovered in the same year.¹⁸⁵ The next step was made by Angie Henderson who mapped the human ribosomal genes to the satellite regions of the acrocentric chromosomes, again using the same technique of

¹⁸³ For further accounts of the history of human cytogenetics, see Ferguson-Smith (1993) and Ferguson-Smith (2008).

¹⁸⁴ Pardue and Gall (1970).

¹⁸⁵ Caspersson *et al.* (1970).

labelled, moderately repetitive ribosomal DNA material made from *Xenopus*.¹⁸⁶ This was the first example of human gene mapping by *in situ* hybridization. Then along came Kurt Hirschhorn and Price whom you will remember in 1972, claimed to map globin.¹⁸⁷ They used rabbit messenger RNA and claimed that the beta globin gene was mapped to chromosome 4. Everybody laughed heartily because, of course, the amount of radioactive DNA they used couldn't possibly have given the results they claimed in their experiment. It took a long time after that before we got the first single copy genes correctly assigned by *in situ* hybridization.¹⁸⁸ During the interval, between 1972 and 1981, when the recombinant DNA we just heard about was developed, the ability to obtain large amounts of the same DNA fragment became possible by cloning it in bacteria and various vectors, including YACs (yeast artificial chromosomes), plasmids, cosmids, and later on BACs (bacterial artificial chromosomes). So in 1980, as I mentioned earlier, Sue Malcolm joined our group to map the globin genes using the highly labelled, cloned DNA.¹⁸⁹ At the time, the only person I could find who would support an application to the MRC for this project was Bob Williamson. Bob joined in and agreed that it might now be possible to map single copy genes. We'd been working on the ribosomal genes before that and knew how to do the *in situ* technique. So when Bob provided the cDNA probes, Sue managed to map both the alpha and the beta globin genes to the short arm of both chromosomes 16 and 11 using *in situ* hybridization with probes labelled with tritiated thymidine. Afterwards, in 1982, we went on to map the kappa light chain genes to chromosome 2.¹⁹⁰ In the same year Harper and Saunders mapped insulin to the short arm of chromosome 11.¹⁹¹ These were the first papers on single copy gene assignments. Now the problem with this work, and I was involved in doing it too, was the terrible business of autoradiography, which involved dipping slides into photographic emulsion, counting grains after three weeks' exposure and trying to do a statistical analysis to see if you got a significant result on any particular chromosome. It was clear that these radio-isotopes had to be replaced by something better. This is where the fluorescent labels came in.

¹⁸⁶ Henderson *et al.* (1972).

¹⁸⁷ Price *et al.* (1972).

¹⁸⁸ Malcolm *et al.* (1981).

¹⁸⁹ See page 29.

¹⁹⁰ Malcolm *et al.* (1982).

¹⁹¹ Harper *et al.* (1981).

The key people who were working on this, around about 1982/83, were David Ward and Sam Latt in Boston, Ton Raap and Hans Tanke and others.¹⁹² Ton Raap, as far as I recall, had some of the best technology.¹⁹³ First, we used confocal laser microscopy and then moved to digital fluorescent microscopy with image processing. That was made possible using a cooled charge device, the CCD camera that was able to identify the signals of very low luminescence which is critical for fluorescent *in situ* hybridization (FISH). FISH soon had many applications in gene mapping, positional cloning of disease genes, aneuploidy detection in interphase and fibre-FISH. I mention fibre-FISH particularly because it had such high resolution for mapping closely linked sequences on chromosomes. Then, in the late 1980s, chromosome painting came onto the scene; first of all using cloned chromosome libraries.¹⁹⁴ The key people in those days were Joe Gray and Dan Pinkel in Livermore lab in San Francisco, who made cloned chromosome libraries from sorted chromosomes, starting about 1972.¹⁹⁵ I was introduced to chromosome sorting in 1980 by Bryan Young, who has been mentioned already in connection with the construction of the X chromosome library for the work on X-linked markers.¹⁹⁶ Bryan came to me one day and asked if I could help in the interpretation of the flow histogram of the MRC cell line with multiple X chromosomes. There were lots of peaks that seemed to correspond to chromosome size, so I suggested that we should sort chromosomes from peripheral blood samples. We did this and were soon able to identify chromosomes and chromosome aberrations from the sorting preps. This took me into a technology that I've stuck with for over 30 years thanks to Bryan Young. In 1992 there was an important development, from a PhD student, Haakon Telenius in my Department of Pathology at Cambridge. He developed a novel method for the amplification of DNA from any source, using random primed oligonucleotides as primers. So, from our sorted chromosomes it was possible to make quantities of fluorescent chromosome-specific DNA probes using DOP-PCR as it was called.¹⁹⁷ Soon we were able to share these paint probes made from sorted chromosomes, labelled in either red or green, with

¹⁹² For Ward, see Lichter *et al.* (1991). See also Latt (1973).

¹⁹³ See, for example, Raap (1986) and van der Ploeg *et al.* (1985).

¹⁹⁴ See, for example, Cremer *et al.* (1988).

¹⁹⁵ Pinkel *et al.* (1988).

¹⁹⁶ See pages 34 and 38.

¹⁹⁷ Carter *et al.* (1992).

our colleagues. Eventually they were distributed around the world by Cambio in Cambridge.¹⁹⁸ These whole-chromosome paints have been used mostly to improve the diagnosis of chromosome rearrangements and, more recently, in phylogenomic studies.¹⁹⁹ A few years later, Thomas Reid at NIH developed M-FISH using our assorted chromosomes, labelling them in different colours from combinations of five different fluorescent colours. This gave a different colour to each individual chromosome in one FISH hybridization, allowing the easier identification of aberrant chromosomes. Identification was also possible by using colour-banding techniques to look for intra-chromosomal rearrangements. We were particularly excited about using gibbon chromosome-specific DNA to generate colour bands in human chromosomes, a method we named Harlequin M-FISH.²⁰⁰ In 1992, I should mention Kallioniemi, who introduced chromosomal comparative genome hybridization (CGH).²⁰¹ In 2001 we had the draft sequence of the human genome that gave us reference BAC clones. So around 2004, roughly, array CGH replaced chromosomal CGH as a way of diagnosing chromosomal aberrations. It's now fair to say that array CGH has almost replaced conventional cytogenetics in the detection of chromosome aberrations. So this has been a most important development. Some people argue about this but I maintain that is what is happening now. In the end, of course, the sequencing of individual genomes will replace both array CGH and FISH. History shows that the emergence of FISH, in the 1980s, rendered obsolete mapping by genetic linkage, somatic cell hybrids, RFLPs and Southern blotting. All these techniques, previously so important in medical genetics, are now replaced because FISH has a far higher resolution. Gert-Jan van Ommen, in particular, claimed that a resolution of one to two kilobases was possible using FISH. So there's still a very strong place for FISH in gene mapping and for some diagnostic work, but I think it will be taken over eventually by individual genome sequencing.

Bobrow: So although cytogenetics and molecular genetics started in different places, actually the subject matter that they deal with is pretty similar and the two have approximated to the point where they are now together at a scientific

¹⁹⁸ Cambio is a company that supplies molecular biology reagents and consumables to scientific research laboratories; <http://www.cambio.co.uk/about/> (visited 1 July 2013).

¹⁹⁹ See, for example, Stanyon and Stone (2008).

²⁰⁰ See, for example, Ferguson-Smith *et al.* (2005).

²⁰¹ Kallioniemi *et al.* (1992).

level. I think there's some interesting discussion as to whether they have come together at a clinical level and how that's going to happen. But we'll come to that.

Weatherall: There is a very nice example of that in the alpha thalassaemia mental retardation syndromes.²⁰² The types that affect chromosome 16, of course, turned out to be due to submicroscopic telomeric rearrangements or deletions. These findings led to the widespread use of screening for other submicroscopic deletions.²⁰³ I think this is a very nice example of interplay between the two worlds.

Ferguson-Smith: Yes, I'm sorry that I skipped over diagnostic FISH rather rapidly and didn't cover all the important techniques. The subtelomeric sequence probes were used for identifying the most frequent parts of the chromosome involved in rearrangements, because it is usually the ends of chromosomes that take part in interchromosomal rearrangements. FISH using the subtelomeric repeat probes played a really important part in identifying cryptic chromosome aberrations in mental handicapping conditions. So this was another important advance in clinical cytogenetics.

Bobrow: Would you just like to give us a name or two associated with that stuff, please, for the record?

Ferguson-Smith: Yes, Jonathan Flint in particular.²⁰⁴

Sampson: It was just to add that FISH was extremely useful for defining mosaicism for deletions, and actually though next generation sequencing will surpass it, it's still much more sensitive for identifying mosaicism than, say, MLPA (multiplex ligation-dependent probe amplification) or the other techniques that are in current use.

Bobrow: I want to ask Pat Jacobs a question because she has been the eminent director of a very large integrated laboratory. Are cytogenetics and molecular genetics still separate disciplines?

²⁰² Weatherall *et al.* (1981).

²⁰³ Professor Sir David Weatherall added: '[This screening] has now become a routine part of cytogenetic analysis for unexplained cases of mental retardation.' Email to Ms Emma Jones, 8 October 2013. See Flint *et al.* (1995).

²⁰⁴ Knight *et al.* (1999).

Jacobs: Unfortunately they are, although we try very hard, but people hold on to what they are familiar with. It is not a popular choice to integrate molecular and cytogenetics people, to realise they're all part of one big team. However, it is happening slowly. I'm not head of the laboratory anymore and haven't been for years. It is very difficult to lose a discipline that has given so much to clinical genetics and to some extent I'm sympathetic because I've been very sad at seeing cytogenetics go because it was, for me, so aesthetically pleasing. I realise that's not why we do science but it should be one of the reasons why we sometimes do science. But for all practical purposes, nobody in our lab now looks down a microscope.

Ferguson-Smith: It's evolution, for goodness sake! Evolution occurs in our science and every other aspect of life in this world. We're all slaves of our technology, as somebody said. So we must make way for new technologies and I think we have to embrace the fact that we simply can't spend the time looking down the microscope counting chromosomes in the way we used to do it, and take so long to give reports to our patients. We have to give them the benefit of the new technology. Okay, array CGH is expensive to begin with but only by applying it to a larger number of people will the costs go down, and that's what always happens with technology.

Bobrow: Well, unlike Pat, I thought that what had actually happened is that cytogenetics, which is aesthetically very pleasing, has really advanced enormously in the sort of resolution that you can now achieve by using slightly different techniques. So I think it's cytogenetics that's won.

Jacobs: Oh good. But it hasn't really because there is little that is aesthetically pleasing about arrays.

Bobrow: No, you're probably right.

Jacobs: Array CGH doesn't look biological but it gives a lot of information. Anyway, it's happening and I don't want you to think our lab's not doing it, because we are.

Bakker: Although, of course, it's outside this window that we're looking at now; since 2006 the two laboratories, molecular genetics and cytogenetics, have become one group. It's called genome diagnostics. Of course, there is a discipline that looks at chromosomes and a discipline that looks at DNA and at arrays, and we're going towards whole genome sequencing but the two will merge, and we still occasionally will need the chromosomes. If you find a

trisomy 21 you need to know if it's a translocation or not. You need to look at these chromosomes to see if it's inherited Down's syndrome or not. So we will keep the chromosomes but at a much smaller level.

Bobrow: Right, we are all in agreement: historic inevitability. I was now going to draw a line under science and look much more directly at clinical application and organizational and patient-facing things for the rest of our time, by asking two people who were involved in managing this at a higher level in England and Scotland to talk to us about the way in which the clinical lab services developed over this period of time.

Dr Rosalind Skinner: Can I, before I go into molecular genetics, just round off something about the picture on the cytogenetic front? I totally sympathized with what Pat was saying and the emotions felt by people who worked for many years in cytogenetics. For 24 years in Edinburgh, I lived next door to Ann Chandley and I had daily sentiments of the same ilk from her.²⁰⁵ But we have moved on, and the two professional associations, the Clinical Molecular Genetics Society (CMGS) and the Association for Clinical Cytogenetics, have just merged and they will have their inaugural joint meeting at the BSHG (British Society for Human Genetics) meeting in September. There is a significant proportion of labs which are now integrated and those that aren't are certainly moving in that direction.²⁰⁶ Cytogenetics was incorporated into the Scottish Molecular Genetics Consortium from about 2007 after our last review.²⁰⁷ So things are moving that way but absolutely no disrespect to the huge input from cytogenetics in the past. Cytogenetics started it all off; I think we have to remember that.

You've asked me to talk about the consortium in Scotland: this developed in the window of time between me leaving front-line genetics in 1983 in Scotland, and re-emerging to organize, as it were, and be involved with, the arrangement of genetic services from the health department in Scotland at the end of 1988. If I could just paint the picture very quickly for folk: by the mid-1980s in Scotland the four university medical centres all had academic interests in medical genetics; they

²⁰⁵ Dr Ann Chandley worked as a cytogeneticist at the MRC Human Genetics Unit in Edinburgh and was heralded by Professor Malcolm Ferguson-Smith as 'an international authority on cytogenetics'. See Ferguson-Smith (1997), quotation from page 3.

²⁰⁶ Dr Fiona Macdonald provided a copy of the Resolution for CMGS members on the formation of a British Society for Human Genetics, c.1994, which will be deposited in the Wellcome Library, London, with the records of this meeting at reference GC/253.

²⁰⁷ Scottish Executive (2006).



Figure 20: Dr Rosalind Skinner

all had people working in medical genetics and there were consultant-led clinical genetics services in three of them, in Aberdeen, in Edinburgh and in Glasgow. In Dundee, although there was academic interest in genetics, there was no clinical geneticist in post in the mid-1980s. That said, Mike Faed, who was a cytogeneticist based in the pathology department there, did his level best to make sure patients there weren't too disadvantaged. They did, in the early 1980s, travel mostly for complicated cases either up to Aberdeen or they came down to us in Edinburgh for counselling. But in 1985, as molecular genetic testing really began to take off, the great foresight of the leaders of the academic centres was to come together and discuss how they could organize genetic testing for Scotland from then on. Malcolm was involved, so I hesitate, but we did discuss it and he said I should lead off, but he will feel free, I know, to chime in if I get any of it wrong. They showed great foresight to come together and see how they could coordinate the development of this new, rapidly developing, field for Scotland. And the people involved were Malcolm, David Brock in Edinburgh, and Alan Johnston in Aberdeen, who was not a trained geneticist but was a physician with a very keen interest in genetics.²⁰⁸

²⁰⁸ David Brock (1936–2004) was Emeritus Professor of Human Genetics at the University of Edinburgh; <http://www.scotsman.com/lifestyle/obituaries/david-brock-1-564914> (visited 23 July 2013). Dr Alan Johnston (1928–2012) was Consultant Physician, Aberdeen Hospitals and Senior Lecturer in Genetics, Aberdeen University. Professor Peter Harper commented on Dr Johnston's career: '... he was actually a trained geneticist: he trained with McKusick but there was no clinical genetics job at the time in Aberdeen.' See also Johnston (2012) and Professor Peter Harper's interview with him, available at <http://www.genmedhist.info/interviews/Johnston> (visited 8 October 2013).

Most of his genetic work was in cytogenetics but he was an assertive man and he was very anxious to build up a proper service in Aberdeen and he did that remarkably well. In Glasgow there was Malcolm and in Dundee was Mike Faed. So, as I said, they came together, there were a few hiccups, but then after some discussion they decided to put a joint bid into the then Scottish Home and Health Department (SHHD) for some development funding to try a new service approach for providing molecular genetic testing for the population across Scotland.²⁰⁹ They were successful and were awarded what was called ‘New Developments in Healthcare’ money by the SHHD but this was relatively short-term funding. None of my ex-colleagues can find the original archive files for me, so I don’t know if it was three-year or five-year funding. What they aimed to do was to fund four labs from this money, one in each of the centres, to provide molecular genetic testing but very wisely decided that, with the population around five million in Scotland, and it is relatively rare disorders we’re dealing with, it would be silly for each of the four centres to try and provide the full repertoire of tests that was becoming available. It would be very wasteful in terms of effort and resources. So they agreed that they should work in a consortium mode and they would agree a list of disorders for which it was possible to provide tests, divide up this list of diseases between the laboratories and each tackle an allocated number of diseases and provide testing on behalf of the whole population in Scotland. The way it was to work was that patients would be seen by their local clinical service; they would receive their counselling from their local clinical service, the blood would be taken and the local laboratory would extract the DNA and then send it to the Scottish laboratory that had been allocated that disease to test. The test was done, the results went back to base and the family was counselled by their own local service. So it was absolutely marvellous for the patient population of Scotland and it provided total equity of access to the whole repertoire of genetic tests that were available at that time and the new developments as they came along. I really have to salute my forebears in this because really and truly I think you (Malcolm) put in place the basis of a model service. I hope we have done you justice in the way we have built it up since then. I came into the Scottish Home and Health Department at the end of 1988. I think I was, it is fair to say, the only person within the walls of St Andrew’s House who’d ever had any contact with genetic services at all.²¹⁰ So, though my remit was really public health, I was

²⁰⁹ Professor Malcolm Ferguson-Smith wrote: ‘All four of us had made separate applications to the SHHD without success. Our joint bid simply amalgamated these bids with additional proposals to share the load. There were no hiccups! The grant awarded amounted to the total sum requested initially.’ Note on draft transcript, 2 June 2013.

²¹⁰ St Andrew’s House is headquarters of the SHHD.

immediately asked, because the consortium funding was coming up for review after five years, would I be prepared to lead a review of the service so they could decide on future funding? I happily agreed to do that. I had able help from some civil service colleagues; we went around, assessed the situation in each of the centres, put a report together. Then, with two very helpful colleagues from south of the border, Peter [Harper] and Rodney [Harris], who agreed to act as external referees, I'm happy to say that all our recommendations were accepted. So, as a result, it was decided the consortium would stay and it was put on a firm funding basis from then on. It would be centrally funded as a national service in Scotland, which meant money would be top-sliced from the 15 health boards – there were 15 in those days – and this put it absolutely on a stable basis. Also, it would continue working in the same mode but we would formalize the arrangements a little bit; we suggested there should be a formal steering group set up. For the first time the users of the service were brought in to have their say on future developments as new funding became available and things gradually began to develop. Laboratory standards were put in place, result turnaround times were agreed, and they were put into contracts for the labs long ahead of any similar contractual turnaround times anywhere else in the UK. The service developed activity units, Welcan, for assessing laboratory activity; workload units, that's the best way to describe them.²¹¹ By the time all that was done, at the end of the 1990s, there was a very stable and successful service in place in Scotland. As I said, it did provide equity of access for the whole range of genetic tests that was available; the funding was available not just to provide testing within Scottish laboratories. If any Scottish families needed tests that couldn't be provided locally, the test could be done in any UK or even European laboratory where it was available and would be funded from this same pot of money. So it did away with all the postcode lottery disputes that have upset people with other services. I really do admire what you started, Malcolm, and give full acknowledgement. I think we must also acknowledge the huge input from David Brock into molecular genetics. Sadly, David died some years ago, long before he should have. He was very young, only 68 when he died, and recently Alan Johnston in Aberdeen has died too.²¹² Lastly, in 2005, after the White Paper in England, each of the countries in the UK took the opportunity again to review where they were with genetics. We had a major review in Scotland and as a result of that we got a large amount of additional funding. I'm delighted to say we got £10 million of additional funding for genetics in Scotland as

²¹¹ 'The Welcan workload measurement system, developed from the Canadian schedule of unit values for clinical laboratory procedures, attempts to provide a series of relative weighted procedure values reflecting labour input.' Quoted from Tarbit (1990), page 92.

²¹² For Brock and Johnston, see note 208.



Figure 21: Dr Ian Lister Cheese

well as some rolling money. So the Scottish Molecular Genetics Consortium was put on an even stronger basis then. Apart from just getting money for consumables and staffing, they now have a rolling capital budget so they don't have to compete with other services within a trust for new equipment in the laboratories, which has been a huge step forward. It was decided, as cytogenetics was increasingly using molecular techniques, it made sense to try and integrate the service and so cytogenetics is now integrated into the genetic laboratory consortium service.

Dr Ian Lister Cheese: My recollections come from about the same time as those from Ros Skinner, 1984 to 1985. But I have rather a different view from the one Ros has just described, a much less tidy one. Donald Acheson had, I think, received a copy of Sir David's (Weatherall) book, the second edition, and he passed it to me.²¹³ That was really the beginning of my responsibility for that area of policy in the Department of Health.²¹⁴ At the same time I got to know a number of people, I might say the leaders in the field, Sir David, Rodney Harris, Marcus Pembrey, Peter Harper, yourself Martin, and many others. What soon became clear was that in the DoH there was no substantive policy for genetics or for matching laboratory services. I think one can say there was no policy for genetics services or laboratory services for almost another

²¹³ Sir Donald Acheson (1926–2010) was Chief Medical Officer, Department of Health (1983–1991). See Weatherall (1985).

²¹⁴ Dr Ian Lister Cheese was a senior civil servant in the Department of Health (1984–1996) and had responsibility for genetics services.

20 years.²¹⁵ In one particular way this didn't greatly matter. It became quite obvious from the existing services that the pattern of genetics services, the organization of services, the conduct of services, the specialties, the components that were needed to give a coherent and cogent genetics service were already in place, but they lacked capacity and the conditions necessary for growth. Our colleagues in the genetics profession who came to the department, before this area was my responsibility, to propose that there should be a development of their existing services, must certainly have known about this problem. But they presented a case, saying: 'Let us evaluate services in three major centres – four originally but Sir David Weatherall's centre didn't participate in the end – in Cardiff, in Manchester and in London, and determine their clinical and cost-effectiveness.' In 1985 the DoH agreed to fund a Special Medical Development (SMD).²¹⁶ The condition of evaluation was to determine the cost-effectiveness and the value to the community and to patients of the introduction of these services into the NHS. A great advantage of this was, I think, that monies were provided to the existing services to expand them. Money was also provided to another unit to evaluate them. It became clear within a very short time that these services were needed and were valued by patients and the outcomes were the outcomes that patients desired. In a way the policy was already there but unwritten. There was a sense in which the SMD was unnecessary, unnecessary for the reason I've given but also unnecessary in the sense that what was going to happen could have been foretold. No one was going to wait or be influenced by the cost-effectiveness evaluation, which didn't appear until two

²¹⁵ Developments for a national policy on genetics during that period included the Government's appointment of a Science and Technology Select Committee (1994–1995) under the banner of *Human Genetics: The Science and its Consequences*, which culminated in the creation of the Human Genetics Advisory Commission (1996–1999), of which Professor Martin Bobrow was a member. This body was absorbed into the new Human Genetics Commission in 1999; <http://webarchive.nationalarchives.gov.uk/+www.dh.gov.uk/ab/Archive/HGAC/index.htm> (visited 2 July 2013). Another policy development was the publication of *Genetics and Cancer Services* in 1996, known as the 'Harper report', after its Chairman Professor Peter Harper, which recommended 'a core service in cancer genetics'. See Department of Health (1996), quoted from page 1. For the later policy that Dr Lister Cheese refers to, see Department of Health (2003).

²¹⁶ Dr Ian Lister Cheese wrote: 'The Special Medical Development (SMD) was led by Professors Peter Harper, Rodney Harris and Marcus Pembrey, and included Drs (now Professors) Angus Clarke and Dian Donnai and Drs Helen Hughes, Helen Kingston and Maurice Super. The interim report was not published formally but was made available to participants.' Note on draft transcript, 1 May 2013. Dr Lister Cheese explains that the SMD was 'to explore the application of new genetic probes in the service context'; quoted from Harper *et al.* (2010), page 57. In the same volume, see also pages 50, 60–1, 79. See also Meredith *et al.* (1988) and Harris *et al.* (1989).

or three years later anyway. That's my view of the SMD. Knowing that the final evaluation wouldn't appear for several years, with the help of Rodney Harris and Marcus Pembrey and Martin Bobrow, we wrote an interim report in which we talked not about cost-effectiveness of the service but simply about the value to patients.²¹⁷ That, I think, was probably the most valuable outcome of the SMD. The department seemed rather refractory to change, and subsequently resisted central direction in favour of a competitive internal market. Malcolm talked about us being driven by technological advance; the department was not driven at all by such advances – it had to be prodded into action. And it is one of the most disappointing features that, given the expert advice it received from outside, none of these things happened as they should have done, as indeed happened in Scotland.²¹⁸ Other colleagues have talked today about the value of their professional meetings. I was a non-geneticist, of course, and I cannot say too much how I valued and learnt from the meetings with colleagues in the profession, in their societies, the Royal College of Physicians' Genetics Committee, the Society – I think it was still called the Eugenics Society at the time but soon became the Clinical Genetics Society.²¹⁹

Bobrow: No, they were different, just for the record, different.

Lister Cheese: But all the elements of a policy had been well-established by authoritative bodies and had been tested, one might say, through collaboration and peer review long before the department set its eyes on them. It's one of the disappointing things, as I said, that the department seemed not to take the authority of external bodies in the development of its own policies.

²¹⁷ See Department of Health and Social Security (1987).

²¹⁸ Dr Ian Lister Cheese wrote: 'At that time, the Department refrained from giving any kind of specific instructions to the NHS. However, the Chief Medical Officer (CMO, Sir Kenneth Calman) and the Chief Nursing Officer (CNO, Yvonne Moores (later Dame)) were able to write a joint Professional Letter on clinical genetics services, and to draw the attention of people to their importance in the developing NHS.' Note on draft transcript, 1 May 2013. See Department of Health (1993). Sir Kenneth Calman was CMO, Department of Health (1991–1998). Dame Yvonne Moores was CNO, Department of Health (1992–1999).

²¹⁹ The Eugenics Education Society was founded in 1907, becoming the Eugenics Society in 1926 and then the Galton Institute in 1989. See Hall (2002). Founded in 1970, the Clinical Genetics Society (CGS) was created 'to bring together doctors and other professionals involved in the care of individuals and families with genetic disorders...'; quoted from <http://www.clingensoc.org/about-us.aspx> (visited 2 July 2013). See also Harper *et al.* (2010), pages 52–3.

Skinner: Could I just say something, a key thing that I forgot to mention on the Scottish scene? When we did the 1989 review and were successful in getting the central funding and the national service set up – what would not happen now at all – we managed to succeed in getting the centre to pay the funding to set up a consultant clinical genetic post in Dundee so that there would be a proper service established in Dundee and equity of access for all the population of Tayside. Following on from what Ian said, he's absolutely right. We found it difficult, to say the least, to communicate between departments because there really wasn't an identified policy group dealing with genetics and it was equally true in Scotland; I was a lone person there doing it as a 'hobby' because I was interested in genetics. Ian was in London. It wasn't until around about 2000 that the Department of Health, I think, put together a genetics team and we began cross-border discussions and greater UK-wide collaboration. It was then, when Mr Milburn was going to make his speech, that I got a call from colleagues to say, 'Do you know this is going to happen? You'd better come and listen; there's going to be a White Paper and you need to know about it.'²²⁰ From then on, we have worked extremely closely together, the departments around the UK, but until then it was difficult because neither side of the border had policy teams that could really talk to one another.

Bakker: In the Netherlands we had a similar situation as in Scotland. When the first probes came out, we sat together with the different centres and divided the diseases.²²¹ That system has continued over the years and all eight centres have, at certain times, done different portfolios of diseases. For the frequent diseases, every lab was setting up diagnostic tests such as for Fragile X and breast cancer. But for the rare disorders, tests were designed in expert centres for the whole of the Netherlands, so each centre had its specific portfolio of genetic tests. The samples had to travel, not the patients. We sent the samples to the different laboratories and results came back and the patients got counselling at the local place. So that has been the system since that time and the major advantage of that is, with the eight centres, we now offer tests for over 1,300 genes at the DNA level, and if each different laboratory should have done that it would have been impossible.

Ferguson-Smith: Can I just say that the organization of services in the Netherlands was really excellent. I was fortunate to be invited to go and talk to people in the Netherlands about genome services some years ago and it was

²²⁰ See note 177.

²²¹ See Professor Bert Bakker's comments on pages 37–8.

really very encouraging to learn about their experience. What I wanted to ask, is why it was that genetics departments in England didn't share conditions in the way that was done in both the Netherlands and Scotland? Well, perhaps they did later on, but it took a number of years for this to happen. It seemed that each lab wanted to do everything.

Bobrow: We have a volunteer in the form of Rob Elles who is going to answer your question.

Elles: I'll comment on that but first I think Ian underestimates the impact of the Special Medical Development on molecular genetics in England and Wales.²²² Locally, I can speak for Manchester. I don't think that molecular genetics would have embedded itself with the speed and scope that it did, in fact, without that core funding over two cycles and I think it was tremendously important. During that period, there was also a tremendous ethos of sharing and collaboration among the laboratories in England and UK more generally; the development quite early on of the CMGS and John (Old) was our first secretary and Andrew (Read) was the first Chair, which brought molecular genetics people together. We were aware of the Scottish model, we were aware of the model in the Netherlands, there were discussions from a fairly early period, certainly the mid-1990s, along the lines of 'not everybody can do everything; we need to share.' It's never been as fundamental as the systems in the Netherlands or in Scotland but nonetheless those discussions were successful and were professionally led in creating the UK Genetic Testing Network and also in influencing policy and the Milburn announcement that has been mentioned. I think this was a brief moment in government, where government listened to the professions. The people who were around at the time, John Burn, Peter Farndon, Di Donnai, and others, acted at a key moment and had the ear of Alan Milburn and that led to what has been the foundation, certainly in England of, at that period, a relatively well-funded genetics laboratory service. So I would say that in some ways that does trace itself back to the Special Medical Development.

Harper: My colleagues will be able to add to this, I think, or correct me, but I absolutely agree that the SMD was key to getting a core of the staffing and expertise off the ground. It was hugely valuable and the fact that it was this grouping of centres, it encouraged interactions. So far as the Netherlands' system of sharing and not duplicating disease diagnostics went, that actually was considered in some detail pretty early but there were two, essentially political,

²²² See note 216.

problems that held it back for a long time. The first was the introduction of the ‘internal market’ in the NHS, across the UK actually, by the government of the time, so that at the precise time when we were trying to collaborate and do things in a complementary fashion, we were being told: ‘No, you must compete with each other.’²²³ So we were having to work against opposition. Then locally in Wales, there was an additional factor: having to some extent survived the difficulties of the internal market, just when England was coming out of this tricky phase, we had a particularly reactionary Secretary of State, banished from Westminster to Wales, who saw it as his aim to disband all centrally funded services.²²⁴ So we had to fight against that. Essentially, there were a number of years when the energies we should have spent improving our patient services were quite largely spent fighting to hold on to what we had, against very unwise political attitudes. I could be wrong on this and my colleagues may correct me.

Sampson: Just to add to what Peter’s already said: certainly the political emphasis was on competition and there was a lack of support for centrally commissioned services. But in Wales there was only one service and that was commissioned through one trust, so we were very dependent on the support of the chief executive of that trust and his team.²²⁵ At the time of those political difficulties, there were also great difficulties at that more local level as funding for genetic services was processed through a trust that may have, and did have, other priorities. It’s true to say that the funding that should have been coming to genetics didn’t; it helped solve financial problems elsewhere. We were fighting against problems at a lot of levels at that time.

Middleton-Price: I want to correct any impression that we might have given that we didn’t share samples and patients from the very beginning. For those very rare conditions, for which specialist services were offered in different centres, we started to send samples around the country in the mid-to-late 1980s. For ICH and Great Ormond Street this included the rare immunodeficiencies and other rare metabolic conditions. Further to this, I have a question for Rob and others: wasn’t one of the reasons why we were, in England, slower in moving towards

²²³ For the ‘internal market’ policy of the NHS reform, see, for example, Best *et al.* (1994).

²²⁴ Rt Hon Mr John Redwood, Secretary of State for Wales from 1993 to 1995; <http://www.parliament.uk/biographies/commons/mr-john-redwood/14> (visited 9 September 2013).

²²⁵ University Hospital of Wales and Llandough Hospital NHS Trust.

sharing more common diseases because each centre had a larger population? In other words, every centre had sufficient patients and samples to develop expertise and provide a full workload.

Lazarou: I was just going to say that the SMD did have an influence because it brought the centres together and it created a community of diagnostic labs, of scientists working at different stages for different disorders.²²⁶ So much so, I actually memorized telephone numbers of the different laboratories and if I was struggling with a particular thing, I would just pick up the phone and talk to a colleague in another centre. John (Old) and Rob (Elles) were very helpful with their molecular experience in helping us set up things within our laboratories, so it was important.

Bobrow: I would like to make a comment myself at this stage. I think that the people involved in that development did their very best with what was happening at the time. The molecular genetics and clinical genetics communities in England did their level best to continue delivering a sensible and reasonable service. But that SMD, although it was undoubtedly very useful for the centres that got the money, actually did very little for moving the thing on over England as a whole. There are 30-odd clinical genetics centres delivering patient services: three of them had money and the rest of them actually just got on and did it. So absolutely no aspersions on the people in the centres or the people outside the centres, but as a policy I think it was a waste of time, just a way of putting off an inevitable planning decision. That's not, of course, what Ian said; that's what I'm saying.

Lister Cheese: That was precisely the point that I was making: the SMD monies were extremely valuable to the centres that received them because they were able to develop but didn't really establish substantive policy one iota. We had to wait nearly 20 years for the White Paper.²²⁷

Yates: Two things: first, I want to address this point of trying to achieve better coordination and say that Peter Harper tried very hard in the late 1980s and early 1990s to improve coordination of services in England by setting up what was called the Joint Medical Genetics Coordinating Committee that brought all

²²⁶ See, for example, 'Minutes of the meeting of SMD Groups', 20 September 1989, deposited with the records of this meeting at the Wellcome Library, reference GC/253.

²²⁷ Department of Health (2003).

the relevant people together with Ian (Lister Cheese) coming along representing the Department of Health.²²⁸ I was secretary of that committee and I think we met in 1988 for the first time and for some years after. It was very frustrating because the message that we were getting from the Department of Health was that they didn't want to facilitate any sort of coordination. They wanted to see cut-throat competition and, of course, that was exactly what you didn't need because laboratories weren't going to set up rival services for less common diseases with only small numbers of patients. Second, just to look at the effect this had on particular diseases, tuberous sclerosis being a particular interest of mine; after the two genes had been identified and mutation testing became an option, both Cambridge and Cardiff set up services and so there were two labs happily sharing the diagnostic workload and that was exactly the model that you might want, but the funding for testing then had to come from individual budgets and individual genetics services.²²⁹ That was not forthcoming in some parts of the country and so even though the service existed, it wasn't being used and we recently published a study looking at a large cohort of children with tuberous sclerosis diagnosed between 2001 and 2005, and access to genetic testing for those families was patchy and the reason was simply that in some centres they didn't have the funds to pay for it.²³⁰

Bobrow: One of the things we haven't mentioned at all is that there were – there still are – some situations in which population screening for monogenic disorders using molecular techniques have been either tried or established in practice.

Modell: Yes. For population screening using molecular techniques in this country, the top candidate would be cystic fibrosis and I hope that we might have some comments about that. But you're asking me about the concept of population screening for genetic disease, or for genetic risk. It's very important to distinguish in the haemoglobin field, because both types of screening occur.

²²⁸ Professor John Yates wrote: 'The Committee had representatives from the Association of Clinical Cytogeneticists, the Clinical Genetics Society, the Clinical Molecular Genetics Society and the Genetic Nurses & Social Workers Association and contributed to the subsequent formation of the British Society for Human Genetics.' Note on draft transcript, 28 March 2013.

²²⁹ For Cardiff's service, see, for example, Professor Julian Sampson's comments in Jones and Tansey (eds) (2013), pages 42 and 66–7. Cambridge's service was, and still is, based at Addenbrooke's Hospital as part of the East Anglian Medical Genetics Service.

²³⁰ Yates *et al.* (2011).

Bobrow: We're talking about identifying, not diagnostic screening, but risk carrier type screening.

Modell: Screening for a genetic disease is often seen as genetic screening in the world out there. It's not, it's case identification. Neonatal screening is case identification for management, like screening for non-genetic diseases. What we're talking about here is screening for identifying carriers in order to inform them of risk, to allow them to manage their risk. So the paradigm is really premarital or antenatal screening for haemoglobin disorders. We now have extensive experience and I'm hoping to push the envelope out a little bit here because we now have global experience. In this country, when it became possible to do prenatal diagnosis for thalassaemia, the local hospitals had some very interested haematologists. The person whose name I want to mention is George Marsh, consultant haematologist at the North Middlesex Hospital, who unfortunately died far too early.²³¹ As soon as prenatal diagnosis became possible, he called meetings at his hospital and said: 'Look, we have the largest Cypriot population in London. For years we have been screening all the pregnant women to see if they carry thalassaemia in order to distinguish iron deficiency from thalassaemia so that we can treat iron deficiency correctly, and what have we done when we've found thalassaemia? Nothing. We have given them no information and I think this is quite wrong.' So he immediately started screening all the pregnant women for fetal thalassaemia and haemoglobin disorders and set up a system for informing the carriers, and advising them to get their husbands tested. Being Cypriots, the husbands came along at once so he picked up the at-risk couples in early pregnancy and referred them to us.²³² That really stretched our prenatal diagnosis service, but it also allowed us to collect statistics on uptake. George collected statistics on how many women got their partner tested and how many couples came to us, and we counted how many asked for prenatal diagnosis and how many terminated when the fetus was affected. Together we found that 96 per cent of Cypriot at-risk couples asked for prenatal diagnosis and 96 per cent terminated, which was really quite convincing information. George was the person who had the vision to initiate the population screening in a way that he could manage because it was under his control. We could come back at this point to clinical geneticists

²³¹ See, for example, Wainscoat *et al.* (1983).

²³² Professor Bernadette Modell wrote: 'Cypriot and Asian husbands almost all come immediately for testing, feel very concerned about the baby, and tend to give the wife priority in decision-making re prenatal diagnosis. "It's her decision. She will be looking after the baby".' Note on draft transcript, 9 August 2013.

and their family pedigrees, because if you're a clinician you start off with an affected person who is surrounded by a cluster of people at risk. You have some control over the situation because you've got the patient and can then proceed at the specialist level to study the family and identify carriers. But if you want to identify carriers of a recessive disorder, you've got to get out there to the population. You've somehow got to find an appropriate point in your service for reaching every member of the population, getting them all to go through a turnstile where you can test them. That differs in different countries. In Cyprus this happened very quickly, because thalassaemia was a priority health problem: one in 144 children born had thalassaemia major and the cost of treatment was completely beyond available resources. Today it might be manageable but once the patients start surviving, in ten years' time it would be hopeless. So the Ministry of Health introduced premarital screening.²³³ The way that worked was the ministry went to the government and said: 'Everybody gets married here. We could mandate a blood test at that time and we could detect all the carriers at a stage when they've actually got a choice.' The archbishop had said he thought it was wrong just to do antenatal screening because people then only have one choice: whether or not to terminate. He thought that they should be tested earlier so that all the choices were available. So what did the Cypriot government say? It said: 'No, that to mandate testing would be an invasion of people's human rights.' So the archbishop said words to the effect of: 'Right. Well if you won't do it, well we will, because everybody gets married in church, practically. We're going to issue a religious ruling that nobody can get married unless they've been tested.' The results of the test are not divulged, all they need is a certificate that the couple have been tested and advised accordingly. So the Cypriots were first off the mark, and that had an extremely rapid effect on the birth rate of thalassaemia major in Cyprus.²³⁴ In this country, there wasn't that option because there was no such thing as premarital testing and anyway people are getting married less and less, so a premarital test isn't really an option. You have to find some other turnstile. The ideal, of course, is for people to be informed early. There's the possibility of testing in high school and

²³³ Professor Bernadette Modell wrote: 'It was the Ministry of Health that took the initiative with suggesting mandatory premarital screening to the parliament. The parliament declined because they considered it would infringe human rights. This left the situation that women would have to be offered testing during pregnancy.' Note on draft transcript, 9 August 2013.

²³⁴ Angastiniotis and Hadjiminis (1981).

this has been beautifully developed in Canada by Scriver and his co-workers.²³⁵ I think this has been extended in Montreal to carrier testing for cystic fibrosis, Tay-Sachs disease and thalassaemia.²³⁶ But it's not a model that has been followed; it hasn't been picked up here because there are just too many problems getting everybody to agree, or getting ministers to talk to each other. An alternative is to get general practitioners to provide carrier testing in primary care. The problem really is that there's no infrastructure in this country for offering this kind of service. It took 20 years from the time that we were able to show, with ample scientific evidence, that people wanted and would use the service to the decision in 2001 that a national sickle cell and thalassaemia screening programme should be set up.²³⁷ In frustration, I feel like tearing out my hair and covering myself with sack-cloth and ashes. I say to my husband, 'This is terrible'. My husband is a GP, and he says, 'Well, we know that in general practice, it always takes 20 years for an approved, tested advance in medicine to get into really universal practice.' So perhaps you shouldn't be so appalled as you are. But anyway, that is this country. Now we have come to the possibility of leapfrogging, not technology, but leapfrogging organizations. We are held back organizationally by the fact that all these advances have been developed slowly piece by piece by our brilliantly talented scientists. When another country decides that it wants to implement these services, they can consider the whole pattern and work out a way of doing it from scratch. The best example I know is Iran, which actually has a genetics office in the Ministry of Health and Medical Education, and a very well-organized primary healthcare system. The Iranians recognized thalassaemia as a 'point of entry' for this kind of technology but as only one

²³⁵ This research concluded that screening interventions for thalassaemia major were more effective in the context of high schools versus community clinics, with an average of 116 attendees at schools' clinics (over 80 per cent of the school population) versus 28 attendees at the average community clinic. See, for example, Scriver *et al.* (1984).

²³⁶ For Tay-Sachs and thalassaemia screening at high schools in Montreal, see, for example, Mitchell *et al.* (1996). See also Kaplan *et al.* (1991).

²³⁷ A national antenatal and neonatal screening programme for England and Wales was introduced in 2001 following the publication of *The NHS Plan* in July 2000; see Department of Health (2000); page 109. See also, the NHS Sickle Cell and Thalassaemia Screening Programme (2011), which notes: 'During the mid-to-late 1980s, national recommendations for sickle cell and thalassaemia began to emerge. ... The 1990s saw a period of heightened lobbying, but despite this and the various recommendations regarding screening for sickle cell and thalassaemia, screening was patchy with some areas carrying out universal screening and some selective screening.' Quotations from pages 4 and 6. See also, for example, Anionwu and Atkin (2001).

part of a comprehensive genetics service, so the country's infrastructure for thalassaemia screening was created as an infrastructure for the entire genetic service.²³⁸ They realised at an early stage they needed to create a cohort of community genetic counsellors, which they've done. In fact, they are organizing a modern genetics service from scratch, having learnt all the lessons about how not to do it that we're still struggling with here. They're just one example but let's hope that it will be followed by others.

Bobrow: That's exactly what I wanted you to bring out and I think we should add that you, firstly, stuck at that with a few other people for decades and it's not at all clear that it would have happened without a few people who really drove it through. Second, without going into details, there are a number of other interesting, similar stories. There is an arcane story about Tay-Sachs screening and religious Jewish sects in New York, which we don't have time to go into now.²³⁹ There is an equally interesting story that Bernadette knows a lot about, which was in relation to an early enthusiasm for population carrier screening for cystic fibrosis, which was widely touted, hugely advocated and failed basically in the face of massive public disinterest.

Modell: I've been very puzzled by that, because the evidence is that when people know they are at risk they use prenatal diagnosis, as far as I remember from Rodney Harris' study on cystic fibrosis.²⁴⁰

Bobrow: There's no country in the world that I know of which ever implemented CF population screening for carriers.

Modell: No. My guess is because it was too expensive. If it was as cheap as haemoglobinopathy screening, why not?

Skinner: The MRC held a workshop more years ago than I care to remember and myself and several others attended. And, I think, the MRC actually funded a suite of studies to look at trying carrier screening in the UK in different settings.

²³⁸ See, for example, Samavat and Modell (2004).

²³⁹ See, for example, for a range of references to this topic, the section on 'Tay-Sachs Disease and Ashkenazi Jewish Uniqueness' in Brandt-Rauf *et al.* (2006); in particular page 1980.

²⁴⁰ In Harris' study, it was reported: 'All but one patient (75/76) booking before 14 weeks of pregnancy accepted the offer of cystic fibrosis carrier testing. ... Overall, 72/75 (99.6%) of patients felt that they had made the right decision to have a cystic fibrosis carrier test in early pregnancy. One patient regretted having the test.' See Harris *et al.* (1996); quotation from page 226. See also Murray *et al.* (1999).

Hilary Harris ran the GP-led service from Rodney's department in Manchester.²⁴¹ Nick Wald did couple screening and David Brock did another form of couples' screening in Edinburgh.²⁴² But at the end of the day we have a thing called the UK National Screening Committee (NSC) that was set up in 1996 and carrier screening has never flown with the NSC.²⁴³ They did agree eventually – I have to measure my words here, as a founder member of that committee; they did once the Wisconsin study on children with CF showed some improvement, clinical improvement shall we say, from early detection and then additional dietary measures.²⁴⁴ The NSC did then agree to the implementation of neonatal screening for cystic fibrosis in 2001.²⁴⁵ As a result of that, of course, there were some carriers detected and that led to a huge discussion then about whether the carrier status that was disclosed through neonatal screening should be disclosed to the parents. The NSC isn't really yet, I think it's fair to say, geared up to look at genetic screening issues. It does work looking at prospective new screening programmes against a set of criteria that are based on the original Wilson and Jungner criteria.²⁴⁶ These criteria have been adapted over time to try to address genetic aspects and Neva Haites ran workshops for the NSC to help with this. They look at some elements and consider possible genetic screening programmes but at the moment it's not a feature that is at the forefront in the UK. They are currently looking at the provision of preconception testing or screening. The

²⁴¹ This study was funded by the Wolfson Foundation, rather than the MRC. See, for example, Harris *et al.* (1993).

²⁴² Research on carrier screening was also conducted at the Wolfson Institute of Preventive Medicine, St Bartholomew's Hospital Medical College, London. See, for example, Wald (1991). For research funded jointly by the MRC and Cystic Fibrosis Trust, see Brock (1996).

²⁴³ 'The UK National Screening Committee was founded in 1996 with Sir Kenneth Calman (Chief Medical Officer for England 1991–1998) as its first Chairman. ... From the outset, the concept of screening doing more good than harm and the importance of quality at every step of the screening journey were at the heart of the work the UK NSC did.' The organization developed a framework for screening and subsequent screening policies that informed this framework for specific diseases. Quoted from *History of the UK NSC*; <http://www.screening.nhs.uk/history> (visited 22 July 2013).

²⁴⁴ See, for example, Farrell *et al.* (2001).

²⁴⁵ For a discussion about the introduction of this cystic fibrosis neonatal screening policy and associated research see, for example, Parsons *et al.* (2003). See also Mrs Rosie Barnes' comments in Christie and Tansey (eds) (2004), page 69.

²⁴⁶ Wilson and Jungner (1968). See also, for example, Petros (2012).

NSC did raise this topic with the Human Genetics Commission (HGC)²⁴⁷ just before it was wound up and there was a joint working party between the NSC and HGC to look at this and see whether there were any legal, social or ethical issues involved that would preclude the NSC doing any further work in this area. The conclusion was there were not, so they are now looking again at preconception testing and making it more available, if it's acceptable. They are about to fund a pilot study. This has all come from the sickle cell and haemoglobinopathy screening programme because there's been huge demand from the populations at risk actually to move in this direction.

Bobrow: I don't disagree at all with what you have said about the NSC but I do, personally, disagree with your assessment of the scientific basis of the public enthusiasm for all of those screening programmes. I think they've been driven very largely by the people who want to screen, rather than the people who would need to be screened. There's a lot of research evidence from years before then suggesting that unless you push people into screening, they are fundamentally not very interested in it.²⁴⁸ But it isn't a very good topic to hammer out in this forum – on some other occasion perhaps.

Harper: Very briefly, largely to confirm what you were saying: Cardiff and the region around was one of the centres where there was a pilot project, which my colleague Angus Clarke led, of carrier screening. Basically, the broad conclusion was that, while it was perfectly acceptable if people were approached in a GP surgery by a helpful nurse while giving information, when it was left with them to take further action it really wasn't pursued very far. So it was very much an initiative coming from the professionals rather than from the families themselves in this case.

Modell: Where haemoglobinopathy screening is concerned, the initiative has come entirely from the professionals. We did not wait for the population as a whole to come and say, 'We want to be screened'. It was our responsibility to tell them.

²⁴⁷ The Human Genetics Commission was created in 1999 and abolished in 2012. It was 'the UK Government's advisory body on new developments in human genetics and how they impact on individual lives ... with a particular focus on the social, ethical and legal issues.' Quoted from the organization's former website 'About HGC' page; <http://webarchive.nationalarchives.gov.uk/20121102204634/http://hgc.gov.uk/client/content.asp?contentid=5> (visited 24 July 2013).

²⁴⁸ See, for example, Bekker *et al.* (1993).

Bobrow: There are two things that I would like to deal with: first, a brief history of the UK Clinical Molecular Genetics Society, which I think is important because it sets the professional background to some of this; and second, I'd like another few words from somewhere about what in the end ought to be and has often been the biggest driver in all of this. We have had very active collaboration and pressure from patients and patient organizations, and I'm not sure we've quite said enough about that yet. First; the CMGS.

Read: Very briefly, there was a time when the molecular geneticists were a relatively small and close-knit band and they had really a fairly different ethos from the cytogeneticists, who were the other laboratory band in genetics, and clearly we needed to organize and be represented in some way, and one option would have been to go in with the cytogeneticists. There were a number of reasons why we didn't do that, some of which were purely personalities, but I think there were some real reasons. One: we were in a very different situation from the cytogeneticists. We were a very rapidly developing, very research-based service. With honourable exceptions, looking to my left and right [at Professors Pat Jacobs and Malcolm Ferguson-Smith], the cytogeneticists were by and large entirely focused on delivering an efficient routine service, and seemed to have little feel for the great scientific excitement of human genetics at that period. We were not like that. The second purely political concern was, since there were large numbers of well-established cytogeneticists in senior professional positions, if we had thrown in our lot with them we would, of course, have been a very small minority. So, for all of those reasons, we opted to set up our own organization.

Bobrow: Succinct and true.

Macdonald: I just brought along a few things. I did collate some information for our annual conference this year and I brought maybe some quirky bits of data and information about what happened. I have the first membership survey that was done in 1988; that's probably three years after the suggestion of having the body formed. At that time there were 43 of us in the CMGS. Our ages ranged – nobody was above 45 years of age, over half of the people appear to have been under 25, with the next bracket probably 35 to 40.²⁴⁹ Interestingly, 38 of the 43 members had no specialist training in molecular genetics at that time. Two years later, Andrew Read was elected Chair of the Society. I have the minutes of that

²⁴⁹ See Appendix 3, page 96.

AGM.²⁵⁰ From that point we'd gone from 43 members to 186, so, very rapidly, the profession was expanding. In 1990, there were quite a few other important things that happened: we put together a training board and we started to think about our A-grade scientists and our B-grade scientists, so that the 38 out of 43 who had no specialist training was quickly altered and we brought training in as an important feature.²⁵¹ That training board went from strength to strength and eventually we had national trainers and regional trainers, until everything changed in the last two or three years with Modernising Medical Careers.²⁵² But from 1990, we'd recognized the importance of training. At the same time we also started our laboratory directory. Unfortunately I threw out the first two editions of that when I moved my office a couple of months ago. I have the third edition here, which is a lot more professional than the first two editions, but in that we began to list the disorders we all did within our laboratories, a kind of early UK Genetic Testing Network. We could see who did what and what level of testing was available. And we collected that data from 1989 onwards. The other thing we did, around the same time, was to start doing our best practice and our quality assurance and the first QA (quality assessment) scheme.²⁵³ We weren't very good at putting the dates on things but Roger Mountford instigated the quality assurance scheme and we did it for cystic fibrosis where we had to type samples for the delta-F508 mutation.²⁵⁴ We did a pilot on DMD RFLP typing and we did a prenatal exclusion for Huntington's disease in the very first of the QA schemes. I have a nice collection of the newsletters of the CMGS (*The Probe*), and I have some of the early ones here, including the one, where apparently Professor Read was unavailable for comment, that shows a certain

²⁵⁰ Professor Andrew Read was elected Chairman of the CMGS after Professor Dame Kay Davies tendered her resignation in 1990. Minutes for the relevant AGM, 19 April 1990, will be deposited with the records of this seminar at the Wellcome Library, London, reference GC/253.

²⁵¹ For details of B-grade training see Appendix 3, pages 97–8.

²⁵² Modernising Medical Careers was a UK Department of Health programme introduced in 2003 to address problems with the postgraduate medical training system. See, for example, House of Commons Health Committee (2008).

²⁵³ For further details of the Quality Assessment Scheme see Appendix 3, page 99.

²⁵⁴ Dr Fiona Macdonald wrote: 'Roger Mountford worked as a clinical scientist in the Manchester Regional Genetics service at that time. He sat on the CMGS executive and was responsible for establishing an external quality assessment group. He was Chair of the CMGS quality assurance sub-committee from 1993 to 1994, then Scheme Organiser 1994 to 1997. He moved to the Liverpool lab in Sept 1995.' Note on draft transcript, 6 September 2013. Mr Mountford is Head of Laboratory at Merseyside and Cheshire Regional Genetics Laboratory, Liverpool Women's NHS Foundation Trust.

Colin Firth on the front cover in *Pride and Prejudice* I believe it was.²⁵⁵ So we began to put these newsletters together from 1990, the very first one when Andrew was Chair.²⁵⁶ These make interesting reading. They go back to explain how we could sometimes sort out our Southern blots or what quality problems people had in the labs, to some slightly more quirky issues, particularly from Lord Genome, who wrote certain articles every edition which weren't always, they were slightly tongue in cheek, shall I say?²⁵⁷ I have some of those newsletters here.

Lister Cheese: We can't pass without mentioning the Genetics Interest Group (GIG), who have been a most responsible and forceful group in representing, one might say, everyone who was threatened or burdened by a genetic disorder regardless of its commonness or rarity.²⁵⁸ Under its aegis they brought together the shared concerns of many individual disease-focused charitable bodies. They are a force, a political force, and I think they have influenced very greatly the formulation of the policies that we now see.

Bobrow: They are too numerous to mention, but an awful lot of patient organizations, single-disease charities who have worked, pressured and funded, some of them funded extensively, a lot of the work that we were talking about

²⁵⁵ The actor Colin Firth played Mr Darcy in the BBC's adaptation of Jane Austen's novel *Pride and Prejudice*, broadcast in 1995.

²⁵⁶ 'A Message From Our New Chairman' by Professor Andrew Read was included in the July 1990 edition of *The Probe*. See Appendix 3, page 95. Copies of some issues of *The Probe* newsletter will be deposited at the Wellcome Library with the records of this seminar, reference GC/253: July 1990; May and December 1991; June 1993; February, August and December 1994; Autumn 1995 and Summer 1997. The newsletters include advertisements for professional training opportunities and career development funding, with reports from grant recipients on funded research trips; articles on professional networks' development, affiliations and regulations; NHS policy issues; news of/reports from international conferences; arts and sports events listings; humorous cartoon strips; informal news on research and development of laboratory techniques from members; notices of the organization's annual meeting and committee elections, and death notices, among other contents.

²⁵⁷ Lord Genome is a pun on Lord Gnome, the fictitious proprietor of the popular UK news and current affairs magazine *Private Eye*, well known for its satirical humour. See, for example, Hislop (1985).

²⁵⁸ Dr Ian Lister Cheese wrote: 'The Genetics Interest Group (GIG), an umbrella organization set up to represent the common interests of societies for those threatened or burdened by a genetic disease, was formed in 1989. It has become an influential national voice.' Note on draft transcript, 1 May 2013. 'GIG was inaugurated on 22 April 1989 with the backing of 60 groups. ... The first management council held its meetings at St Mary's Hospital, London.' Quoted from Genetic Interest Group (2006), pages 9–10. The Wellcome Trust was a key funding contributor to GIG, which in 2010 became Genetic Alliance UK.

over that period of time. So we should note those and it was Bernadette who mentioned patients themselves and the pressure they put on for clinical stuff and we should just remember that there has been a lot of that, and very welcome it is too.²⁵⁹

Sampson: Just in relation to the Genetics Interest Group, I think we really should point out specifically Alastair Kent's leadership role there and that the GIG is now the Genetic Alliance [UK], still headed by Alastair.²⁶⁰

Bobrow: Quite so. It remains for me to thank the speakers; that's you, and to thank our hosts for having me here, because I've enjoyed listening to you.

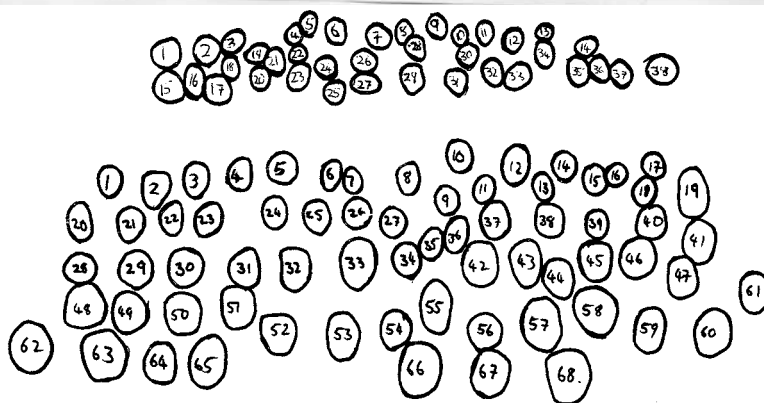
Tansey: It's been a great privilege to hear all your stories today. I want to thank Martin because he has kept you all under control, even though he thought he didn't have to, and he's done the best job the Chairman does: he gets us to the drinks at six o'clock. So thank you very much indeed Martin.

²⁵⁹ See page xiii for a list of relevant single-disease charities and patient advocacy groups.

²⁶⁰ Alastair Kent is Director of Genetic Alliance UK, a consortium of more than 150 patient organizations representing those who are affected by genetic conditions. See http://www.geneticalliance.org.uk/teammember_director.htm (visited 24 July 2013).

Appendix 1

Delegates attending *The Molecular Biology of Thalassaemia* conference, organized by Bob Williamson, Kolimbari, Crete, 1978²⁶¹



²⁶¹ Identifications taken from key with original photograph.

Standing

- 1 Emma Whitelaw
- 2 Francesco Ramirez
- 3 Koula Sofroniadou
- 4 Dina Politis
- 5 Lionella Camba
- 6 Yves Beuzard
- 7 Guglielmina Pepe
- 8 Michael Jenson
- 9 Bernadette Modell
- 10 Wilma Gabutti
- 11 Antigone Karoulis
- 12 Michel Goossens
- 13 Amalia Bosia
- 14 Michel Cohen-Solal
- 15 Mirijam Belhani
- 16 Marco Lucci
- 17 Roula Lagoyanni
- 18 Mauritzino Ferrari
- 19 Sergio Ottolenghi
- 20 M. Karagiorga-Lagana
- 21 Francesco Bernardi
- 22 Barbara Giglioni
- 23 Bruno Colombo
- 24 Stella Haralambidou
- 25 Sylvana Gargano
- 26 Anna Manitsa
- 27 Maria-Guilia Farace
- 28 Aris Antsaklis
- 29 George Chalavelakis
- 30 Thomas Zarvalis
- 31 Jules-Cassius De Linval
- 32 Francesco Conconi
- 33 Elizabeth Letsky
- 34 Nick Proudfoot
- 35 David Weatherall
- 36 Art Bank
- 37 George Maniatis
- 38 Nicholas Zeikos

Seated

- | | |
|--------------------------|-------------------------------|
| 1 Douglas Higgs | 36 Vasilios Berdoukas |
| 2 Guy Trabuchet | 37 Nick Anagnou |
| 3 Charles Coutelle | 38 Martin Steinberg |
| 4 Sue Malcolm | 39 R. Krishnamoorthy |
| 5 Minas Hadjiminias | 40 Phillipa Darbre |
| 6 Toula Sofocleous | 41 Carla Perotta |
| 7 Aphrodite Anagnostou- | 42 Chris Ricketts |
| Loutradi | 43 Beppe Saglio |
| 8 Abdoullah Kutlar | 44 Max Herzberg |
| 9 Mary Mouzouras | 45 Nica Cappelini |
| 10 Apostolos Voutsadakis | 46 Regina Stathopoulou |
| 11 Marios Matsakis | 47 Ray Dalgleish |
| 12 Mohammed Cherif | 48 Nicolas Constanzas |
| Beldjord | 49 Willy Sciarratta |
| 13 Mike Angastiniotis | 50 Cathy Anderson |
| 14 Tzwoffia Henni | 51 French Anderson |
| 15 Graham Cowling | 52 Hashemi Nasab |
| 16 Anna Metaotou- | 53 Mohsen El-Hazmi |
| Mavrommati | 54 Joseph Tam |
| 17 Bill Wood | 55 Luciano Vettore |
| 18 Lynn Pressley | 56 Blanche Alter |
| 19 Beppe Bandini | 57 Rich Propper |
| 20 Irene Kontopoulou | 58 Laura del Senno |
| 21 Josee Pagnier | 59 John Old |
| 22 John Christakis | 60 Bernie Forget |
| 23 Nikos Zoumbos | 61 Jim Palis |
| 24 Guiseppe Russo | 62 Bob Williamson |
| 25 Antonio Cao | 63 Dimitris Loukopoulos |
| 26 Gino Schilliro | 64 Bessie Aleporou-Marinou |
| 27 Anna Skalicka | 65 Nancy Kunkle |
| 28 Chaido Tsantali | 66 Peter Little |
| 29 Chintana Sirinavin | 67 Y.W. Kan |
| 30 Vassilis Ladis | 68 Panos Ioannou |
| 31 Gulzar Niazi | |
| 32 Boyd Webster | And – Sharma, who is not in |
| 33 Gabriel Cividalli | the photo because he took it. |
| 34 Anita Li | |
| 35 Alma Marcolongo | |

Appendix 2

Extracts from the laboratory manual of the University of Leiden postgraduate course in *Restriction Fragment Length Polymorphisms and Human Genetics*, 1982²⁶²

PLP 2 - 52

Outline of Experiments

The course has been divided into a series of experiments which will be partially performed in parallel. The following gives an outline ~~of each~~ intended experiment.^s

This is the same
(Experiment 1) involves most of the basic techniques aspects involved in defining DNA restriction site polymorphisms.

We regard the techniques as absolutely essential to restriction site analysis and it is anticipated that the participants will remain with this experiment until they have successfully completed it. However, the experience of some participants will permit them to move quickly to other experiments.

Essentially DNA probes consisting of arbitrary human DNA segments cloned in either the bacterial plasmid pBR322. or λ phage will be used to reveal polymorphic sites in the DNA of unrelated humans. Technically, this experiment requires isolation of DNA from white blood cells or other tissues, digestion of DNA with restriction endonucleases, preparation of agarose gels, electrophoretic separation of DNA fragments, preparation of southern transfer filters, radiolabelling of DNA probes, hybridisation of the probes to the filters, preparation and development of autoradiograms.

Experiment 2. Investigating the mendelian segregation of defined restriction site variants within families.

Experiment 3. Defining the chromosome localisation of an unique sequence DNA probe, firstly by hybridisation to a somatic cell-hybrid panel containing defined subsets of human chromosomes, secondly by quantitative hybridisation of the probe to DNA of cell-lines containing various numbers of a particular chromosome to reveal 'gene' dosage.

Experiment 4. Isolation of recombinant plasmids containing chromosome specific human DNA. This experiment will serve as a representative of cloning DNA from various sources such as total DNA, isolated chromosome fractions, somatic cell hybrids etc. Human X-chromosome DNA, previously isolated by cell sorter and has been cloned in λ -wess. (clone bank K.

²⁶² 'Outline of Experiments' is from manual's introduction, pages 2–3; and, following this, 'large scale isolation of plasmids (Leiden)' is a sample experimental protocol from the manual, pages 51–2. This manual will be available, in full, in the Wellcome Library with the records of this Witness Seminar under reference GC/253.

Davies et al.) following restriction with *ECO* R1 and insertion into the *ECO* R1 site of *-wes*. Part of the bank has been screened for repetitive sequences using the Benton and Davis hybridisation method. Bacteriophage clones containing presumptive non-repeated sequences have been recultured and the participants will be provided with DNA from a series of such clones. The human insert will be removed by *ECO* R1 digestion followed by gel separation. The insert will be isolated from the gel and recloned using pBR322 as the vector and *E.coli* K12, HB101 as the host. The inserts will then be rescreened for repeated sequences using both Benton and Davies and Southern Blotting techniques. Suitable plasmids will then be tested for demonstrating polymorphism with normal human DNA samples.

Experiment 5. Isolation of human chromosome specific sequences from a hybrid-cell line.

The participants will be provided with duplicate filters containing DNA from λ -plaques derived by transformation with DNA isolated from a chinese hamster/human hybrid cell-line containing a single human chromosome. The filters will be screened for the presence of human inserts by hybridising the filter to human and chinese hamster repetitive DNA respectively. Phage from plaques identified as containing human sequences will be brought into culture, DNA isolated and then treated further as the last part of experiment 4.

Experiment 6. Isolation and purification of particular restriction enzymes from suitable bacterial strains and assessment of endonuclease activity and specificity. The economic advantages of self preparation as opposed to purchase will be discussed.

Experiment 7. In situ hybridization of DNA probes to human metaphase chromosomes. Aspects of emulsion type, chromosome identification, estimation of exposure times, defining acceptable levels of background and grain count analysis will be at least discussed. Hopefully some of you will also be able to complete a whole experiment.

8.7. Large scale isolation of plasmids (Leiden)

1. Dilute a 6-8 hour miniculture of 10 ml in 1 l. selective ^{N24} ~~L~~-broth and grow overnight.
2. Spin at 7,000 rpm. for 5 minutes in GSA rotor.
3. Resuspend pellet in 36 ml lysis buffer: 50 mM glucose,
25 mM Tris, pH 8.0 and
10 mM EDTA.
Add ~~10 mg~~ 10 mg lysozyme.
Leave at 20°C for 10 minutes.
4. Add 80 ml 0.2 N NaOH, 1% SDS, leave 5 minutes on ice.
5. Add 40 ml cold 3 ^{M NaAc} ~~M NaAc~~, pH 4.8 (5 M Ac⁻) and mix well. Incubate on ice for 15 minutes.
6. Add 10 ml H₂O. Spin 5 minutes 8,000 rpm. in GSA rotor.
7. Pour supernatant into a fresh bottle through a gauze to remove large aggregates of debris.
8. Add 0.6 volume equivalent (80 ml) 2-propanol. Mix and spin at 8,000 rpm. for 5 minutes in GSA rotor.
9. Drain of supernatant well.
10. Dissolve pellet in 9 ml 10 mM Tris, 1 mM EDTA, pH 7.5. Add 10.2 g CsCl and 1 ml Ethidium bromide (10 mg/ml). Spin 16-24 hours at 50,000 rpm. in an ultra centrifuge Beckman 70 Ti rotor.
11. Remove plasmid band with a syringe. Dilute two times with 10 mM Tris, pH 7.6.
12. Add 2 volume equivalents ethanol 96%. Plasmid precipitates at R.T. spin 4,000 rpm. for 10 minutes.

13. Dissolve pellet in 1 ml 10 mM Tris, 5 mM EDTA, pH 7.5. Extract Ethidium bromide with phenol:chloroform:isoamyl alcohol (1:1:24), 2-3 times.

14. Add 0.1 volume equivalent 2 M NaAc, 2 volume equivalents 96% ethanol, mix, place at -70°C for 15 minutes and spin at 10,000 rpm. for 10 minutes.

15. Dissolve pellet in 1 ml 10 mM Tris, 5 mM EDTA. Add 20 mg/ml RNase.

16. Add equal volume phenol:chloroform:isoamyl alcohol (1:1:24), mix and spin at 4,000 rpm. for 5 minutes.

17. Take upper layer, add 0.1 volume equivalent 2 M NaAc, pH 5.6, 2 volume equivalents 96% ethanol, mix and place at -70°C for 15 minutes.

18 wash pellet with 70% Ethanol.

19. Dissolve pellet in 10 mM Tris, pH 7.5.

20. Determine concentration by absorbance A_{260} .

Appendix 3

Archival material of the Clinical Molecular Genetics Society²⁶³

Number 2 *The Probe* July 1990
The Newsletter of the Clinical Molecular Genetics Society

Editorial

Welcome to the first edition of "The Probe" for 1990. Those of you who attended the Annual General Meeting of the CMGS in Newcastle this year will already know we now have several new committee members, a new Chairman and a new editor for "The Probe". A few words from Andrew Read, our new Chairman, are included in this issue.

It is intended that this newsletter will help to maintain some cohesion between members of our ever increasing society, which is now over 200 members strong. To do this we need your help to let us know what you want! We will do our best to keep you informed of future meetings and workshops for the Society. We also plan to have a "Jobs Wanted and Vacant" section with relevant positions for Molecular Geneticists. We will be introducing a "Helpful Hints" section for the 'hands on' members of our Society. This will run at its best with contributions from members to keep it going. Have you come across any lately, such as new methods for old or just old ones improved? PCR has found a niche in most, if not all, of our labs by now, so we will be including review articles on methods and machines currently available in future issues.

Are there any other matters you as a member would like to see in future editions. For instance: pieces of equipment; methods; policies; politics; people in science; self-catering holiday places. Please let me know. A simple phone call is all it will take and this newsletter will be once again off the ground. Please keep in touch.

Carolyn Williams, Editor, "The Probe"
 Department of Biochemistry and Molecular Genetics,
 St. Mary's Hospital Medical School,
 Norfolk Place,
 LONDON
 W2 1PG
 Phone: (071) 723 1252, Ext 5491 or FAX: (071) 706 3272

A Message From Our New Chairman

"When you did me the honour of electing me as Chairman of the CMGS, I hadn't appreciated how it would change my life. Not two hours later there we were, me and the Lord Mayor, pressing the flesh of the proletariat (you know, Rodney Harris and the like). What further ambition could a man have?"

Now that normal service has been resumed, we can get on with business. The first thing to say is how extremely well the CMGS has done. Five years ago, we were a bunch of enthusiasts beavering away at exciting, pioneering work, but quite unsure whether we were biochemists, maverick cytogeneticists or just plain misfits. I think the formation of the CMGS has catalysed much of our development into a recognised profession.

The challenge now is to continue the professional development without losing the excitement and motivation. Heaven forbid that we should ever come to see audit, registration and workload statistics as more interesting than primers and recombinants - but we absolutely must take these things on board. It's part of being a self-governing profession. If we don't govern ourselves, someone else will govern us. There is tremendous goodwill from our clinical colleagues, as everyone who has taken part in the discussions about consortia will know. If we can do all these boring things well, while still keeping scientific excellence as our top priority, then our discipline and our careers will prosper.

One thing I promise: while I am Chairman, I shall rule out of order any discussion about a Society tie".

All best wishes,

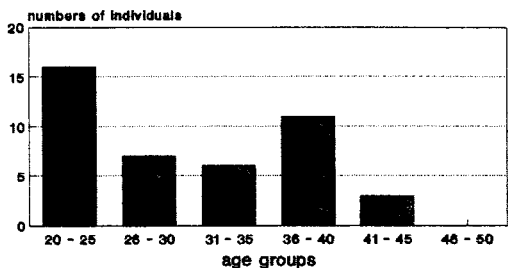
Andrew Read

²⁶³ This appendix includes: title page of the Society's summer 1990 newsletter (this page); membership survey, 1998 (reproduced in part); a letter to members on professional qualifications and training c.1990; details of the Quality Assessment Scheme, 1991; and a sample page of the CMGS laboratory directory. Copies of *The Probe* will be deposited with the records of this meeting in the Wellcome Library, under reference GC/253. For further details of their contents see note 256.

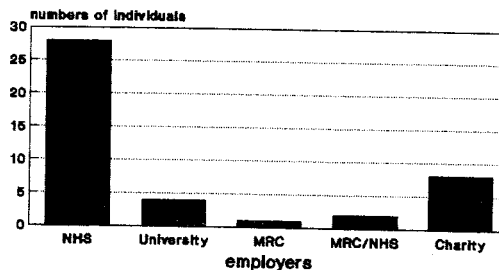
Clinical Molecular Genetics Society Membership survey 1988

Individual survey

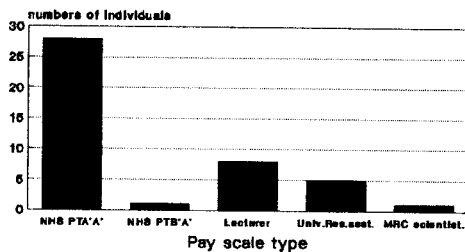
Age range
N = 43



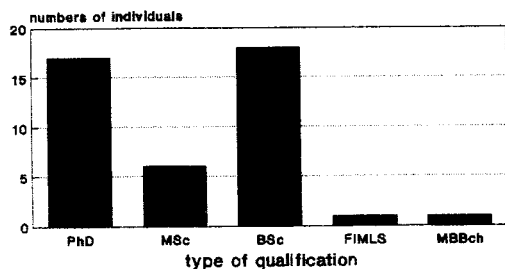
Employers
N = 43



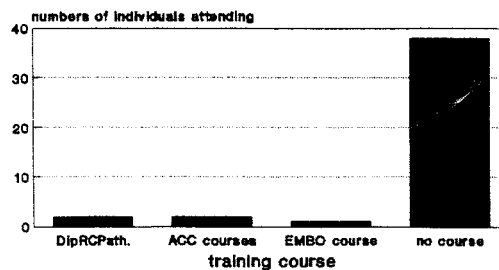
Pay scales
N = 43

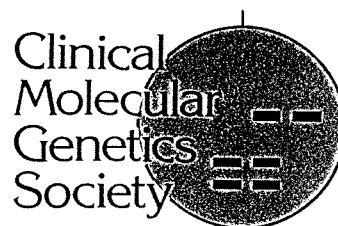


Highest qualification
N = 43



Formal specialist training
N = 43





Dear Colleague,

The 12th September 1990 heralded the inauguration of the C.M.G.S. training committee. Hastened or rather chastened, by rabid public demand we set out to address the pressing problems of "A" grade and in particular "B" grade training.

B GRADE TRAINING

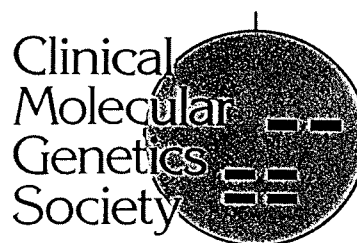
Many scientists in DNA laboratories have arrived at the diagnostic bench via a colourful range of weird and wonderful related disciplines having only encountered the world of human genetics "en passant". In order to accommodate these brave "voyagers", we feel there is a need for an elaborate hitchhikers guide to the discipline, a comprehensive course of directed study over a long period in preference to the traditional one week mind-blowing "binge" approach. Sue Malcolm kindly offered to organise such a course (poster enclosed) starting 9th January 1991. Demand will dictate the feasibility of running a parallel course in different parts of the country at a later date to partially offset travel problems of candidates coming from far and wide.

The course itself is designed to groom candidates for the Diploma in Clinical Cytogenetics and Molecular Genetics. The Diploma is awarded by the Royal College of Pathologists, subject to college regulations. Holders of the Diploma are eligible to become Diplomates of the Royal College (DipRCPath - Molecular Genetics) on payment of an annual fee.

Both the Diploma and Membership qualifications are regarded as appropriate qualifications for entry to more senior grades in our profession. Although, technically, no formal qualifications for promotion to the relevant scientific grades are demanded, such formal proof of competence is obviously an asset, providing useful currency within the profession.

The Diploma and Membership are unique to, and therefore recognised by, our profession and are quite distinct from a Ph.D or MSc which stand as valuable hard-won assets in their own right. Not wishing to reinvent the wheel or use such tired old clichés to steer you through the maze of college regulations I shall take the

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easy option and refer you to the ACC publication Training and Higher Qualifications in Clinical Cytogenetics obtainable from Dr Tony Andrews (Tel: 061-276-1234) who kindly assures me he would be happy to forward this useful booklet for a nominal fee to non-ACC members.

The diploma itself comprises one 2-hour written paper, including both multi-choice and essay type questions, a practical and an oral exam. The multi-choice is taken by all candidates but they may elect to take the written/practical/oral examination in either clinical cytogenetics or molecular genetics.

The examinations are normally held at 6 month intervals in the spring and autumn. The date and location for each examination is announced in appropriate journals and newsletters. Full details of examinations may be obtained from:

The Registrar, Royal College of Pathologists
2 Carlton House Terrace, London SW1Y 5AF
Tel: 071-930-5861 (hatchcode 6365)

Best of luck,

John F. Harvey

**Clinical Molecular Genetics Society
Training Committee**

Chairman: John Harvey,
Committee: Andrew Read, Rob Ellis, Sue Malcolm,
Anneke Miciak, Scott Higgins.

Quality Assessment Scheme



As many members will no doubt be aware the CMGS has set up a quality assessment (QA) scheme recognising the role of effective quality assurance in laboratory investigations to ensure reliable patient care. External QA schemes have stimulated and demonstrated improved performance in other disciplines (Whitehead, TP., Woodford, FP., J Clin Path 1981;34:947) where participation is now accepted as an integral part of professional laboratory management. Participation in this scheme is voluntary in accordance with other national schemes, and individual performance data will be confidential. There will be no charge for participation during 1991/92, and development funding will be sought to cover 1992/93. The initial pilot scheme will assess a laboratory's ability to type control DNA samples for given probes/mutations and will be limited at first to CF, DMD/BMD and

HD. A questionnaire has been sent out to all service labs in order to establish a consensus as to which markers/mutations will be assessed. If successful the scheme will be expanded to other diseases and will address the question of interpretation of data. The scheme will use extracted DNA samples rather than cells. The DNA from cell lines is being provided by the European Human Cell Bank at the PHLs center for applied microbiology in Porton Down. We are very grateful to the Human Genome Mapping Project at Northwick Park for their assistance in setting up this scheme.

Initially the scheme will be operated from the Wolfson Research Labs(WRL) Queen Elizabeth Hospital, Birmingham, under the supervision of Dr David Bullock. This center has over 20 years experience in operating such schemes in clinical chemistry. Using the laboratory codes already in use for the CMGS audit scheme the samples will be despatched from and results returned to WRL. The anonymous results will be passed to the QA-sub committee for appraisal and the resulting reports will be distributed to the participants from the WRL.

If a laboratory obtains a false result it will be the responsibility of that lab to investigate the cause. Additional aliquots of the DNA samples will be available and subcommittee members may be approached for consultation and guidance.

The QA sub-committee would welcome any suggestions or comments on this pilot scheme of related matters.

Roger Mountford, Elaine Robertson, Scott Higgins, Martin Schwarz.

An Investigation of Non-Paternity Rates in a Sample of CF Families from Several DNA Labs around the UK

We have looked at 521 CF families, informative for one or other of the CF mutations and the number with inconsistencies compatible with undisclosed non-paternity. We found 7 cases of non-paternity out of the 521 or 1.35%. This figure is probably only strictly relevant to the UK although may be useful for some other diseases and populations. For more information contact Tony Shrimpton, Human Genetics Unit, Western General Hospital, Edinburgh.



CLINICAL MOLECULAR GENETICS SOCIETY

LABORATORY DIRECTORY

TITLE DNA Laboratory, Regional Genetic Services

ADDRESS Yardley Green Unit
 East Birmingham Hospital
 Bordesley Green East
 Birmingham
 B9 5PX

TELEPHONE 021-766-6611 ext 2450/2321/2323/2326

LABORATORY CONTACTS Dr Fiona Macdonald
 Mr Max Rindl
 Professor Maj Hulten

DISEASES / SPECIALITY and EXPERIENCE

Myotonic Dystrophy

Familial Adenomatous Polyposis

Adult Polycystic Kidney Disease

New Service Laboratory, January 1989, therefore experience is still limited.

FUTURE DEVELOPMENTS

Research interests include some X-linked and associated conditions such as Lesh-Nyhan, Lowe and Rett Syndromes, the Fragile X as well as conventional chromosomal Syndromes - origin and DNA diagnosis

COMMENTS

A Regional Polyposis Coli register has been established.

Blood samples from patients with Lowe Syndrome will be transferred from Manchester since Dr McKeown has moved here.

Biographical notes*

Professor Egbert (Bert) Bakker
 PhD (b. 1951) studied chemistry in Delft (BSc), continuing his studies at Leiden University (1975–1976) where he was also a technician (1977–1989). During this period he worked closely with Professor Peter Pearson and pioneered molecular genetic techniques, which led to the first prenatal diagnosis of Duchenne muscular dystrophy (DMD) in 1985. In 1989 he completed his doctoral research on DMD (Bakker (1989)) and, the same year, was awarded the Lustrum Prize by the Dutch Human Genetics Society. In 1990 he became Head of the DNA diagnostic section in Leiden University's Clinical Genetics Centre and became Associate Professor at the Department of Human Genetics. In conjunction with these roles, he was Head of the Forensic DNA-Laboratory at Leiden (1994–2000). He was appointed Professor of Molecular Genetic Diagnosis at Leiden University Medical Center, where he is now Head of the Laboratory for Diagnostic Genome Analysis.

Professor Martin Bobrow
 CBE FRCP FRCPATH FRS
 FMedSci (b. 1938) came to Britain after graduating in South Africa. He worked in Edinburgh and Oxford and held Chairs of Medical Genetics in Amsterdam and Guy's Hospital before becoming Professor of Medical Genetics in Cambridge in 1995. He has been on the council of the MRC, a governor of the Wellcome Trust, National Chairman of the Muscular Dystrophy Campaign, and Chairman of the Clinical Genetics Society. He has also held posts as Chairman of COMARE (Committee on Radiation in the Environment), ULTRA (Unrelated Living Transplant Regulating Authority), Deputy Chairman of the Nuffield Council on Bioethics and a member of the Human Genetics Advisory Commission.

Professor Dame Kay Davies
 CBE DBE FMedSci FRS
 (b. 1951) studied at Somerville College and was Guy Newton Junior Research Fellow at Wolfson College, Oxford (1976–1978). From 1978 to 1980 she was Royal Society Postdoctoral Fellow at

* Contributors are asked to supply details; other entries are compiled from conventional biographical sources.

the Service de Biochimie, France, returning to the UK to become Cystic Fibrosis Research Fellow at St Mary's Hospital Medical School (1980–1982). Senior Research Fellowships followed at the MRC (1982–1984) and, still within the MRC but based at the Nuffield Department of Clinical Medicine, at John Radcliffe Hospital, Oxford. She joined Oxford's Institute of Molecular Medicine in 1989, remaining there until 1995 in an MRC external staff post. Within this period, from 1992 to 1994, she was also Research Director of the MRC Clinical Sciences Centre, Hammersmith Hospital. From 1995 to 1998 she was Professor of Genetics at Keble College, Oxford. Also at the University of Oxford, in 1998 she was elected Dr Lee's Professor of Anatomy. The following year she started the MRC Functional Genomics Unit at Oxford, of which she remains Director and leads the Neurological Disease Group. This group studies the pathogenesis of muscular dystrophy, and researches its potential treatments, as well as neurodegenerative and behavioural disorders. From 2008 to 2011 she was also Head of the Division of Medical Sciences of the University of Oxford's Department of Physiology, Anatomy and Genetics, of which she is now Associate

Head. She has conducted research into Duchenne muscular dystrophy for over 20 years and is currently working with colleagues on the development of therapies for this disorder. In October 2013 she was appointed Deputy Chairman of the Wellcome Trust.

Dr Rob Elles

FRCPath (b. 1951) worked as a research technician at St Mary's London helping to characterize probes for X-linked conditions from a DNA fragment library. In 1983 he moved to Manchester University, completing a PhD while helping to build the molecular diagnostics laboratory aided by a DoH Special Medical Development award. In 2002 his laboratory was awarded a DoH contract to develop a National Genetics Reference Laboratory specializing in informatics and quality. He was Secretary of the Clinical Molecular Genetics Society in the 1990s, and was involved in training and professional standards and many areas of development of diagnostic genetics in the UK. In 1998 he coordinated a European Commission research project that developed the European Molecular Genetics Quality Network. He was Co-chair of the expert group that developed guidelines for Quality Assurance in Molecular Genetic Testing adopted by the OECD. As

the Chairman of the British Society for Human Genetics, he gave evidence to the House of Lords enquiry on Genomic Medicine and contributed to the service configuration work-stream of the Human Genomics Strategy Group that reported in January 2012. He retired as the Clinical Director of Genetic Medicine, Manchester, in 2013.

Professor Malcolm Ferguson-Smith

FRCPATH FRCP FMedSci FRSE FRS (b. 1931) is Emeritus Professor of Pathology, University of Cambridge, UK. He graduated in medicine at Glasgow University in 1955 and, while undertaking postgraduate training there in pathology, was introduced to research on sex chromatin under Bernard Lennox. An interest in Klinefelter's syndrome in 1957 to 1958 led to his appointment as Fellow in Medicine at Johns Hopkins University, Baltimore, in 1959 where he established the first chromosome diagnostic service in the USA and undertook cytogenetic research into Turner syndrome. Returning to Glasgow University in late 1961, he was appointed successively Lecturer, Senior Lecturer, Reader and Director of the West of Scotland Regional Genetics Service before becoming Burton Professor of Medical Genetics in 1973. In 1987 he was

appointed Professor and Head of Pathology at Cambridge University and Director of the East Anglia Regional Genetics Service. Research interests include molecular cytogenetics, karyotype evolution, vertebrate sex determination and comparative genomics. In 1998, he moved to the Department of Veterinary Medicine to establish the Cambridge Resource Centre for Comparative Genomics. He is joint author of *Essential Medical Genetics* (See Tobias E, Connor M, Ferguson-Smith M. (2011)).

Professor Peter Harper

Kt FRCP (b. 1939) graduated from Oxford University in 1961, qualifying in medicine in 1964. After a series of clinical posts, he trained in medical genetics at the Liverpool Institute for Medical Genetics under Cyril Clarke and at Johns Hopkins University, Baltimore, under Victor McKusick. He was Professor of Medical Genetics at the University of Wales' College of Medicine, Cardiff, from 1971 until his retirement in 2004, when he was appointed University Research Professor in Human Genetics, Cardiff University (Emeritus since 2008). As a policy adviser for the Chief Medical Officer, in 1996 he authored the government report *Genetics and Cancer Services*, more commonly known as 'The Harper Report'.

He served on the UK's Human Genetics Commission from 2000 to 2004 and from 2004 to 2010 with the Nuffield Council on Bioethics. He has been closely involved with the identification of the genes underlying Huntington's disease and muscular dystrophies, and with their application to predictive genetic testing. He has also been responsible for the development of a general medical genetics service for Wales. His books include *Practical Genetic Counselling* (Harper (1981)), *Landmarks in Medical Genetics* (Harper (2004)), *First Years of Human Chromosomes* (Harper (2006)) and *A Short History of Medical Genetics* (Harper (2008)). For the past decade he has led an initiative, supported by the Wellcome Trust, to preserve and document the history of human and medical genetics (<http://www.genmedhist.org>; visited 8 November 2013). He is a consultant to the 'Makers of Modern Biomedicine' project for the History of Modern Biomedicine Research Group, Queen Mary, University of London.

Professor Rodney Harris
CBE FRCP FRCPATH (b. 1932)
is Emeritus Professor of Medical Genetics at the University of Manchester, having been Professor

of Medical Genetics from 1980 to 1997. From 1982 to 1989 he was Consultant Adviser in Medical Genetics to the Chief Medical Officer at the Department of Health. He was Chairman of the UK National Confidential Inquiry into Genetic Counselling from 1986 to 1990, Chairman of the Royal College of Physicians' (London) Committee on Clinical Genetics and subsequently Chairman of the EU concerted Action on Genetic Services in Europe. He was also Coordinator of the EU-funded GenEd measure based at Manchester.

Professor Patricia Jacobs
DSc FRS FRSE (b. 1934)
graduated from St Andrews University with a BSc in Zoology in 1956. She spent a year in the USA as a graduate assistant, then returned as Scientist in the MRC Clinical Effects of Radiation Research Unit in Edinburgh. Her entire scientific life has been spent as a cytogeneticist, with a special interest in the epidemiology of human chromosome abnormalities, firstly under the mentorship of Professor Michael Court Brown and, from 1972 to 1985, in the University of Hawaii Medical School with her husband Professor Newton Morton. In Hawaii, her major interests were in mental retardation, with emphasis on

Fragile X, and the cytogenetic abnormalities associated with pregnancy loss. From 1985 to 1987 she was Professor in the Department of Paediatrics at Cornell University Medical College in New York City. In 1988 she returned to the UK where she was Director of the Wessex Regional Genetics Laboratory in Salisbury until her retirement in 2001. From 1988 she has been Professor of Human Genetics at the University of Southampton Medical School where she continues her interest in the epidemiology of human chromosome abnormalities.

Professor Yuet Wai Kan

FRCP FRS (b. 1936) was Associate Professor of Pediatrics at Harvard Medical School from 1970 to 1972 and was Associate Professor of Medicine in the Departments of Medicine and Laboratory Medicine at the University of California, San Francisco from 1972 to 1977. Since 1977 he has been Professor of Laboratory Medicine and Medicine at the University of California.

Mr Lazarus Lazarou

BSc DipRCPath (b. 1962) graduated from University College Cardiff in 1984 with a degree in Biochemistry. On graduating, he took up a research technician position in the Medical Genetics Department at the Welsh National

School of Medicine, to set up a DNA bank and to map the adult polycystic kidney disease (ADPKD) gene. In 1987 he became Scientific Officer for the newly formed Molecular Genetics Diagnostic Laboratory at the University Hospital of Wales, where he remains. He has had interests in and published work on inherited conditions, in particular ADPKD and autosomal recessive polycystic kidney disease, Huntington's disease, myotonic muscular dystrophy, cystic fibrosis, Fragile X syndrome (A, E and F), X-linked hypohidrotic ectodermal dysplasia, myotubular myopathy, Rett and Rett-like syndromes, lissencephaly and, more recently, has been involved with the delivery of stratified medicine analysis in lung, colorectal, skin and gastric cancer. In 1998 he became a diplomate of the Royal College of Pathologists and has served on the executive committee of the Clinical Molecular Genetics Society (1998–2001, 2007–2008).

Dr Ian Lister Cheese

PhD FRCP FRCPH (b. 1936) read natural sciences followed by training in research (Professor W T J Morgan) and qualified in medicine in 1966 at Cambridge & St Thomas's. He was a Medical Registrar at Radcliffe Infirmary, Oxford and then joined general

practice in Wantage, Oxfordshire. He was also a tutor in general practice, a trainer in a vocational training scheme, and served in NHS management in Oxfordshire. In 1984 he entered the senior civil service with appointments in the Department of Health and the Department of Education, in posts that included responsibilities for the fitness of teachers, hospital services for children and genetics services. He has been Secretary of both the Standing Medical Advisory Committee and the Gene Therapy Advisory Committee. He also served on the Royal College of Physicians' Clinical Genetics Committee. Following notional retirement in 1996, he served as adviser to the DoH on matters relating to clinical governance and the working of the Abortion Act. He has undertaken policy work for the Royal College of Physicians and the Academy of Medical Royal Colleges, and served as a member of the editorial board that prepared the new *Paediatric Formulary*, and as a trustee to voluntary bodies concerned with the support of disabled children and their families.

Dr Fiona Macdonald

PhD (b. 1954) graduated from Edinburgh University and completed a PhD at Leicester University. After spending some time working in the Department of

Surgery at Birmingham University on gastro-intestinal cancers she was appointed to head the Molecular Genetics Section of the Regional Genetics Laboratory at Birmingham Heartlands Hospital, establishing a service for inherited colorectal cancer as a priority. In 1997, the two genetics laboratories in Birmingham merged on a single site and she headed the Molecular Genetics Laboratory within the merged lab. Her research interests are inherited cancer syndromes, development of molecular genetics-based methods for rapid prenatal diagnosis and translation of service for rare autosomal recessive conditions into the diagnostic services.

Professor Sue Malcolm

PhD FRCPATH was educated at Somerville College, University of Oxford, and at the Beatson Institute, University of Glasgow. Since 2002, she has been Emerita Professor of Molecular Genetics at the Institute of Child Health, University College London. She is also faculty member of the Faculty of 1000 Ltd. Her blog *Me and My Genes* takes a 'light-hearted look at how genes rule your life' and can be viewed at <http://blogs.ucl.ac.uk/clinical-molecular-genetics/> (visited 29 May 2013).

Dr Linda Meredith

PhD DipRCPATH (b. 1955) studied at Cardiff University, graduating with a doctorate in biochemistry. She was a Scientific Officer at Cardiff University's College of Medicine from 1980 to 1985, during which time she collaborated with the research team at St Mary's Hospital (London) that localized the gene for Duchenne muscular dystrophy, and worked within the team that localized and cloned the gene for myotonic muscular dystrophy. From 1985 to 1988 she was a Senior Scientific Officer at the All Wales Medical Genetics Service (AWMGS), where she piloted a molecular diagnostic service for Wales. She was Head of the molecular diagnostic section of the AWMGS from 1987 to 2000, where she now works part-time as Clinical Scientist and leads staff training and professional development programmes.

Dr Helen Middleton-Price

PhD FRCPATH (b. 1955) graduated with a BA in psychology from the University of Durham in 1976 and a BSc in biochemistry from the University of London in 1982. Following postgraduate research in neurochemistry at the Karl Marx Universität, Leipzig and at the Institute of Neurology, University of London, she embarked on her PhD in human genetics in 1985 at the

Institute of Child Health (ICH), University of London. In 1989 she transferred to lead the Regional Clinical Molecular Genetics Laboratory at ICH/Great Ormond Street Hospital for Sick Children, with overall responsibility for the delivery of the laboratory service, and gained her MRCPATH in 1994. In 1996 Helen joined the Science Museum in London as Biomedical Science Adviser in Genetics for the new Wellcome Wing exhibitions, which opened in June 2000. In 2003 she was awarded FRCPATH and in the same year she became Director of Nowgen, a centre of excellence in biomedical public engagement, patient-centred research, second-level education and professional training. Recently, Helen has collaborated with artists on projects relating to modern genetics, including with Tempered Body Dance Theatre on the production 'It goes here now'.

Professor Bernadette Modell

PhD FRCP FRCOG (b. 1935) undertook her first degree in zoology, predominantly in genetics and embryology, Oxford, 1955; followed by her doctoral research in developmental biology, Cambridge, 1959. She qualified in medicine at Cambridge and University College Hospital in 1964, aiming to investigate the application of genetic knowledge in medical

practice. She subsequently worked at University College London and University College London Hospitals until her retirement in 2000, where her work focused on thalassaemia as an example of a common genetic disorder. She was involved in developing effective treatment for thalassaemia major and prevention of the disease through community information; population screening and genetic counselling; and methods for prenatal diagnosis – including the first trimester diagnosis by chorionic villus sampling and DNA analysis. In collaboration with the WHO she has helped to extend programmes for the treatment and prevention of haemoglobin disorders to many parts of the world. She is currently Emeritus Professor of Community Genetics at the UCL Centre for Health Informatics and Multiprofessional Education, where she works on the global epidemiology of congenital disorders, and developing informatics approaches to the provision of genetic information for communities. She is also Director of the WHO Collaborating Centre for Community Control of Hereditary Disorders.

Dr John Old

FRCPath (b. 1949) graduated from Liverpool University in 1971 (BSc) and in 1974 with a PhD in biochemistry. He was a postdoctoral research scientist in Professor Sir David Weatherall's laboratory at the Radcliffe Infirmary and the John Radcliffe Hospital in Oxford from 1974 to 1981. He was then employed as a Clinical Scientist to run the newly established National Haemoglobinopathy Reference Service until his retirement in 2012. He is an Honorary Reader in Haematology, Oxford University. His research activities focused on the molecular basis of the haemoglobinopathies and the development of molecular diagnostic techniques for the detection and prenatal diagnosis of the thalassaemias and abnormal haemoglobins. He has collaborated with many international thalassaemia laboratories on identifying the mutations underlying the haemoglobinopathies, and helped to establish molecular diagnostic programmes for the prevention of thalassaemia in Cyprus and India. He has been actively involved with the development of the profession of clinical molecular genetics, helping with the establishment of the CMGS, the development of

examinations for membership of the Royal College of Pathologists, and the establishment of state registration for clinical molecular geneticists.

Professor Marcus Pembrey
MD FRCP FRCPCH FRCOG
FMedSci (b. 1943) trained in medical genetics in Liverpool (1969–1971) and Guy’s Hospital, London (1973–1978). In 1979 he moved to the Institute of Child Health, London, as Head of the Mothercare Unit of Paediatric Genetics, where he led a team that helped to introduce DNA testing into clinical genetics in the 1980s. He was also Consultant Clinical Geneticist at the Hospital for Sick Children, Great Ormond Street, London (1979–1998) and Consultant Adviser in Genetics to the Chief Medical Officer, Department of Health (1989–1998). He led the genetic component of the Avon Longitudinal Study of Parents and Children (ALSPAC) from 1988. After early retirement from the ICH in 1998, he continued as Director of Genetics within ALSPAC, University of Bristol, until 2006. He continues to be Visiting Professor at the University of Bristol. He is the founding and current Chair of the Progress Educational Trust; publisher of

BioNews (<http://www.bionews.org.uk/home>; visited 12 December 2013).

Professor Andrew Read
PhD FRCPath FMedSci
(b. 1939) trained at Cambridge University as an organic chemist. After postdoctoral positions in the Max-Planck Institute for Medical Research, Heidelberg and University of Warwick he moved to Manchester University in 1967 and joined the Medical Genetics Department there in 1977. Initially he worked on neural tube defects (NTD), including the vitamin trials that first showed vitamin supplementation could greatly reduce the incidence of NTDs, and on various computer projects. In 1982 he set up the molecular laboratory and spent many of the following years establishing molecular genetic services. He was Chairman of the CMGS and Founder Chairman of the British Society for Human Genetics. His research focused on mapping and identifying disease genes, especially for hereditary deafness.

Professor Julian Sampson
DM FRCP FMedSci (b. 1959)
is Clinical Professor of Medical Genetics and Head of the Institute of Medical Genetics at Cardiff University and the University Hospital of Wales. He graduated

in medicine from Nottingham University (1982) and trained in Medical Genetics at the Duncan Guthrie Institute, Glasgow with Professor Malcolm Ferguson-Smith and at the Institute of Medical Genetics, Cardiff, with Professor Peter Harper. His research interests in tuberous sclerosis have ranged from gene identification to clinical trials, and in colorectal cancer have included identification and characterization of a novel autosomal recessive form of polyposis colorectal cancer, *MUTYH*-associated polyposis (MAP).

Dr Rosalind Skinner

MD FRCPE FFPH (b. 1946) qualified in medicine at the London Hospital Medical School in 1969. After a series of clinical posts in England, she went to the University Department of Human Genetics in Edinburgh to train in genetics with Alan Emery. As a member of the clinical academic staff of the department, she played a full role in the clinical genetics service and its neuromuscular genetics research activities until 1983. After leaving the University, she retrained in Public Health and in 1988 joined the Scottish Health Department where she remained until her retirement in 2010. During this time, she played a lead role in the creation and

implementation of genetics policy and the development of NHS genetics services in Scotland.

Professor Sir Edwin Southern

Kt PhD FRS (b. 1938) was awarded his PhD from the Department of Chemistry, University of Glasgow in 1962. From 1963 to 1967 he was a Research Assistant at the ARC Low Temperature Research Station in Cambridge. Returning to Scotland, he was a Research Assistant at the MRC Mammalian Genome Unit in Edinburgh (1967–1980). He became Director of the MRC unit (1980–1985) and during this time he was also Deputy Director of the MRC's Clinical and Population Cytogenetics Unit, where he pioneered human genome mapping with molecular methods. From 1985 to 1991 he was Whitley Professor of Biochemistry at Oxford, Director of the CRC Chromosome Molecular Biology Research Group and Head of the Department of Biochemistry, now Emeritus Professor.

Professor Tilli Tansey

OBE PhD PhD DSc HonFRCP FMedSci (b. 1953) graduated in zoology from the University of Sheffield in 1974, and obtained her PhD in *Octopus* neurochemistry in 1978. She worked as a neuroscientist in the Stazione

Zoologica Naples, the Marine Laboratory in Plymouth, the MRC Brain Metabolism Unit, Edinburgh, and was a Multiple Sclerosis Society Research Fellow at St Thomas' Hospital, London (1983–1986). After a short sabbatical break at the Wellcome Institute for the History of Medicine (WIHM), she took a second PhD in medical history on the career of Sir Henry Dale, and became a member of the academic staff of the WIHM, later the Wellcome Trust Centre for the History of Medicine at UCL. She became Professor of the History of Modern Medical Sciences at UCL in 2007 and moved to Queen Mary, University of London (QMUL), with the same title, in 2010. With the late Sir Christopher Booth she created the History of Twentieth Century Medicine Group in the early 1990s, now the History of Modern Biomedicine Research Group at QMUL.

Professor Sir David Weatherall
MD FRCP FRS FMedSci (b. 1933) qualified in medicine at Liverpool University in 1956 and, following periods in Liverpool, Baltimore and Oxford, became Emeritus Regius Professor of Medicine, University of Oxford in September 2000 upon retirement. His major research contributions have been in the elucidation of the clinical and molecular basis and population

genetics of the thalassaemias and the application of this information for the control and prevention of these diseases in developing countries. In 1989 he founded the Institute of Molecular Medicine in Oxford, which now bears his name. He has received a number of national and international awards and is an overseas member of the National Academy of Sciences, USA.

Professor Robert (Bob) Williamson

AO FRCP FRCPATH FRS FMedSci (b. 1938) was awarded his PhD from University College London in 1963. From then until 1967 he was a lecturer at the University of Glasgow, then Senior Scientist in molecular biology at the Beatson Institute for Cancer Research, Glasgow (1967–1976). He became Professor of Molecular Genetics and Biochemistry at St Mary's Hospital Medical School, University of London (1976–1995). From 1976 to 1991 he was also a member of the UK Genetic Manipulation Advice Committee. In 1995 he moved to Melbourne, Australia, to become Director of the Murdoch Institute and Professor of Medical Genetics at the University of Melbourne, until his retirement in 2004. He is Honorary Professor of Medical Genetics at the Murdoch Institute. Williamson's

research has been instrumental in the identification and cloning of the genes for thalassaemia, cystic fibrosis, craniofacial abnormalities, heart disease and Alzheimer's disease.

Professor John Yates

FRCP (b. 1948) graduated with a degree in physics from Oxford University in 1970 and subsequently studied medicine at University College Hospital, London, qualifying in 1977. He trained in paediatrics and then in medical genetics, initially in Edinburgh with Alan Emery and then in Glasgow with Malcolm Ferguson-Smith. He moved to an academic post at the University of Cambridge in 1987 where he subsequently became Reader (2001) and then Professor of Medical Genetics (2003). He was an Honorary Consultant at Addenbrooke's Hospital, Cambridge and, for many years, was Clinical Director of the East Anglian Regional Genetics Service. His research has focused on the identification of human disease genes and their molecular pathology. He contributed to the mapping of the X chromosome and has carried out extensive genetic studies of the hereditary diseases X-linked ichthyosis (steroid sulphatase deficiency); retinoschisis; Emery-Dreifuss muscular

dystrophy; Stickler syndrome, and tuberous sclerosis. He has also worked on the identification of genetic factors predisposing to age-related macular degeneration (AMD), the commonest cause of blindness in Western populations. Since his retirement from Cambridge in 2008 he has continued working on AMD at the Institute of Ophthalmology and is an Honorary Professor at University College London.

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* Please note that references with four or more authors are cited using the first three names followed by 'et al.'. References with 'et al.' are organized in chronological order, not by second author, so as to be easily identifiable from the footnotes.

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