HUMAN GENE MAPPING WORKSHOPS *c.*1973–*c.*1991

The transcript of a Witness Seminar held by the History of Modern Biomedicine Research Group, Queen Mary University of London, on 25 March 2014

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 and remained so 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

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[1] See pages 141–6 for a full list of Witness Seminars held, details of the published volumes, and other related publications.

funds principally 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, a glossary, 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.

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2 See our Group's website at www.histmodbiomed.org

ACKNOWLEDGEMENTS

Many thanks to Professor Peter Harper for suggesting this meeting, and to Professor Sue Povey and Professor Ian Craig who also advised us in planning the seminar. Additionally, Sue Povey generously lent us her precious copies of many of the HGM volumes.

Professor Sir Walter Bodmer kindly provided a photograph of the participants at the EMBO 1973 conference that he convened in Oxford, and we are very grateful to him and Professor Veronica van Heyningen for identifying many of its participants; and to other Witness Seminar participants who have engaged enthusiastically and helpfully in the editorial process.

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 are also grateful to 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 Debra 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 thank the Wellcome Trust for supporting the Witness Seminar programme.

Tilli Tansey

Emma Jones

School of History, Queen Mary University of London

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ABBREVIATIONS AND ANCILLARY GUIDES

CEPH	Centre d'Étude du Polymorphisme Humain
cDNA	Complementary DNA
EMBO	European Molecular Biology Organization
EU	European Union
GDB	Genome Database
HAT	Histone acetyltransferase
HGM/W	Human Gene Mapping/Workshops
HLA	Human leukocyte antigen*
HUGO	Human Genome Organization
ICRF	Imperial Cancer Research Fund
LOD	Log of the odds on linkage
MRC	Medical Research Council
NIH	National Institutes of Health
RFLP	Restriction fragment length polymorphisms
UCL	University College London

OMIM (Online Mendelian Inheritance in Man) is a reliable information source for human genes and phenotypes: http://www.ncbi.nlm.nih.gov/omim

HUGO Gene Nomenclature Committee has a search facility for internationally-approved gene nomenclature; http://www.genenames.org/

(Websites visited 21 April 2015).

* See note 68 in main transcript about HLA nomenclature.

INTRODUCTION

Scientific events that become part of everyday culture are rare but I can quote two from my lifetime: the determination of the structure of DNA and sequencing the human genome. Human gene mapping is one of the links between these two.

The famous double helix was first described in 1953 – two years after I was born, although I suspect that coincidence is linked only in my mind. And now a trick question – when was the correct number of human chromosomes determined? The answer to this question is 1956, three years after Watson and Crick's famous paper.[1] There are many technical and social reasons for the failure to accurately count what could be seen down a microscope. The technical reasons were to do with culturing cells, capturing them in metaphase and spreading the fixed chromosomes. There were two social reasons. The first was the knowledge that the correct number was 48; everyone 'knew' this because Painter had concluded that 48 'was' the number in the early 1920s.[2] The second reason is that human genetics was not regarded as that important by many scientists so why worry about chromosome numbers? Obviously, the biochemistry of inherited diseases was a field of active study but there was nothing that could be done about the genetic component. People inherited what they inherited and that was that. This view was still strong in the late 1970s when I was asked to teach immunology on a course for genetic counsellors at UC Berkeley. I was surprised to discover that 50% of the students were nuns. When I asked them how they worked out risks for the repeated inheritance of syndromes, they showed me empirically derived tables. It was ironic that they did not apply the rules of the monk Mendel.

In 1972, I joined Walter Bodmer's lab in Oxford to do a PhD. Walter and the others in the Genetics Laboratory in Oxford created an environment where as a student I could dream and thrive. It was the perfect start to my journey as a scientist. In the world I joined, human genetics was mostly a part-time, arcane pursuit of slightly eccentric people. The descendants of Haldane, Fisher and Wright talked to each other about population structures that did not exist, using equations that most of us could not understand (see Sue Povey's comments about Newton Morton, page 9). The descendants of Galton and Garrod were studying enzymes, and Race and Sanger were looking at blood groups. Unknown to me, two techniques were poised to change the world of human genetics – somatic cell genetics and chromosome banding. I had joined Walter's lab to study the

[1] Watson and Crick (1953); Tjio and Levan (1956).

[2] Painter (1922).

biochemistry of HLA but the somatic cell genetics stuff seemed both easy and fun. I wanted to play this game, so in secret from Walter, with help from my friends and mentors, I mapped the gene for beta 2 microglobulin to chromosome 15. I was hooked; I was part of the small group of scientists mapping the human genome.

As I read the comments and recollections of my friends at this Witness Seminar, I realised the obvious truth that history is very context dependent. Their history is not precisely mine but, at one level higher, we shared a vision that one day a map of the human genome would be useful. This vision was also shared internationally. I would particularly mention the contribution of Victor McKusick who relentlessly championed the importance of gene mapping. He collected and collated any and all data and he photographed all of us – all the time. He was a wise and gentle man.

Somatic cell genetics put hundreds of genes onto the human gene map. While this was happening, DNA cloning and DNA sequencing were beginning to be developed. Another revolution was going to happen – within a decade molecular biology was to be combined with human genetics. Direct access to DNA sequences provided an unlimited number of genetic markers. The maps of the human genome became useful; if you could map a gene you could clone it. Mapping and cloning genes provided tools for beginning to help patients and families afflicted with genetic disease. Five years later, in 1994, Jean Weissenbach produced the first complete recombination maps of the human genome and soon after the Human Genome Project introduced big science to biology.

Mapping genes and constructing maps connected the determination of the structure of DNA and sequencing the human genome. Without gene mapping it would not have been possible to sequence the genome – despite the rhetoric of some, 'shot-gun' sequencing of the whole human genome was impossible. The sequencers needed maps to tell them where they were.

The mapping of the human genome was a collaborative activity that was co-ordinated by the Human Gene Mapping Workshops. The meetings allowed practitioners to learn best practice, share rumours, steal ideas and do all the things that humans do when put together in a group. Sequencing the genome superseded the need for gene mapping – it was inherent in the sequence. Like many waystations in science, time and progress made gene mapping largely irrelevant. But capturing the spirit of the meetings and tracing the lineage of

ideas adds something important to the process and progression of science. I congratulate my friends who attended the workshop and greatly enjoyed reading their thoughts and anecdotes.

Scientists go through several stages of evolution. First, the apprentice is driven by love for new knowledge. Secondly, the journeyman is looking to produce the masterpiece to guarantee a career in research. Thirdly, the professional is fund-raising to feed a laboratory of apprentices and journeymen. And at last, the philosopher looks backwards and writes introductions to books of historical reminiscences.

Professor Peter Goodfellow
Canterbury, April 2015

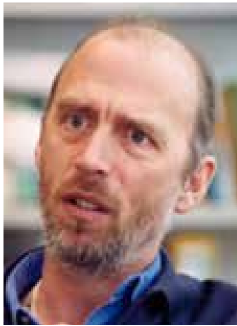

Figure A

HUMAN GENE MAPPING WORKSHOPS *c.*1973–*c.*1991

The transcript of a Witness Seminar held by the History of Modern Biomedicine Research Group, Queen Mary University of London, on 25 March 2014

Edited by E M Jones and E M Tansey

HUMAN GENE MAPPING WORKSHOPS *c.*1973–*c.*1991

Participants*

Professor Bert Bakker
Professor Tim Bishop
Professor Sir Walter Bodmer
Professor Ian Craig
Professor Malcolm Ferguson-Smith
Professor Peter Harper (Chair)
Professor Veronica van Heyningen
Professor Maj Hultén
Professor Sue Malcolm
Professor Michael Morgan
Professor Sue Povey
Professor Chris Rawlings
Professor Ellen Solomon
Professor Tilli Tansey
Dr Susan Wallace

Apologies include: Professor Dirk Bootsma, Professor Dame Kay Davies, Professor Albert de la Chapelle, Professor Peter Goodfellow, Professor John Yates

Figure 1: Participants at the Witness Seminar on Human Gene Mapping Workshops

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

Figure 2: Professors Veronica van Heyningen, Bert Bakker and Tilli Tansey

Professor Tilli Tansey: Good afternoon and welcome to this Witness Seminar on the history of Human Gene Mapping Workshops. I'm Tilli Tansey and I'm the Head of the History of Modern Biomedicine Research Group at Queen Mary, University of London. This format of Witness Seminars was set up some years ago, when we were part of the Wellcome Trust, to record living, recent history. Basically, what we want to hear is what really happened, the stories behind the published literature: who did what; who were the main drivers; who were the main resisters? What really went on? To that purpose, everything that is said today is recorded and will be transcribed, then published. This topic is part of a focus we have on genetics as part of a Strategic Award from the Wellcome Trust. We're focusing on five main areas in modern biomedicine, clinical genetics being one of them.[1] Peter Harper has been our expert consultant adviser for nearly two years, on devising workshops and Witness Seminars on modern genetics. This is the fifth meeting we've held on this topic,[2] so we're already building up quite a corpus of related information and knowledge, and I know there are many people here who have already contributed to a previous meeting. We've also had

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1 For further details about the History of Modern Biomedicine's Strategic Award from the Wellcome Trust for 'Makers of Modern Biomedicine: Testimony and Legacy', see http://histmodbiomed.org (visited 1 October 2014).

2 Witness Seminars have previously been held on the histories of genetic testing, clinical genetics, cancer genetics, and molecular genetics. See Christie and Tansey (eds) (2003); Harper, Reynolds and Tansey (eds) (2010); Jones and Tansey (eds) (2013); Jones and Tansey (eds) (2014). A Witness Seminar was also held in 2014 on 'Medical Genetics: Development of the Ethical Dimension in Clinical Practice and Research'.

Figure 3: Professor Peter Harper

a lot of help from Sue Povey and from Ian Craig in setting up this meeting. It seemed absolutely ideal that Peter should chair this meeting, to which he readily agreed and therefore, without further ado, I'm going to hand over to Peter.

Professor Peter Harper: Well, thank you, Tilli, and it's good to see everybody. Yes indeed, I'd like to thank Sue Povey and Ian Craig because they've given a lot of input to this. I'm not entirely sure why they proposed me as Chair except that I think it's the principle that a Chair should know a little bit about a subject but not too much, and perhaps I fulfil that.[3] I'm really glad though that we are having this Witness Seminar on human gene mapping and specifically on the Human Gene Mapping Workshops (HGMW). That's for several reasons. I suppose the first is that gene mapping has always been at the centre of genetics, not just human genetics but genetics overall, and that really goes back to the very beginning of genetics. We've just passed the centenary of the first gene map, which was the one made by Alfred Sturtevant in 1913 on *Drosophila*.[4] I'm not sure whether there was an anniversary meeting of any kind held in connection with that?

Professor Malcolm Ferguson-Smith: The European Cytogeneticists Association had a special session on this at their Dublin meeting in June 2013. I talked about Alfred Sturtevant and his paper in the *Journal of Experimental Zoology*, and so did Evan Eichler and Pat Harrison.[5]

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3 See Harper (2008), in particular Chapter 7, 'The human gene map', pages 194–212.

4 Sturtevant (1913).

5 For the programme of the '9th European Cytogenetics Conference', 29 June to 2 July 2013, see http://www.eca2013.org/en/scientific-information-programme.html (visited 1 October 2014).

Harper: Good. I hope that has been or will be published or made available in some form?

Ferguson-Smith: Well, there's an account of it in the Association newsletter.[6]

Harper: That's good to know. A second reason that I'm very glad we're having this meeting is that it's quite urgent in terms of documenting people's memories of the field, because just to look through the participants' lists from the various workshops shows that there are already a number of the main people involved who are no longer with us. So it's good that we've got a core at least of those from the UK, and representation from the Netherlands too. You can see from the programme that our remit today is the series of Human Gene Mapping Workshops that were held between the early 1970s and the early 1990s. But I hope we won't interpret that too strictly and I'm quite sure people will cover, or go over the area of human gene mapping more generally. But there's no way that we can possibly hope to cover the entire field of human gene mapping in a single afternoon. One particularly difficult decision was whether to include the later workshops on individual chromosomes, and to what extent, which then led into the Human Genome Project. Really, this was a question of logistics because, if one had tried to cover that as fully as the early workshops, then it would have meant involving a lot more people, many of them from America whom we can't afford to bring over for just one afternoon's meeting. And so we've compromised, in the sense of including the X Chromosome Workshop, which I believe was the first of the specific Single Chromosome Workshops.[7]

Ferguson-Smith: May I just add another thing here?

Harper: You can, Malcolm.

Ferguson-Smith: It's not necessary perhaps to go over all the Single Chromosome Workshops. I was coordinator and Bronwen Loder did most of the work of organizing them.[8] But about 24 were done in the 3 years after the 11th Human Gene Mapping Workshop and another 22 were done up until 1998. There might even have been one or two in 1999; I forget. But anyway, these are recorded in various publications and also in the reports from the human genome analysis book from the European Commission.[9]

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[6] ECA Newsletter, No. 32, July 2013.

[7] Cook-Deegan *et al.* (1990). See pages 78–90.

[8] See note 257.

[9] See Ferguson-Smith (1998), which contains a list of all Single Chromosome Workshops from 1993 to 1997, and lists the journals in which they were published; see pages 342–5.

Meeting	Date	Location	Organiser/Convenor	Editor/s
HGM1	1973	New Haven	Frank H Ruddle	Frank H Ruddle, Dirk Bootsma, Victor A McKusick, Harold P Klinger
HGM2	1974	Rotterdam	Dirk Bootsma	Dirk Bootsma, Daniel Bergsma Frank Ruddle, Victor McKusick, Harold P Klinger
HGM3	1975	Baltimore	Victor A McKusick	Daniel Bergsma, Victor A McKusick, Harold P Klinger, Dirk Bootsma, Frank H Ruddle
HGM4	1977	Winnipeg	John L Hamerton	Daniel Bergsma, John L Hamerton, Harold P. Klinger, Victor A McKusick, H John Evans
HGM5	1979	Edinburgh	H John Evans	H John Evans, John L. Hamerton, Harold P Klinger, Victor A. McKusick
HGM6	1981	Oslo	Kåre Berg	Kåre Berg, H. John Evans, John L. Hamerton, Harold P Klinger
HGM7	1983	Los Angeles	Robert S Sparkes	Robert S Sparkes, Kåre Berg, H John Evans, Harold P Klinger
HGM8	1985	Helsinki	Albert de la Chapelle	Albert de la Chapelle, Harold P Klinger
HGM9	1987	Paris	Jean Frézal	Jean Frézal, Harold P Klinger
HGM9.5	1988	New Haven	Frank H Ruddle	Frank H Ruddle, Kenneth K Kidd, Harold P Klinger
HGM10	1989	New Haven	Frank H Ruddle, Kenneth K. Kidd	Kenneth K Kidd, Harold P Klinger, Frank H Ruddle
HGM10.5	1990	Oxford	Ian Craig, Walter Bodmer, Ellen Solomon[10]	Ian Craig, Chris Rawlings, Harold P Klinger
HGM11	1991	London	Walter Bodmer, Ellen Solomon, Harold P Klinger	Ellen Solomon, Chris Rawlings,

Table 1: List of HGMW with dates of meetings, convenors, and editors of publications[11]

[10] The published version of HGM10.5 credits Bodmer and Solomon as convenors, but correspondence from this Witness Seminar indicates the correct attribution should be Craig, Bodmer and Solomon. This change has the agreement of all relevant parties; see various items of e-mail correspondence, March 2015, in the archives of this meeting held at the Wellcome Library, London, Archives and Manuscripts, GC/253.

[11] All details taken from the journal *Cytogenetics and Cell Genetics* published by Karger.

Harper: This is something we can come back to because you will see from the programme that that's our last item and hopefully we'll have time for you to say a bit more about that then. On the topic of publication, you can see that on the table we've actually got a complete series of the Human Gene Mapping Workshops volumes. I find it a little confusing, firstly that they were duplicate publications, which is probably a good thing, but also that in many cases the publication was a year after the workshop. [12] Anyway, that's enough from me. To set the scene we've asked Sue Povey to give a general introduction to the workshop. I can't think of anybody better than Sue, not just because of her own contributions but because she's been based all these years at the Galton Laboratory, London, which has really been one of the key centres for human gene mapping from the very beginning.[13]

Part 1

- Beginnings of human gene mapping
- Founding and organization of the Human Gene Mapping Workshops
- The first workshops (Yale 1973, Rotterdam 1974)
- Protein polymorphisms and other early genetic markers
- Somatic cell hybrids and cytogenetic markers
- DNA polymorphisms and the workshops

Part 2

- Linkage analysis and informatics
- Nomenclature
- Comparative gene mapping
- Evolution of the workshop series
- The final Human Gene Mapping Workshop (London 1991)
- The first chromosome-specific workshop (X and Y); beginnings of HUGO and Human Genome Project

Table 2: Outline programme for Witness Seminar[14]

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[12] They were published as books by the National Foundation March of Dimes/Karger, and in the journal *Cytogenetics and Cell Genetics* (Karger).

[13] For a summary of the Galton Laboratory's history at University College London, see http://www.ucl.ac.uk/museums/galton/about/history (visited 1 October 2014). See also Jones (1993); Harper (2008), pages 235–40.

[14] The outline programme was circulated to the seminar participants for their input a month in advance of the Witness Seminar.

Figure 4: Professor Sue Povey

Professor Sue Povey: Thank you Peter. I'm sure I'm not standing here because I really witnessed the early human gene mapping but, as Peter said, I was in the Galton Lab where there had been very early involvement in human gene mapping and, of course, there had been an interest in the Galton Lab and in other places, but very largely in the Galton Lab in the first half of the twentieth century. And the first actual linkage found was, of course, as you would expect on the X chromosome, which was in 1937: Julia Bell and Haldane finding the linkage between haemophilia and colour blindness.[15] And even at that time, they actually thought about the way this might be used for prediction of disease and, actually, what you now call eugenics.[16] There had been a tremendous amount of theoretical work conducted in the Galton Lab by Fisher and Haldane and Hogben on how we would possibly ever compete with the *Drosophila* map, which was already very good in 1936.[17] And the tiny bits of information you can

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[15] Bell and Haldane (1937). Julia Bell FRCP (1879–1979) was at the Galton Laboratory from 1920 to 1965. See for example, Bell (1922) and Bell (1935). J B S Haldane (1892–1964) was Professor of Genetics at UCL, and also Weldon Professor of Biometry (1937–1957), and Head of the Biometry, Genetics and Eugenics Department, of which the Galton Laboratory was a part. See, for example, Clark (1968).

[16] See Hall (2002).

[17] Ronald Aymer (R A) Fisher was Chair of the Galton Laboratory, University College London from 1934 to 1943, where he set up a blood grouping unit; see UCL Archives, Galton Laboratory Records (1825–1998); http://tinyurl.com/o4tpowg (visited 17 November 2014). Lancelot Hogben (1895–1975) was Professor of Social Biology at University College London from 1930 to 1937.

get out from human families compared with what you can get from *Drosophila*. And so a tremendous amount of mathematical effort went into, for example, the next paper that I found interesting, which was by C A B Smith and Haldane about a refinement of this linkage between haemophilia and colour blindness, and by rather complex mathematics they managed to reduce, just by a small amount, the risk that was given to a mother of whether she would have a child with haemophilia. And the interesting thing to me about this paper was at the end of it they said, 'It may appear a rather trivial advance but it may be in some centuries hence that a similar map may be available for humans as is available for *Drosophila* and the prediction of inherited disease and the prevention of congenital abnormalities will be routine.'[18] I think to some extent in the next 20 years it looked like that estimate might be right because the actual number of autosomal linkages found before the Human Gene Mapping Workshops was only about four. And most of those, I have to say, were something to do with the Galton Lab. The linkage between Lutheran and Secretor by Mohr was not done at the Galton Lab, but I believe he had been in the Galton.[19]

Then, of course, there was ABO and nail patella syndrome and ABO and AK a bit later.[20] And then there was one interesting one, which I think was nothing to do with the Galton; it was Newton Morton finding that some forms of elliptocytosis were linked to rhesus.[21] I think that one of the things that really carried forward to the Human Gene Mapping meetings was a paper of Newton Morton's in 1955, which people, learned people, tell me says that if you get a lod score of three, honestly without cheating, without throwing anything out, if you ever get a lod score of three you can probably publish.[22] If you read that paper you might not take home that message but I believe that's what it's meant to be, and that really persisted throughout the Human Gene Mapping Workshops, didn't it? The only other two autosomal things really known before 1970 were the assignment of the Duffy blood group to chromosome 1 by Donahue in

[18] Haldane and Smith (1947); for quotation see page 30.

[19] Mohr (1963).

[20] Renwick and Lawler (1955) and Rapley *et al.* (1968).

[21] Morton (1956).

[22] Newton Morton's paper introduced the lod score from sequential analysis into genetic linkage analysis; see Morton (1955). See also page 55. Where a polymorphic gene and a gene related to a genetic disease are located in close proximity, on the same chromosome, lod (log of the odds on linkage) scores are a statistical measure of: a) the chance that a disease is linked to the locus of the polymorphic gene; b) the most likely recombination frequency between them.

the States, and of haptoglobin to chromosome 16 in the UK, both of them by going with a visible chromosome polymorphism. [23] So that was the scene really, just a very short time before the first Human Gene Mapping Workshops. But in those intervening years, a great revolution had occurred in the possible ways of mapping. So that was about all I was going to say.

Ferguson-Smith: Sue, was the haptoglobin one Bette Robson?

Povey: The haptoglobin was Bette Robson, yes.[24] That was a Galtonian thing, of course. Lionel Penrose had become Galton Professor by then and he encouraged people to maintain an interest in mapping.[25] He was very mathematically orientated and he hired people like C A B Smith, who was also very productive in many things that were afterwards applied.[26]

Harper: On the topic of that linkage of Jan Mohr, I was able to interview him before he died and I was really interested that, when I asked him, as I've asked other people, 'Who would you consider the main influence on your work?', he was definite that it was Penrose.[27] That's the case for so many people. So the field of human gene mapping has got a pretty distinguished background before the workshops began. Is there anyone who wants to say anything about those early years before we move on to the founding of the workshops themselves?

Professor Sir Walter Bodmer: We should remember that there was a lot of mapping of the sort that contributed to the workshops for several years before the first workshop. Maybe that's something I could comment on?

Harper: Yes, I think that would be good to develop, because you're referring specifically to the cell hybridization work? Before throwing things open on the founding of the workshops, I'd just like to quote a piece from Victor McKusick's autobiographical article, which he published a couple of years before he died, and

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[23] Donahue *et al.* (1968); Robson *et al.* (1969).

[24] Professor Elizabeth (Bette) Robson (b. 1928) was a founder member of the MRC Human Biochemical Genetics Unit at UCL (1962), and she was Galton Professor of Human Genetics at UCL from 1978 to 1993.

[25] Lionel Sharples Penrose (1898–1972) was Galton Professor of Eugenics (1945–1962) and Professor of Human Genetics at University College London (1962–1965).

[26] Cedric Austen Bardell Smith (1917–2002) was Weldon Professor of Biometry at the Galton Laboratory, UCL, from 1964 until the end of his career, where he developed several statistical methodologies.

[27] Professor Peter Harper's interview with Professor Jan Mohr is freely available to download from the Genetics and Medicine Historical Network's website: http://www.genmedhist.info/interviews/Mohr (visited 1 October 2014).

Figure 5: Professor Sir Walter Bodmer

then ask whether people here think that actually is correct, or whether there are other things that need to be brought in. What he says is: 'The annual or biannual Human Gene Mapping Workshops initiated in 1973 were Frank Ruddle's idea. A regular member of the faculty of the Bar Harbor Short Course in Clinical Genetics, Ruddle solicited my collaboration in the organization of the HGM Workshops. He trusted that I would be able to arrange funding from the March of Dimes, which funded the Bar Harbor course and the Clinical Delineation of Birth Defects conferences and on whose medical advisory committee I'd served since 1959. The idea of the HGM Workshops was enthusiastically received by the March of Dimes and was implemented by Dr Daniel Bergsma, vice president for professional education.' [28] I've always felt that, regardless of the role of the Galton and places elsewhere in human gene mapping, the actual idea and initiation of the workshops came from the American side as Victor McKusick states there. I'd be interested to know from those people who were around at that time whether you think that is indeed correct?

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[28] McKusick (2006); see pages 12–13. Victor McKusick (1921–2008) founded Johns Hopkins University's division of medical genetics in 1957, becoming Professor of Medical Genetics there in 1985. For an overview of the scientific context in the 1960s and 1970s leading up to the Human Gene Mapping Workshops, see Ruddle (1984). See also biographies for McKusick and Ruddle on pages 104–5, 107.

Bodmer: I think you've really got to go into the background, and early history of the tremendous contribution that came from somatic cell genetics to gene mapping because it's that that actually initiated the idea of the workshops through Frank Ruddle, although he wasn't the first person to do linkage in somatic cell hybrids.

Harper: Maybe that's a good time, Walter, for you to say a bit more about that early hybridization work?

Bodmer: Well, I think it's important to be aware of the history because, as I see it really, it was the opportunity to do genetics with somatic cells that was the next major leap forward. One can have the other sort of main leaps, well obviously the use of restriction mapping, which Ellen (Solomon) and I emphasized in 1979, and then, of course, the whole sequencing work.[29] Just to give a bit of history, and it's personal history, I actually spent the summer of 1959 in Pontecorvo's lab, late summer, and Pontecorvo and Lederberg were the two people who'd actually suggested the idea that one might do somatic cell genetics.[30] Pontecorvo, by the analogy of what he'd done in *Aspergillus* and chromosome segregation there, and Lederberg had the idea that one might actually do it by crossing cells.[31] When I went to be a postdoc with Josh Lederberg at Stanford, which was in 1961, I actually had the ideas in the back of my mind as something that one might get into. One of the reasons I went there was because some very early work with tissue culture had been done by Len Hertzenberg when he was still, I think, at the NIH (National Institutes of Health) before he came to Stanford,[32] and I thought that it would be a good place to start this. But in fact, it wasn't till five years later that I was able to get started in my own lab and we did the first hybrids between lymphocytes and an 8-azaguanine resistant mouse cell line. The precursor to that, as I'm sure many people know, is that 8-azaguanine resistance

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29 Solomon and Bodmer (1979).

30 Guido Pontecorvo (1907–1999) established a genetics research department at the University of Glasgow in 1945, of which he became Professor of Genetics in 1955. He worked there until 1968 when he moved to the Imperial Cancer Research Fund laboratories in London until his retirement. For an obituary see Anon (1999). His papers are held at the library of the University of Glasgow Archive Services, reference GB 0248 UGC 198. Joshua Lederberg (1925–2008) was a bacteriologist and geneticist, and a Nobel Laureate in 1958.

31 Pontecorvo and Käfer (1956); Lederberg (1956).

32 Leonard Hertzenberg (1931–2013) was based at the National Institutes of Health from 1957 to 1959, where he worked in the laboratory of Harry Eagles on mammalian somatic cell genetics. See Hertzenberg and Hertzenberg (2013).

had been actually used by Szybalski to select using something like the HAT regime.[33] Then it was Littlefield in a paper published in Cold Spring Harbor in 1964, possibly there was earlier work, who made the first hybrid selectively using thymidine kinase minus cells and 8-azaguanine resistant cells so that you could do the HAT (histone acetyltransferase) selection, so the only things that would survive would be the hybrid.[34] We had the idea that you could simplify that by taking human lymphocytes, which couldn't divide anyway and then having a mouse cell line that was 8-azaguanine resistant, so you could then select hybrids only having the selection on the one side of the mouse because the non-dividing cells could provide the compensation that you needed. This would be a way of wide-scale sampling of different humans. About that time, I think the initial, the first real, experiment that showed linkage mapping in hybrids was Weiss and Green, who used the hybrid technique but not with lymphocytes, and they investigated the chromosomal localization of the thymidine kinase marker that was ultimately shown to be on chromosome 17.[35] That was really the first case that you could associate a marker with something that you'd selected for, and interestingly enough, although Mary Weiss did further work, they never really followed that up.[36] So actually, the first somatic cell hybrids that really showed linkage beyond that were in a paper that we published in *Nature* in 1969, and had talked about in a meeting in 1968.[37] This first of all showed, the most obvious thing it showed, was that in tissue culture the 8-azaguanine, the *HPRT* mutation, was on the X chromosome – which of course was already known because the Lesch–Nyhan syndrome was a mutation in that.[38] We'd been made aware of that by Howard Green actually. I think in that paper we also showed, certainly, that we did something with LDH – we suggested that the genes for *LDHA* and *LDHB* were not linked – and then that was really the first paper beyond Weiss and Green that did any mapping. The next paper, there were two papers, one from my lab and one from Frank Ruddle in which we

[33] Szybalski and Smith (1959).

[34] Littlefield (1964).

[35] Weiss and Green (1967); Miller *et al.* (1971).

[36] Mary Weiss worked in Boris Ephrussi's laboratory at the New York University School of Medicine, Department of Pathology, and also led the Institut Pasteur's Genetics of Differentiation Unit in Paris.

[37] The meeting was 'Heterospecific Genome Interaction' at the Wistar Institute of Anatomy and Biology, 22–23 October 1968. See Nabholz, Miggiano and Bodmer (1969) and Miggiano, Nabholz and Bodmer (1969).

[38] See Felix and DeMars (1969).

extended that, and we were using electrophoresis to distinguish human and mouse enzymes. Then we could show that we could use a random assortment of the chromosomes because what Weiss and Green had importantly shown was that you lost human chromosomes more or less randomly in the hybrids, so you got a range of cell lines that had different combinations of human chromosomes in the presence of a mouse background that allowed you to associate human markers with each other and then eventually with the identification of the chromosomes. In the same issue of *Nature* in 1970, we published at the same time as Frank Ruddle that, for instance, LDH A and B were definitely not linked and that LDH was linked with peptidase B.[39] Actually, at that time Frank Ruddle and my lab were the only labs that were doing this sort of hybridization in the very early days. I used to have to referee all Frank Ruddle's grants and no doubt he did mine. So, without going into a lot more detail I think it was that stimulus that immediately made one realise you could enormously extend the range of mapping using those techniques. That was the stimulus for the idea that one had to get the data together to do this and I think it's correct that Frank Ruddle had that idea and got Victor McKusick involved, of course, the first HGM Workshop was in 1973. Of the people here, I know that Ian Craig went.

Ferguson-Smith: Ruddle also went to Pontecorvo in Glasgow in the 1960s.[40] He went there specifically because he was influenced by the parasexual cycle that Pontecorvo had proposed first in *Aspergillus*.[41]

Bodmer: Well, he was only a year or two after me on that.

Ferguson-Smith: Yes, he was probably a year or two after you. He went also at the same time to John Paul to work on cell culture.[42] Some of the earlier work that Pontecorvo had done is beautifully summarized in his book *Trends in Genetic Analysis*.[43]

Bodmer: Ponte's work was extremely elegant. I had the honour of bringing *Aspergillus* to the Cambridge genetics department from Glasgow. His ideas were

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[39] Santachiara *et al.* (1970); Ruddle *et al.* (1970).

[40] See biography on page 107.

[41] Pontecorvo, Roper and Forbes (1953); see also Pontevorvo *et al.* (1953).

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

[43] Pontecorvo (1958).

Figure 6: Professor Ellen Solomon, Professor Malcolm Ferguson-Smith

very influential but they were not actually the way that somatic cell genetics eventually developed; it developed more along the lines that Lederberg had suggested through crosses.[44] By the time of the first Gene Mapping Workshop, certain people here have got their names on papers, they'd actually extended the mapping quite a lot. With Victor McKusick's enormous contributions in *Mendelian Inheritance in Man*, it became a sensible idea to try and gather together what was known and keep track of it from time to time.[45] That's the way I see the origin of those workshops.

Harper: Can I ask one thing to anyone here? Am I right in that, although Henry Harris with John Watkins was the initiator of the actual hybrid techniques, and Pontecorvo was very much involved also, I don't think either of them were involved in applying this to human gene mapping.[46]

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[44] See note 31.

[45] McKusick (1966). See also note 172.

[46] Sir Henry Harris (1925–2014) was Professor of Pathology at the University of Oxford (1963–1979) and Head of Department in the Sir William Dunn School of Pathology, Oxford (1963–1994). John Frederick Watkins (1927–2003) was based at the School from 1959 to 1966; see Morgan and Westmoreland (2003). For Pontecorvo, see note 30.

Bodmer: I can say. I was in Oxford at about the time when Henry Harris was doing that. Neither of those are quite true: Pontecorvo never actually did anything himself with somatic cells. He had a guy there you may know, Eugene Bell, who was a visitor in his lab at the time, who tried to implement some of the ideas. I don't know whether that was before you went there, Malcolm?

Ferguson-Smith: It wasn't for want of trying. I mean right up to 1968 he was still trying to work with human somatic cells, and then he came with Michael Stoker to ICRF (Imperial Cancer Research Fund).[47]

Bodmer: Could I just comment on the Henry Harris thing? The first hybrids that were made were long before Henry Harris, they were Littlefield's.[48] Those were the first somatic cell hybrids that were made. Then there were others, Boris Ephrussi and others.[49] Henry Harris, his introduction was the use of *Sendai* virus that came from John Watkins, who was a reader at the Sir William Dunn School of Pathology, and he knew about viruses that stimulated the formation

Figure 7: Professor Ian Craig, Professor Malcolm Ferguson-Smith

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[47] Michael Stoker (1918–2013) was the Director of the Imperial Cancer Research Fund laboratories from 1968 to 1979.

[48] For Littlefield, see note 34.

[49] See Weiss (1992).

of hybrids.[50] Harris never really did any genetics as such with that. Pontecorvo came to the ICRF; it was in 1968 he must have gone with Michael Stoker and it was a few years after that he introduced the polyethylene glycol fusion by analogy with work in plants, as an alternative to somatic cell fusion by *Sendai* virus.[51]

Professor Ian Craig: That was a really important breakthrough because *Sendai* virus was a real pain to use and Pontecorvo definitely helped in pushing forward the polyethylene glycol approach.

Bodmer: Oh yes he did, and he commented on the fact that it was surprising that we, being in Oxford, actually took that up because he thought that no one in Oxford listened to what he did. That was true but all the early work that we did led to a lot of the hybrids that you guys (Ian Craig and Veronica van Heyningen) worked on was done with *Sendai* virus.

Harper: Coming now back a bit to the workshops themselves, their founding and organization, and we'll come on specifically to the Yale 1973 workshop in just a moment: the character of the workshops – coming in a good deal later myself – always seemed to me to be very hands-on and, am I right, that that was the case from the beginning? Who was around at the time of the first workshop by the way?

Craig: I was actually at the first workshop. I represented Walter Bodmer's lab, reporting work done with Veronica van Heyningen and Walter.[52] Well, you, (Walter) didn't go but some of the work that you'd been doing went. The workshop was very much hands-on, it evolved on the spot as it were, in Yale, as a system of committees and reports. That persisted all the way through for the next 20 years and you could even argue that the later, Single Chromosome Workshops worked on the same principle. I have a strong recollection of arriving very nervously late at night in Yale and being introduced to a cocktail party. I think it was already quite late English time, and this very impressive, tall character, Frank Ruddle, came and said, 'You have to talk first thing tomorrow morning', which was not the best news. But over the next three or four days it did evolve; the system worked. There were committees – I can say a little bit

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50 See, for example, Harris and Watkins (1965). This paper states that the *Sendai* virus was 'supplied by Dr H G Pereira of the National Institute for Medical Research, Mill Hill', quoted from page 640.

51 Pontecorvo (1975).

52 Craig *et al.* (1974).

more about what they were – and the actual reports, but the point is that the workshop actually was self-regulating and it was with fairly easy, hands-on from the top as I remember.

Harper: Tell us a little bit about the structure of the workshops as you saw it, that first workshop.

Craig: Well, you have to imagine arriving on the scene not knowing how it was going to work and whether or not you were going to talk, or precisely how it was going to happen. But we started off essentially with individual reports, which gave everybody an opportunity to present on their own little pet topic, specific hybrid or whatever, gene assignment, etc.[53] Then, as time went by, the assignments were collected together and you also introduced your information at a working group session, which was, I remember, held in the Kline Biology Tower in goldfish bowl-like lecture rooms. I think I was in one of the committees called 'Autosomes other than One'.

Harper: Yes, you were. You were with Dirk Bootsma, who sadly can't be here.[54]

Craig: Exactly. And John Edwards used to go around, working from committee to committee, introducing relevant information on lod scores and such like.[55] But in this glass sort of cubicle, it was a little bit confusing and in fact John got up from the table in the workshop I was at, and tried to exit via the glass wall and bounced off, but he didn't seem to be at all perturbed by the process. There were 65 people at the first workshop and, with Adam Wilkinson's help, we've got some photographs of the people who were there and their names; a lot of those then went on to be major figures in the field.[56] And, as I said, the pattern of the committees in the workshops basically persisted. In the introduction to the HGM1 book, talking about the contribution of somatic cell genetics as Sir

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[53] For all the published papers from HGM1, see Ruddle *et al.* (eds) (1974a).

[54] Professor Dirk Bootsma represented Erasmus University, Netherlands, at HGM1, and was a participant/ Conference Scientific Editor of subsequent workshops; see *Cytogenetics and Cell Genetics* for further details of his contributions. His career as a geneticist is discussed by Hans Galjaard in an interview with Professor Peter Harper, http://www.genmedhist.info/interviews/hans-galjaard-interview (visited 23 January 2015).

[55] Victor McKusick noted in his obituary of Edwards: 'John was a regular and important participant in the international Human Gene Mapping Workshops held between 1973 and 1991. His input was in relation to linkage analysis and reporting, and to the comparative mapping, particularly of mouse and man.' McKusick (2007). See also a biography on page 101.

[56] See Appendix 1 for reproductions of these photographs. Mr Adam Wilkinson is the Project Manager for the History of Modern Biomedicine Research Group, and coordinator of the Witness Seminar events.

Walter has been talking about, it said, 'Moreover these new data – i.e. the data coming in from somatic cell genetics – have proven exceptionally useful to those investigators who have employed kindred analysis for the purpose of genetic mapping. The combination of the two has been particularly productive.'[57] And I think that's exactly where the two worlds met. There were lots of committee reports, there was 'Chromosome 1', 'Autosomes Other than One', 'the X Chromosome', and, interesting to note, the Y chromosome wasn't mentioned and didn't have anything on it apparently.[58] There was also a committee on *in situ* hybridization, markers, and also on nomenclature, which I'll come back to in a moment. But just to give you an idea of the overall pattern at the workshop, there were four presentations of classical linkage analysis, there was one on meiotic frequency organization, then there was an appendix provided by John Edwards comprising 12 pages of lod scores for various populations, a feature that did not persist in the later workshop reports, although a lot of people felt like they should: so there were about four or five papers from linkage in that case; there were six from somatic cell hybrid assignments by markers and synteny; there were 18 on chromosome analysis and regional assignment; there was one on dosage; and there were a few on biochemical techniques and such like in cytogenetics. It was interesting to see that *in situ* hybridization was already operating at that time, although obviously having to work with multiple gene copies. 5S RNA was assigned to chromosome 1. But there was a very memorable statement in the report from the hybridization committee: 'Possible localizations included haemoglobin, to 2q and Bq[59] by 'hot' mRNA and cDNA, but this occurred despite theoretical objections to its feasibility', which proved very true.[60]

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[57] Ruddle *et al.* (eds) (1974b).

[58] Hamerton and Cook (1974); Bootsma and Giblett (1974); Gerald and Brown (1974).

[59] Several contributors noted 'Bq' as somewhat unusual terminology; however, in email correspondence Professor Ian Craig clarified: 'The original report for HGM1 clearly states Bq as one of the localizations. I think they had problems in identifying individual chromosomes because of the hybridization conditions messing up banding and therefore assigned signals to one of a group A, B, C, etc.' Email to Ms Emma Jones, 20 March 2015. Professor Bert Bakker further elucidated, 'The chromosomes were sorted by size and centromere position, Bq then refers to the long arm of either chr 4 or chr 5 (these are B-group chromosomes). At that time there was no chromosome banding yet. The D group contains the chromosomes 13, 14 and 15.' Email to Ms Emma Jones, 25 March 2015.

[60] Hirschhorn and Boyer (1974), quotation on page 56. Professor Ian Craig wrote, 'This observation which was memorable for the succinct coverage of a heated debate and the eventual localizations of alpha haemoglobin to chromosome 16 and of beta haemoglobin to chromosome 11.' Note on draft transcript, 3 March 2015.

Figure 8: Professor Veronica van Heyningen

There was a committee on 'terminology', which produced the categories of confirmed, provisional, and contradictory assignments, which persisted as far as I know pretty well all the way through. In that report it was also very presciently mentioned that a new distance unit should be introduced, which was for physical mapping, and the committee suggested what was called the 'mega nucleotide' as a mapping unit – that was a very interesting introduction for that time.[61] So that was where things more or less were then. Apparently people said there were 100 markers defined at the time. In fact, I only counted 84 that were actually on Frank Ruddle's data sheet.[62]

Harper: There are a couple of things that interested me when I was going through the workshop volumes a little while ago, and the first in relation to that first workshop – there was no actual map drawn of the autosomes. There were some lists but there wasn't actually a map in that volume; that didn't appear until I think the following workshop.

Professor Veronica van Heyningen: I went to the second workshop in Rotterdam with Walter. That was one of the first meetings I went to following my PhD, and I had to report disproving one of Frank Ruddle's chromosome assignments. He'd assigned MPI, mannose phosphate isomerase, to chromosome 7, but we had assigned very firmly the mitochondrial malate dehydrogenase to

[61] McKusick and Frézal (1974).

[62] Ruddle (1974).

chromosome 7 and it didn't co-segregate with MPI.[63] Then, later on, we put MPI on a different chromosome, on 15.[64] So I remember being very nervous about having to disprove Frank Ruddle's assignment but he said, 'Oh yes, I think we can find evidence for that and publish it back to back with you.'[65]

Craig: I think there was a general enthusiasm for producing information, even if it was only provisional. The way that somatic cell hybrids work, the chromosomes do funny things as everybody knows, and it very often led to mis-assignments of one sort or another. Hence evolved the idea of provisional and then confirmed assignments based upon that kind of thing.

van Heyningen: Exactly, yes. Going back to 1973, I just remembered sitting here, and that I happen to have on my iPad a photograph of an EMBO (European Molecular Biology Organization) conference on somatic cell genetics that Walter organized in Oxford.[66] It's a lovely photograph with lots of very well-known faces on it.

Bodmer: I've got an anecdote for that. Ephrussi and Henry Harris completely disagreed on the question of whether transformation, if you could call it that in culture, was dominant or recessive. Ephrussi had written a book, and I was very friendly with him you see, I'd met him in Lederberg's lab, and he said, 'Do you think Henry Harris has read my book?' And Henry Harris told me, 'Why on earth should I read Ephrussi's book?', because they really didn't get on terribly well, and that appeared at that EMBO meeting too.

van Heyningen: They're quite close together in the photograph. Mary Weiss was there, Gordon Tomkins, who died not very long afterwards; John Minna; loads and loads of people: Meera Khan, Harry Harris, Hoppy – David Hopkinson.[67]

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[63] Craig *et al.* (1974).

[64] van Heyningen *et al.* (1975a).

[65] Kucherlapati *et al.* (1975). See also Ruddle and McMorris (1975).

[66] See Appendix 2 for photograph with key, pages 96–7. Archives relating to Professor Sir Walter Bodmer's organization of the 1973 EMBO conference are available in the Bodleian Library, University of Oxford, Archives and Manuscripts, reference MS. Bodmer 1–2216.

[67] For Mary Weiss, see pages 14–15 and note 35; for Gordon Tomkins, see the University of San Francisco's 'A History of UCSF, People: Gordon M Tomkins (1926–1975)', http://history.library.ucsf.edu/tomkins.html; for John Minna, see the University of Texas, Southwestern Medical Center's website for details of his career in the 1970s, http://profiles.utsouthwestern.edu/profile/14991/john-minna.html (websites visited 16 December 2014); for Meera Khan, see page 30; for Harry Harris, see biography on page 103, and for David Hopkinson, see note 76. See also Appendix 2.

Figure 9: Professors Veronica van Heyningen and Sue Povey with 1973 EMBO conference photograph: see Appendix 2 for original with key

Bodmer: When was that? What year was that?

van Heyningen: 1973.

Bodmer: It was really quite early. Could I just make a very brief comment on the nature of the workshops? You may recall the HLA field?[68]

Harper: Yes, I was going to ask you about the links.

Bodmer: The HLA field developed through workshops that were in many ways analogous to the HGMW and, certainly as I became more involved, I saw clear parallels between the way that they worked, although they were in a different area, with different issues, they had similar problems of reproducibility. They were very much workshops from the ground up, from the people who wanted to work together with no formal organization, no major committees, no society. We just got on and compared notes and eventually did collaborative experiments on seeing how things matched up with each other. Of course, that totally disappeared with the development of the Human Genome Project.

van Heyningen: You exchanged theory a lot, didn't you?

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[68] Professor Sir Walter Bodmer noted: 'I was responsible for that nomenclature and the 'A' was for the first locus, it's not for antigen as is always assumed.' Note on draft transcript, 24 March 2015.

Bodmer: We exchanged theory and cells and did combined analysis, all those things. That had been happening since 1964.

van Heyningen: I have a very minor, tiny little anecdote of Peter Goodfellow coming to the lab and he came to work on the HLA system.[69] He did do some mapping as well. Neither Walter nor he really liked being bled, but, of course, one of the things if you worked in this lab was that you got bled and you donated whatever was necessary, sometimes after going on an exercise bike. We had a little bleeding room and Peter said, 'Well, I'll get better at it, I'll watch Walter being bled.' And Peter fainted across him while Walter was being bled.

Bodmer: No, it was a little worse than that. There was a little room, which was next to Julia's [Bodmer's] office and he actually banged the back of his head on the bench as he fell down; it was not a very good thing to do actually.[70] I didn't like being bled but I've often been bled. I didn't suffer the way that Peter did – the reason they did exercise at that time is because it increased the proportion of circulating B cells.

Harper: But you should have known always to bleed people lying flat because it's impossible to faint when you're lying flat.

Bodmer: Usually sitting down is alright.

Harper: Usually but not always.

Bodmer: That's what we'd done quite a lot for many years.

van Heyningen: But Peter wasn't being bled, he was just watching.

Harper: Any other comments about the first workshop in Yale? Because that did set the tone in a way for a number of years after?

Ferguson-Smith: I think, whereas some people were invited, it was also an open meeting, which was nice because everything was shared. I remember being very proud to put in the first localization using chromosomal deletions: that was red cell acid phosphatase to chromosome 2 short arm.[71] There were other chromosomal translocations and rearrangements and, of course, *in situ*

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[69] See introduction and biography on pages xiii–xv, 102.

[70] For Julia Bodmer, see note 165.

[71] Ferguson-Smith *et al.* (1973).

mapping started off with radioactive tritiated thymidine and autoradiography. Fluorescent probes came in in the late 1980s.[72]

Harper: One other thing that I've noted looking through the New Haven workshop and the list of committees: at the bottom after 'terminology' there was one headed 'Organization of Future Meetings', which was represented by John Edwards and Daniel Bergsma.[73] But it obviously worked very well, so perhaps John going around everybody else's was part of the organization?

Craig: Just to add to that, the scientific editors, were Frank Ruddle, Dirk Bootsma, Victor McKusick, and Harold Klinger. And what they wrote in that final report was that the purpose of these annual meetings was to publish reports: 'It is our aim to review progress on human gene mapping on a yearly basis. … The meetings should provide a standard terminology and nomenclature, which will facilitate future developments', and I think that's a really important thing to note.[74] Of course, informatics was really interesting. You could see John Edwards and Bette Robson going around and calculating lod scores on the backs of envelopes and telling people whether their linkage was significant or not, or whatever, but that was basically how it worked.

Harper: I think at this point it would be a good idea to get back to the actual markers involved. Sue, we're working you very hard today but I think appropriately so. So the theme of protein polymorphisms and other early genetic markers, again you being at the Galton gives you a good vantage point for talking about this part of the field.

Povey: Before I start on that, you may laugh at John Edwards organizing things, but actually he used to organize very good meetings in Oxford, and in Birmingham.

Harper: Yes, you're absolutely right and I think we laughed in a sympathetic way because John made such huge contributions, but he just wasn't quite like anybody else in the way he did things.

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[72] Professor Malcolm Ferguson-Smith wrote, 'Mary Lou Pardue and Joe Gall were the first to use *in situ* techniques. In 1970 they showed that mouse satellite DNA was located at centromeres. Angie Henderson next used the same technique in 1972 to map human ribosomal genes to the short arms of the acrocentric chromosomes.' Note on draft transcript, 3 January 2014. Pardue and Gall (1970); Henderson, Warburton and Atwood (1972).

[73] Bergsma and Edwards (1974).

[74] Ruddle *et al.* (1974b).

Povey: Protein polymorphisms, there were many there before I was involved. The blood groups were, of course, protein polymorphisms and the HLA field and that was well established really.

Bodmer: Not applied to hybrids.

Povey: No, they were not applied to hybrids. The main interest in protein polymorphisms in our lab under Harry Harris, and anyone that came to the lab was in biodiversity. That was very much helped by Oliver Smithies' discovery of starch gel electrophoresis,[75] and then Harry, and particularly Hoppy,[76] were very, very expert in working out a good system for visualizing each enzyme and making quite sure that it was actually the enzyme you thought it was. A lot of them had a final common pathway of PMS (phenazine methosulphate) and MTT (methyl thiazolyl tetrazolium) and so you got a particular colour and you did really need to make sure that every ingredient was essential for getting this band, otherwise it might be something completely different. In fact, Harry was more interested in the biodiversity than he was in gene mapping, but there were a lot of people around, such as Bette Robson and Peter Cook, who were interested in gene mapping even in the Galton Lab.[77] The contribution originally, I think, to the somatic cell hybrids was the discovery of the ways of looking at the separation of proteins in this way, in starch gel electrophoresis. In the lab, any new person in the lab was given a new system to look at and you had to look at 500 people before you were allowed to say it wasn't polymorphic. [Laughter] That represented a considerable change later on when, in the construction of a comprehensive human genetic map with microsatellites by the group of Jean Weissenbach, the only loci used were those that showed at least three different alleles in the four individuals tested.[78] The starch gels, of course,

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[75] Smithies (1955). In 2007 Oliver Smithies became a Nobel Laureate for his contributions to stem cell research; see http://www.nobelprize.org/nobel_prizes/medicine/laureates/2007/smithies-facts.html (visited 16 December 2014).

[76] Professor David Hopkinson (b. 1935) was Director of the Medical Research Council Human Biochemical Genetics Unit from 1976 to 2000, now Emeritus Professor of Human Biochemical Genetics, University College London.

[77] Professor Sue Povey wrote, 'Peter Cook was the main analyst of linkage in the Galton Lab during the workshops up to about HGM6 and was almost entirely responsible for the overall maps of chromosome 1.' Email to Ms Emma Jones, 12 June 2014. For Elizabeth (Bette) Robson, see note 24.

[78] Gyapay *et al.* (1994). Jean Weissenbach was Director of the Généthon gene mapping project in France from 1990 to 1996. For its history, see http://www.genethon.fr/en/about-us/history/ (visited 5 March 2015).

the major thing about them was you didn't need biodiversity within the species, you only needed to be able to separate the mouse and the human. Those protein polymorphisms as Walter said they did, or somebody said, they did interact with the linkage because, although it was a fantastic amount of work to use the protein polymorphisms for linkage analysis in families, it did tie in with using them in somatic cell hybrids. The protein polymorphisms were useful for a long time and even quite late in finding, for example, Batten's disease, which was found in 1989 to be linked to chromosome 16 by Eiberg with haptoglobin, but, of course, had been put on 16 a long time before.[79] I think all the major somatic cell groups looked at enzymes in their somatic cells for mapping, and eventually people at the Galton Lab did that as well, but we were a bit slow to get into actually making hybrids. We were busy looking at other people's hybrids.

Harper: Can I ask you, Sue, about the links between the folk working on enzymes at the Galton and the blood groupers, Ruth Sanger and Robert Race,[80] because my impression was always this was incredibly close and if one sent a sample it got passed around in a circle so that everybody could use it for both blood groups and enzymes.

Povey: Yes, that's actually correct. We collected enormous numbers of placentas from Edgware General Hospital, I think probably with no permission from anybody.[81] We had at least 3,000 and then we looked and we had blood samples from the families of anything where we found variants, we pursued them. Then those samples, and many other samples sent to us by clinicians, were subject to being blood grouped by Race and Sanger, and anything that was going that was polymorphic was done.[82] And there was a central system of logging everything

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[79] Eiberg, Gardiner and Mohr (1989). See also Magenis, Hecht and Lovrien (1970).

[80] Dr Ruth Sanger (1918–2001) was on the Scientific Staff of the Medical Research Council's Blood Group Unit from 1946 to 1983, and Dr Robert Race (1907–1984) was the Unit's Director from 1946 to 1973. See Race and Sanger (1950). See, for example, an overview of their work in the introductory text to archives held at the Wellcome Library, London, as part of the 'Codebreakers: Makers of Modern Genetics' collection, 'The Robert Race and Ruth Sanger papers'; http://wellcomelibrary.org/collections/digital-collections/makers-of-modern-genetics/digitised-archives/robert-race-ruth-sanger/ (visited 16 December 2014). See also Christie and Tansey (eds) (2003).

[81] For another discussion of acquiring placentas for blood samples, see Overy, Reynolds and Tansey (eds) (2012); pages 42–5.

[82] Professor Sue Povey wrote, 'In the search for useful heterozygosity most families were tested for about 25 loci. There were a mixture of blood groups and enzymes and other proteins which could be detected by starch gel electrophoresis or iso-electric focussing.' Note on draft transcript, 26 February 2015.

found. And so linkages were found but it was an awful lot of work to find a linkage, most of it analysed by Peter Cook, who sadly died suddenly in 1982, at the age of 42.[83]

Ferguson-Smith: I just want to mention Jim Renwick here because, with Marian Izatt in Glasgow, he set up a linkage lab there.[84] Twenty-three polymorphisms were looked at and this included all the blood groups as well as serum markers and red cell enzymes, and we used all these in collaboration with him for many years until he left for London in 1968. I continued the marker lab when he left, and later added DNA markers to our armamentarium.

Povey: Yes, I think we had about 23. I think that was about the number we had that was routinely done. But of course many of them were not informative in every case.

Bodmer: I'd just like to comment on that and enlarge on what Sue said. The polymorphisms, of course, were important for the family studies. They didn't really play a dramatic role in the somatic cell hybrids. As Sue said, the main thing there which made it so easy to start with, you would expect to find, to a large extent, starch gel electrophoresic differences between the species and that helped enormously because all you needed to have was a way of deciding whether you had the human version of the enzyme. But there were other techniques that came into play fairly early – Veronica might like to comment. One idea we had was to immunize mice with the human enzymes and then to use Ouchterlony plates and analyse enzyme activity.[85] Actually, the blood groups never, as such, played a major role because it was very hard to establish blood group determinants on the hybrids and it was not really until the HLA work, when we began to have monoclonal antibodies in the late 1970s, which enabled the use of surface antigens as markers began. We made some specifically, so we looked for some antigens that were chromosome-specific and things that Puck's group had developed.

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[83] For a tribute to Peter Cook's work on gene mapping, with biographical details, see Robson (1982).

[84] Professor James Renwick (1926–1994) worked at the Department of Genetics, University of Glasgow in the 1960s. He was responsible for some of the earliest human genetic linkage studies, as well as for developing computerized approaches to genetic linkage analyses. Further details of his career are available on the 'Codebreakers: Makers of Modern Genetics' website; http://wellcomelibrary.org/using-the-library/subject-guides/genetics/makers-of-modern-genetics/digitised-archives/james-renwick/ (visited 8 October 2014).

[85] For the 'Ouchterlony double diffusion in agar' technique, see van Heyningen, Craig and Bodmer (1973).

Ted Puck, who has not been mentioned so far, had a completely different approach, and an important one to somatic cell genetics.[86] He was looking for mutations in CHO (Chinese hamster ovary) cells that seemed to be mainly haploid.[87] So there were these other techniques that one could begin to use and, of course, that all completely changed when DNA studies came in. It's an interesting point, the differences in techniques: one of the early papers from Frank Ruddle's group was solution hybridization to try and identify whether you had a human or a mouse gene.[88] Then there was the *in situ* hybridization but then what really changed it was Southern blotting.[89] And the first paper on the mapping, I think, Ian, your name's on it with Alec Jeffreys, was a pioneering paper that actually mapped the haemoglobin genes using Southern blotting.[90] I looked it up the other day and it's only been referenced 58 times, yet I think it was actually the pioneer of really being able to use DNA-based techniques for doing gene mapping before you got sequencing.

Harper: We'll come on to that, Walter, if we may when we deal with the DNA polymorphisms in detail.

van Heyningen: My PhD was to look at the mitochondrial enzymes that are encoded by the nucleus and look at their segregation.[91] Human mitochondrial DNA is lost in somatic cell hybrids and so you only have the nuclear DNA contributing, therefore we could only look at the nuclear components. But many of them could not be distinguished readily on electrophoresis, they had the same specific charge. First of all, I think mitochondrial enzymes migrated to the negative electrode and also we couldn't separate the mouse from the human, and that's why we started having to make the antibodies to distinguish them. So we had to prepare more semi-purified enzymes to inject into rabbits and make the anti-sera. We also found it quite difficult to be as skillful as the Galton labs in running starch gels and we switched to cellulose acetate, which was very

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[86] For an obituary of Ted Puck (1916–2005) see Rowley (2006).

[87] See Puck, Cieciura and Robinson (1958).

[88] Deisseroth *et al.* (1978).

[89] Southern blotting was a technique developed by Professor Sir Edwin Southern (b. 1938) for DNA analysis; see Southern (1975).

[90] Jeffreys, Craig and Francke (1979).

[91] van Heyningen (1973).

good. It was much quicker and we didn't have to pour the gels, but, of course, you couldn't slice the cellulose acetate and you couldn't therefore compare one enzyme with another.

Craig: I always felt we were slightly inferior beings when we went to visit the Galton labs and Harry said, 'You've done that on cellulose acetate?' The starch gels were much better at the Galton, I think.

Bodmer: We did actually collaborate. You were co-authors on many of our papers because of your starch gel electrophoresis skills.[92] Just a couple of things on the points that Veronica made: by doing the enzyme activity on the Ouchterlony plates, you got a measure of specificity so even if your anti-serum had a mixture of different things, you could see whether or not you got a band that was human.

van Heyningen: Yes, in the Ouchterlony plates I also got spurs from the mouse because there was cross reaction so it was a polyclonal serum and it had components, which were specific to the human and components that were shared with mouse.

Bodmer: Another point, if I might make it, on the question of mitochondrial DNA and the hybrids, was actually work that we had done earlier with David Clayton at Stanford, which he wanted to publish on his own and we managed to stop him.[93] And that was an interesting story because what happened was you lost the human mitochondrial DNA if you didn't have enough human chromosomes in there. So, in other words, there was a human/mouse incompatibility in the maintenance of the mitochondria if you only had a predominantly mouse protein component for the mitochondria.

Craig: This is what we followed up in Oxford. It was actually extremely difficult to find any human mitochondria in any normal type hybrid; you had to have a hybrid that reverse-segregated. In other words, it had a complete set of human chromosomes, which is an interesting thing to do with retention of mitochondria and the interactions between the mitochondria and human genome.[94]

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[92] The last three authors of van Heyningen *et al.* (1975b) were from the Galton Lab: Sue Povey, S E Gardiner and David (Hoppy) Hopkinson.

[93] Clayton *et al.* (1971).

[94] Professor Ian Craig wrote, 'This work eventually led to our isolation of mitochondrially encoded chloramphenicol resistant cell lines with Lawrence Siegel.' Note on draft transcript, 14 August 2014.

Figure 10: Professor Bert Bakker

Professor Bert Bakker: I entered the lab of Peter Pearson in 1974, so that's around the time of the meeting in Rotterdam.[95] I didn't go to the Rotterdam meeting because I was just a junior technician in the lab. But at that time Meera Khan in the lab was running all these starch gels and later also the cellulose acetate for the somatic cell hybrids that were made together with the people in Rotterdam – Dirk Bootsma and Andries Westerveld and all these people there.[96] They used patients carrying chromosomal translocations to prepare somatic cell hybrids, to map different pieces of a chromosome, parts of chromosome 1, parts of chromosome 17; just to segregate it out. One other thing that has not been mentioned yet, is the analysis of the chromosomes – staining techniques for chromosomes to distinguish between the mouse and the human chromosomes. For example, G11 staining, all very new, and heterochromatin staining, the latter described by Martin

[95] Dr Peter Pearson was Head of the Human Genetics Department at Leiden University (1972–1989). He is now Co-director of the National Institute for Stem Cell Research in Genetic Diseases, São Paulo, Brazil.

[96] At the time of the HGM2 workshop, Professor Meera Khan (d. 1998) worked at the Sylvius laboratory in the Department of Human Genetics, University of Leiden; Dirk Bootsma worked at the Department of Cell Biology and Genetics, Erasmus University, Rotterdam, as did Andries Westerveld. Bootsma was a Conference Scientific Editor, Khan and Westerveld were Assistant Editors of the *Human Gene Mapping 2* publication; see Bergsma *et al.* (1975). For Andries Westerveld see also Appendix 2.

Figure 11: Professor Ellen Solomon

Bobrow *et al.* in a *Nature* paper.[97] These techniques were very important at that time because they helped a lot. I tried to do the staining, of course, I got the paper, and Peter said, 'Do the staining.' I looked through the microscope and I couldn't see a difference. Then Peter came and he looked through the microscope and he said, 'Oh, beautiful! Oh look!' I couldn't see it. It appeared I was colour blind. [Laughter] So at that he said, 'Okay' and he took a kind of spectrum filter, he put on the light source and shifted a little bit and then I saw it. The difference between the human and the mouse chromosomes was very clear. And at that time we could just use all the different hybrids. There were many hybrids selected against TK (thymidine kinase) and we used them to segregate out all these chromosomes.

Professor Ellen Solomon: I was just saying, I think we used the selection of the X chromosome, the *HPRT*, which from a patient was fused to chromosome 15 and it was the first X autosomal mapping because we could select the X and then mapped a whole number of genes to 15 including beta 2 microglobulin, which was on chromosome 15 and not in the HLA region on chromosome 6.[98]

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[97] See Friend, Chen and Ruddle (1976); Bobrow, Madan and Pearson (1972). Professor Sir Walter Bodmer commented: '[Heterochromatin staining] was actually done in the Bodmer laboratory in Oxford.' Note on draft transcript, 26 May 2014.

[98] Solomon *et al.* (1976) and Goodfellow *et al.* (1975).

Bodmer: Yes, and just to add, that was the reason we started doing hybrids with lymphocytes, with peripheral blood lymphocytes so you could take lymphocytes from anyone who had such changes and put them into a hybrid and you didn't have to have a cell line.[99] That was, I think, an important part of why the somatic cell genetics became so useful.

Bakker: I want to go back a little bit to the family studies. When I came in the lab, my blood was taken and chromosomes were made and these were lying on Peter's [Pearson's] desk. Then Kamlesh Madan, a cytogeneticist from the Free University of Amsterdam came in, and she looked at the chromosomes, and said, 'Hey, there's a polymorphism on chromosome 6 centromere'. It turned out that I seemed to have two different centromeres of chromosome 6. Kamlesh wanted to confirm segregation of these variants in a pedigree. So not only was I bled again but also the whole family. So at a birthday party, someone came and blood was taken. The polymorphisms segregated nicely in the family as was expected. *GLO* was typed, HLA was typed, and *PGM3* was typed. Within my family we could order those loci in the region and the orientation of the HLA locus relative to the centromere of chromosome 6, place *GLO* between the centromere and HLA, and put *PGM3* outside this linkage unit, probably on the q arm, where it later turned out to be. That was one of the first papers where you needed information from the somatic cell hybrid data, such as some gene locations, a chromosome polymorphism, and segregation from the family analysis to put it all in place.[100] I think that was a nice, early mapping effort.

Harper: We're coming on right now to cytogenetic markers, but before we leave the early protein marker area, I'd just like to again emphasize the role of the Copenhagen lab, which I really do think was very great indeed. I interviewed both Jan Mohr and Hans Eiberg, and Hans was Jan's right-hand person absolutely, one of these people with green fingers who could essentially get any technique to work.[101] But I am amazed how much, as Sue was saying, they managed to do with protein markers, which many of the DNA folk rather forgot later on. For instance, cystic fibrosis was first mapped using paraoxonase.[102] It's important not to forget this very considerable role. The other thing to bear in mind all the time

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[99] See note 37.

[100] Bakker *et al.* (1979).

[101] See notes 19 and 27 for Jan Mohr. For the Hans Eiberg interview, see http://www.genmedhist.info/interviews/eiberg-interview (visited 8 October 2014).

[102] Eiberg *et al.* (1985); Schmiegelow *et al.* (1986). See also Christie and Tansey (eds) (2004).

is the role that diseases played as markers, Mendelian diseases. Because really, in the early years, they were some of the chief markers and large segregating families could give a lot of information.[103] Again, this is something that I think gets downplayed, that if one looks at the evolution of the human gene map, it's very patchy and there tend to be islands focused around important diseases like cystic fibrosis, Huntington's disease, or myotonic dystrophy or a lot of others, quite largely because that was what the work was funded for.[104] There were quite extensive areas that were mapped first with early markers and then later on very intensively with DNA. And all along this whole area of work carried a big clinical contribution. If you got that wrong, and people's statuses were misassigned or they were misdiagnosed, as happened with some key individuals supposed to have Huntington's disease, that could really screw up the work completely and send people off in the wrong direction.

Now, cytogenetic markers: Malcolm, anything you want to put in at this point, thinking in terms of the early workshop years?

Ferguson-Smith: Yes, of course, the first one was the Duffy blood group locus on chromosome 1, centromeric polymorphism, and a lot of us were excited about this because many of us had seen polymorphisms on other chromosomes, mostly on the heterochromatic regions of chromosome 16, chromosome 9, and the acrocentric chromosomes.[105] I was encouraged immediately after the Donahue paper to get a grant application off because we had collected loads of these families with chromosome polymorphisms. This project turned out to be a complete waste of time, because we had only these few markers, the 23 blood group and serum protein markers and red cell enzyme, and after typing these over a period of three years in many large families, we didn't get a really decent lod score with any of them. This was because none of these happened to be close to any of the chromosome markers that we were using, as was confirmed later on. I don't know whether other people had similar bad luck at the time but, anyway, that was a very big lesson for us. Fortunately, we switched to using families that we had identified with chromosomal deletions and duplications,

[103] For a related discussion of familial genetic studies, specifically in hereditary non-polyposis colorectal cancer (HNPCC), see Jones and Tansey (eds) (2013), pages 33–8.

[104] For the mapping of cystic fibrosis to chromosome 7 see Tsui *et al.* (1985), and for the identification of the *CFTR* gene and the delta F508 mutation in 1989 see Tsui *et al.* (1989); for the mapping of Huntington's disease to chromosome 4 see Huntington's Disease Collaborative Research Group (1993), and for myotonic dystrophy's mapping to chromosome 19 see Shaw *et al.* (1985).

[105] Donahue *et al.* (1968); Robson *et al.* (1969).

together with our 23 markers, particularly the red cell enzyme polymorphisms in which we could also measure enzyme dosage. Our first assignment in 1973 was red cell acid phosphatase (ACP), in which gene dosage was halved in our patient heterozygous for a 2p deletion, who had failed to inherit an ACP allele from one of the parents.

Working with Jean de Grouchy, we assembled a group of families with chromosome 9 duplications and deletions, some due to translocation. This led to mapping a number of genes in 1976 at the end of the long arm of chromosome 9, including the ABO blood group Npa-1, and *AK1*.[106] We followed this with deletion mapping of *GOTs*, *NP*, *ABL*, *HP*, *GALT*, and *ADA*.[107] So this approach proved really useful. By using the same system and these few polymorphisms and chromosome aberrations, it was possible to exclude from a lot of the genome regions which could not contain these loci. John Edwards was helpful to us in trying to work the best way of presenting these data in a joint publication at the Rotterdam Conference.[108] For a number of the human genome workshops, David Aitken and I put in our exclusion map based on these deleted regions of the chromosome, which proved helpful in narrowing down the MNS blood group locus, for example.[109] I think that was quite useful, although pretty low key and didn't require very much imagination.

Povey: I was just going to say that Peter Cook also was very interested in what he called 'desperation mapping' [laughter], which was excluding things.[110] One of the things that was quite funny was, when we were finding that *ABO* must be on chromosome 9 – because *AK1* was clearly on chromosome 9, which was a bit controversial – some of these reports have ironed out the differences between the workers at the meeting and what turned out to be in the report. Anyway, at

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106 Ferguson-Smith *et al.* (1976).

107 For GOT_s, see Aitken and Ferguson-Smith (1978a); for *NP*, see Ferguson-Smith and Aitken (1978b); for *HP*, see Ferguson-Smith and Aitken (1978); for *GALT*, see Aitken and Ferguson-Smith (1979); for *ADA*, see Aitken and Ferguson-Smith (1978c).

108 Ferguson-Smith *et al.* (1975).

109 See, for example, Aitken and Ferguson-Smith (1978d). David Aitken was Senior Scientist responsible for biochemical genetics in the Department of Medical Genetics (Malcolm Ferguson-Smith's department), Royal Hospital for Sick Children in Glasgow.

110 Professor Sue Povey explained to Professor Peter Harper in an interview, '… Peter Cook had very much developed what he called desperation mapping from the families, which was that although it was almost hopeless to try and put things anywhere, you could exclude them from large bits of the chromosome …'; http://www.genmedhist.info/interviews/Povey%20Sue (3 February 2015).

Figure 12: Professor Maj Hultén

the time when we said from hybrids that *ABO* was on chromosome 9, Peter said, 'I've excluded it absolutely from everywhere except the real tip of chromosome 9. Most of chromosome 9 has a lod score of -50 and it can't be there.' But it was, right on the tip. He did say that he did not get a positive lod score anywhere but you can't actually exclude it from the tip. So some was done by linkage analysis but in this case the hybrids and chromosome deletions were conclusive.

Ferguson-Smith: There is a great deal of recombination at the end of chromosomes!

Harper: Maj, I wonder if you'd like to say a bit about meiotic work because I think it's part of the gene mapping story and links with the physical map?

Professor Maj Hultén: When we did the meiotic work we didn't have a clue about the mapping situation and it's only other people who have alluded to the type of work that we did. I was interested in the recombination patterns *per se*.

Ferguson-Smith: You do not do justice to your contribution. You did almost all the work at the time [in the late 1970s] on the location and frequency of chiasmata.[111]

Harper: Yes, I think you underestimate what you did, Maj, honestly because most of the molecular folk didn't really register what meiosis was, or things like

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[111] See, for example, Morton *et al.* (1977) and a paper presented at HGM4, Hultén *et al.* (1978).

the sex differences in recombination, or the distances along the chromosome. I think the fact that your, and similar, work was going along at the same time, well it helped the later work retain a physical map alongside the linkage and then later the sequencing data.

Hultén: Well I'm glad to hear that, but from my own point of view it was pure curiosity.

Ferguson-Smith: Yes, but, come on Maj, your lab and my lab were the only labs that were actually counting the number of chiasmata in humans and where they were.[112]

Hultén: Did you not do it from curiosity then?

Ferguson-Smith: Of course. We stopped this work after Brenda Page departed. Brenda Page, who was much engaged in this, was tragically killed before much of the work was published.[113]

Hultén: Yes.

Ferguson-Smith: So after that our meiotic work stopped, but you carried on using all the new immunofluorescence technologies for more precisely identifying recombination sites, etc.

Hultén: But still it didn't map a single polymorphism [laughs].[114]

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[112] See, for example, Ferguson-Smith and Page (1973).

[113] The cytogeneticist Brenda Page was murdered in her home on 14 July 1978, in Aberdeen. Her killer was not identified nor brought to justice, ironically it seems because of the limitations of DNA analysis at that time. For an article about her case, see http://www.scotsman.com/news/getting-away-with-murder-1-509980 (visited 13 October 2014). Professor Malcolm Ferguson-Smith wrote: 'Brenda was my PhD student in Glasgow working with me on human meiosis from patients with chromosome rearrangements. She wrote an excellent thesis and became an outstanding scientist.' Note on draft transcript, 8 February 2015. See, for example, Page (1973).

[114] Professor Maj Hultén wrote, 'I am sorry not to have explained why we have not been able to map any genes *per se*, but our research has only provided the framework for the gene mapping. One of my main research interests has concerned the behaviour of meiotic chromosomes, as seen by microscopy of human fetal ovarian biopsies and testicular biopsies from adult men. At first meiotic prophase the homologous chromosomes pair and crossing over/recombination takes place between parental chromatids, eventually as the homologues contract and separate, only held together at the points of crossing-over/recombination, now identifiable as chiasmata. The chiasmata delineate the borders of the loops, which I have called linkage loops, that can be readily identified and measured. This research has thus not been able to identify the positions of any genes *per se,* but it has provided a framework for the gene mapping, i.e. by giving information on the areas of linkage along the individual chromosomes.' Email to Ms Emma Jones, 1 October 2014.

Harper: We've reached a point on the programme where we get to DNA, and DNA polymorphisms, but before we go on to that, anything more on other kinds of early markers involved in the workshops?

van Heyningen: There were also quite a lot of cell surface markers, you know, when people started making monoclonal antibodies. I suppose it was a bit later, yes, 1980.

Bodmer: Well I guess we did the first work really with monoclonal antibodies and hybrids. They didn't come along until the end of the 1970s.

van Heyningen: Yes, you did. 1980.

Bodmer: No, late 1970s. The first paper we did on W6/32, this was the first pan HLA-ABC monoclonal antibody published with César Milstein and Alan Williams in 1978.[115] Then I also remember Francis Brodsky's whole PhD thesis and the detailed thesis was on monoclonal antibodies to HLA: that was in the late 1970s.[116] So that came then, but it coincided with the discovery of restriction fragment length polymorphisms and using restriction fragment differences to assign sequences and with Southern blotting.[117]

Solomon: Just to add to that conversation, in addition to membrane proteins, the structural proteins with non-enzymatic proteins were devilishly difficult largely because they were highly interspecies conservations, very hard. We made possibly the first structural gene mapping of collagen, which is very highly conserved, and we had to make antibodies too; I think we did chicken and sheep and goat and rabbit and mice, and whatever, until we got something that would distinguish them, so moving on to DNA was a huge relief.[118]

Povey: If I can just say a final word on an avenue that was probably not a very good one to pursue that we did with Mary Weiss.[119] We made hybrids with rat hepatoma cells to try and activate the liver-specific enzymes and we only ever mapped one enzyme successfully; that was *GPT* which did map to chromosome 8. Of course, that was entirely overtaken by DNA cloning of these genes.

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[115] Barnstable *et al.* (1978).

[116] Brodsky (1979).

[117] For Southern blotting see note 89.

[118] See Weiss *et al.* (1982).

[119] Jeremiah *et al.* (1984). See also note 36.

Bodmer: Maybe one should mention the phenomenon of extinction here. It was a strange phenomenon that was absolutely key, of course, to the discovery of monoclonal antibodies because the phenomenon of extinction was that you genuinely didn't make some of the cell-specific products in hybrids, so when we first made some hybrids with Mel Cohn, between trying to look for immunoglobulin in hybrids with mouse cells, you found you didn't see the immunoglobulin.[120] One could already predict at that time that the only way you'd get the tissue-specific products was actually to use a B cell and that's what, eventually, (Georges) Köhler and César Milstein did.[121] It was actually quite an obvious idea at the time but that phenomenon of extinction is still not explained. It's a very interesting phenomenon: what happens, what are the mechanisms that prevent you from being able to express a tissue-specific product in a hybrid between cells of different tissue types?

Craig: Just one more thing on structural proteins, since structural proteins are kind of a minority topic in this area. A lot of work went into solubilizing mitochondrial proteins, which were under the control of mitochondrial DNA and looking at how they were different in various different organisms, particularly humans and mice, and Alec Jeffreys did a lot of work on that which was interesting at the time.[122]

Harper: I'm going to suggest that for DNA polymorphisms, where it perhaps started, I think I'm right in saying that in terms of the workshops that it was the Oslo workshop where they first came in, or at least when people in the gene mapping community rather suddenly became aware that this was something rather new but it was going to be a major avalanche. The thing that I remember that it brought in, quite apart from the new techniques and the new information, was a completely different community of people, most of whom had never been involved in gene mapping before, and some of them had never really heard of it very much. I think it's little short of amazing that some kind of, not merger, but a sort of integration occurred and that the two areas didn't just stay totally apart because they were really very different indeed. It's actually to the credit of the original gene mapping community that they were pretty tolerant of these brash

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[120] This research was unpublished. Note on draft transcript from Professor Sir Walter Bodmer, 8 February 2015.

[121] Georges Köhler (1946–1995) and César Milstein (1927–2002) shared the Nobel Prize in Physiology or Medicine in1984 with Niels K Jerne; see Köhler and Milstein (1975). See also Tansey and Catterall (eds) (1997).

[122] Jeffreys and Craig (1976).

incomers who really didn't know anything much about genetics, but I think it's also to the credit of the molecular folk that they soon realised what they didn't know and sat down and learnt. Now Bert, in Leiden you saw and were responsible for some of the first X chromosome DNA polymorphisms coming in, and again I wish Peter Pearson was here too.[123] Peter is very elusive, quite apart from being in Brazil, but it would have been nice to have him as well.

Bakker: He should have been here.

Harper: You'll have to deputize for him. Tell us a little bit about this.

Bakker: I think it was in 1978 when the paper of Kan and Dozy came out with a polymorphism in the beta globin gene.[124] At that time Peter said, 'We should have more of these types of restriction site length polymorphisms on the map', and he came across another paper from 1956, which gave him a prophecy on using markers on the genome that were highly polymorphic, and which could be used like the ABO blood group to follow genes on the genome.[125]

Bodmer: That idea was older than the 1950s.

Bakker: Earlier? Anyway, it was the thing that Peter showed me at that time, and he said, 'We should use these RFLPs, these restriction fragment length polymorphisms, to put them on the map.' But there were no probes, there was nothing. So I said, 'I can try to make some.' So I got from the hospital a placenta, isolated DNA from that, digested some DNA with EcoRI, a restriction enzyme, ran the digested DNA through the sucrose gradient, took fractions of 1kb, and 2kb, ligated these fragments into plasmid – we used a vector called pAT153, transfected the plasmids into bacteria, had some plates with bacteria, and each of these bacteria colonies had one plasmid carrying a probe, a specific piece of human DNA. I selected then the unique ones by hybridizing with total human DNA and some probes turned out not to be hybridizing so we used these bacterial clones to grow them up, isolated the plasmid, and put them on Southern blots to see if they were single, unique EcoRI fragments. In a single experiment, which I could not do in Leiden, I had to go to the MRC's National

[123] See note 95.

[124] Kan and Dozy (1978).

[125] Professor Bert Bakker selected this quotation from Edwards (1956): 'It should eventually be possible for most prospective parents with inherited disorders transmitted by single genes to obtain a fairly precise estimate of the likelihood of their coming child being affected in the twelfth week of pregnancy…' Note on draft transcript, 4 March 2015.

Institute for Medical Research in Mill Hill, London, to the lab of Dick Flavell because there we could put the plasmids in bacteria and grow them.[126] I went back to characterize them in Leiden, and a few weeks later again I went back to London to grow a larger batch of these clones. In total, I had 216 of these probes, of which 23 turned out to be unique, and I hybridized them to different DNA samples digested with different restriction enzymes, ran Southern blots, and found out that many of these were polymorphic. This was published at the Oslo [HGM6] meeting. We had 23 probes showing polymorphisms throughout the human genome.[127] Thirty per cent of all DNA polymorphic markers were known at that time, and these were called, because the nomenclature was then started, D1S2, D2S1; these probes were the early type of polymorphic probes. One of these probes on the X chromosome was L1.28, or DXS7, for Duchenne muscular dystrophy, and in the group in London at that time, where Kay Davies worked in Bob Williamson's lab, and, together with Rob Elles, had cloned the RC8, or DXS9, and that was located also on the X chromosome.[128] These two were flanking the Duchenne locus and therefore we could use them for carrier detection. From that time on, many more probes had to be cloned to fill the gap, to gain informativity, so Maarten Hofker in our lab started phage lambda cloning of X chromosome fragments to clone more probes and the number of probes expanded.[129]

Harper: How about the autosomal probes that you generated?

Bakker: Yes, there were some autosomal probes. There was one located on chromosome 2. Peter (Pearson) asked me to use *in situ* hybridization for fine mapping, because in 1977/1978 I also went to the lab of Ken Jones in Edinburgh to learn *in situ* hybridization techniques.[130] I used mouse satellite DNA isolated from a band from a caesium gradient and hybridized that back to mouse

[126] At an earlier meeting on clinical molecular genetics, Professor Bakker explained that regulations over DNA cloning in the Netherlands prevented certain aspects of his research, hence the need to use MRC facilities; see Jones and Tansey (eds) (2014), page 10, note 20.

[127] Pearson, Bakker and Flavell (1982).

[128] Davies *et al.* (1983). At St Mary's Hospital Medical School, University of London, Kay Davies was Cystic Fibrosis Research Fellow (1980–1982), and Bob Williamson was Professor of Molecular Genetics and Biochemistry (1976–1995); see full biographies and further details of this research in Jones and Tansey (eds) (2014), pages 33–5, 101–2, and 111–12.

[129] See, for example, Hofker *et al.* (1985).

[130] See, for example, Jones (1970).

chromosomes and only saw the centromeres and these types of things.[131] So the technique worked, but for unique probes it did not work so well. So in 1981 we tried it with the chromosome 2 probe we had. I labelled that L2.30 probe with tritium, hybridized it to human chromosomes. I knew its chromosome assignment from the somatic cell hybrids because we localized all these probes by Southern blotting on DNA of somatic cell hybrids available in the lab of Meera Khan next door to us.[132] So I looked at *in situ* hybridization slides. They had to have a three-week exposure of this tritium hybridized cells, and after three weeks I developed them, there was a lot of background, and started counting. I knew it was on chromosome 2 so I counted a lot of silver grains on the chromosome 2s in different cells, only the chromosome 2s, and it came out that there were significantly more grains on the tip of the p-arm of chromosome 2. So I said to Peter, 'It's on the tip of chromosome 2', and he ran to the microscope, looked in the microscope and started counting. Scrolling and scrolling and he said, 'I don't know, I don't know'. So it was put aside and *in situ* hybridization was not used; we used the somatic cell hybrids' DNA, with Southern blotting and also translocation hybrids to localize our probes, until, from the lab of Tobias Gedde-Dahl, a request came. At one of the HGM meetings Peter met him and was told that red cell acid phosphatase was on chromosome 2 and Tobias now had evidence that it was on the tip of chromosome 2.[133] Then Peter said, 'Okay, maybe we can look at linkage with this marker of ours.' Our L2.30 marker on chromosome 2 seemed closely linked and, by *in situ* hybridization we knew that it was localized also on the very tip of the p-arm of X, so at that time we could localize both of them on the tip of chromosome 2p and my *in situ* data was also published in the same article of Lothe and Tobias Gedde-Dahl.[134] That was in 1986, so five years after I did the experiment.

Ferguson-Smith: It was mapped first by us in 1973 at exactly the same spot.[135]

Bakker: Oh sorry, but this was linkage and *in situ* hybridization, localizing both *ACP1* and D2S1 more precisely to the tip of 2p.

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[131] Singh, Purdom and Jones (1977).

[132] For Meera Khan, see note 96.

[133] HGM3, Baltimore, 1975. Bergsma (ed.) (1976).

[134] Lothe *et al.* (1986).

[135] Ferguson-Smith *et al.* (1973).

Bodmer: Some of the radiation hybrids, that was one thing that Henry Harris did. He had a student called Steven Goss who, using X-rays, produced the broken chromosomes and we did one little paper with him in one of the workshops that showed you could use those for regional mapping.[136] Then Peter Goodfellow did a lot of mapping. That must have been in the late 1970s because it was while we were still in Oxford. So 1978/1979, something like that probably. Then Peter made a lot of radiation hybrids. That was much later; that would have been in the 1980s.[137]

Bakker: The sorting of chromosomes was also important to make sorted libraries and have a library of the X chromosome or a library of chromosome 21.

Harper: I should say, it's a shame that Kay Davies can't be here because of the combination of the sorting with the chromosome-specific libraries.[138] The sorting was done in Glasgow, by Bryan Young's lab.[139]

Ferguson-Smith: Bryan Young, and Rob Krumlauf, who was with him at the time, did the early work. Their first venture used an MRC cell line that had several copies of the X chromosome.[140] Kay Davies used this X library to isolate X markers for Duchenne muscular dystrophy.[141]

Professor Sue Malcolm: That was because Bryan Young had been taken on at the Beatson Institute as a physicist to help with all problems around physics and he then very naturally got into chromosome sorting.

Harper: Sue, nobody here apart from yourself has been in Bob Williamson's lab – I think I'm right? In that case, tell us a bit about this beginning of DNA polymorphisms as seen from the perspective of that lab.

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[136] Buck, Goss and Bodmer (1976).

[137] For a useful review, see Walter and Goodfellow (1993).

[138] Professor Dame Kay Davies (b. 1951), now Director of the MRC Functional Genomics Unit, Oxford and Deputy Chairman of the Wellcome Trust, was at St Mary's Hospital Medical School, London (1980–1982), Senior Research Fellow at the MRC from 1982, joining Oxford's Institute of Molecular Medicine in 1989. See also note 128.

[139] Bryan Young was a Research Fellow at the Beatson Institute, Glasgow, from 1972 to 1984.

[140] Young *et al.* (1983).

[141] Davies *et al.* (1981).

Figure 13: Professor Sue Malcolm

Malcolm: My role was in 1975, I was the postdoc go-between between Bob Williamson and Malcolm Ferguson-Smith's labs with a project to set up *in situ* hybridization for gene mapping, which I hadn't quite appreciated at that time was probably a little bit more challenging than I'd realised. So, to begin with, we were doing repetitive DNA 5S ribosomal gene locus and we were all in Glasgow, and then half of us moved and I shuttled between the two. The little breakthrough then was we were looking for ribosomal probes and Don Brown from the Carnegie in Baltimore came through one day and we had a tea break, and he said, 'Why aren't you using recombinant DNA?' There was a kind of shocked silence because you know all this stuff had happened in the States about recombinant DNA, and we thought it was so terribly daring so we diverted into setting up the right sort of committee to do it and getting the permissions and everything.[142] And from then on we used plasmids.

As it turned out, when we got it to work, the signal from the plasmid vector was what gave us enough signal to be able to do the experiments. So we then did that along with translocations, which Malcolm had and he always stressed to Bob, and to a lesser extent myself, that we didn't really appreciate just the sheer importance of gene mapping – we were always trying to look for medical connotations and so on. Then we tried to use cloned genomic probes and we realised straight away there were Alu repeats all over the genome and that was

[142] See, for example, Berg *et al.* (1974). See also Berg and Singer (1995).

a little paper.[143] Then, as an aside, because it was inevitable to do, we cloned globin in order to have the probes to do this, but obviously other people were interested as well. I went to Zurich to Charles Weissmann's lab but all the RNA that got sent was in a little tube that got smashed in the post by somebody obviously pushing it through to try and frank it. So that didn't happen until we got back to London. Then my role was to carry on with the *in situ* bit, for which the real breakthrough was the immunoglobulin heavy chain on chromosome 2 because it was the first gene where you didn't already know more or less where it was.[144] Of course, we hit gold dust because it was next to c-*myc* and then we showed that you could have translocations on either side of c-*myc*, all by the same techniques.[145] That was tremendous. But then we all went – I know this has been mentioned already in one of the other Witness Seminars – to this very influential workshop in Crete where we all heard Y W Kan give a talk.[146] That was the first time we'd heard it anyway. It was a thalassaemia workshop and from then on, from that day on, we were just saying, 'Well, we need these probes for polymorphisms'. But Bob was very, I'm sure he still is, focused on the medical side and not the gene mapping for its own sake.[147] He was really looking, always, for a practical application.

Ferguson-Smith: But the first ones that you mapped *in situ* were the globin genes because we knew which chromosomes the globin genes were on from the solution mapping that has already been mentioned. However, their location on the chromosomes was not known. But you were able to show, doing those wretched silver grain counts, that beta globin mapped to the short arm of chromosome 11 and alpha globin to the short arm of chromosome 16.[148]

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[143] Malcolm, Barton and Ferguson-Smith (1981).

[144] Malcolm *et al.* (1982).

[145] Professor Veronica van Heyningen commented, 'The IgH heavy chains map to chromosome 14; kappa light chains to 2 and lambda light chains to chromosome 22. c-*MYC* (or *MYC*) is on chromosome 8. Translocations in Burkitt Lymphoma move *MYC* to one or other Ig chain vicinity which then drive expression of the oncogene in these lymphoma cells. The chromosome 8 breakpoint can be either side of *MYC*.' Note on draft transcript, 1 September 2014.

[146] For a discussion of the Crete workshop, see Jones and Tansey (eds) (2014), pages 20–1, and a photograph of 'The Molecular Biology of Thalassaemia' conference delegates, with key, on pages 88–9.

[147] See note 128.

[148] Malcolm, Barton and Ferguson-Smith (1981); Barton *et al.* (1982).

Bakker: And was that before the paper of Harper and Saunders where they put insulin on 11p?[149]

Ferguson-Smith: That's correct. Exactly. The beta globin result was published the same year.

Bakker: Harper and Saunders showed for me that *in situ* hybridization for a single copy probe was possible; that's why I pursued it that year but it took longer.[150] [Laughs]

Harper: Sue, were you in Bob's lab at the time of his transition from working on haemoglobin to other diseases?

Malcolm: Yes, moving from Glasgow to London.

Harper: This was something I saw from the outside, or semi-outside, with our involvement with the diseases but how did that transition seem from the point of view of you as part of the lab?

Malcolm: Well, perfectly logical I think. I mean, Bob had no medical background at all but he'd got into the thalassaemias because he had a very good working relationship with David Weatherall.[151] I mean extremely close, and the groups met and John Old would travel backwards and forwards.[152] And so then, that was the way he realised the medical potential of what he was doing and then started to apply it to other things and cystic fibrosis was the main one and, of course, he did not find the genes but his contribution was to explain to patients, GPs, and respiratory physicians why they needed to collect samples and families. He really got people involved in it. From then on he saw how to conduct such a study in terms of engaging with families, and that became very influential.

Harper: Veronica, do you want to say something about cystic fibrosis?

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[149] Harper, Ullrich and Saunders (1981).

[150] See note 134.

[151] Professor Sir David Weatherall (b. 1933) was Nuffield Professor of Clinical Medicine at the University of Oxford (1974–1992), where he founded the Institute of Molecular Medicine. For his contributions to thalassaemia research, see, for example, Christie and Tansey (eds) (2003), pages 11–14, 32, and a biography in Jones and Tansey (eds) (2014), page 111.

[152] Dr John Old was a postdoctoral research scientist in Professor Sir David Weatherall's laboratory in Oxford from 1974 to 1981.

van Heyningen: I went to a meeting in New York in 1982, which was called by the Cystic Fibrosis Foundation; you know they supported it. Bob was definitely there, and I remember encouraging everybody to make lymphoblastoid cell lines from the patients because then they would have a permanent source of DNA, and all sorts of other possibilities, through having the cells. I think that started being much more routine around that time, especially for disease samples where you might not be able to go back to the same family. We were in New York when the Falklands War broke out.[153]

Malcolm: I don't think Bob ever cared which chromosome cystic fibrosis was on; he just wanted a linkage to a disorder. His research was really focused in that respect whereas Malcolm (Ferguson-Smith) would keep saying, 'We're interested in the map'.

Ferguson-Smith: But I'm a medic and we were also interested in translating what we'd learnt into patient care and this is what we did.

Bodmer: But the idea that you could actually find the gene from its position, it was certainly something I suggested in 1980 and was a strong stimulus for the mapping and one of the major rationales for it as Victor McKusick always said as well.[154] And I remember trying to tell Bob Williamson, explain linkage disequilibrium to him to say how he might be able to use that to get a bit closer to the gene. And in the end, in fact, it was that approach, but not by him, that led Lap-Chee Tsui to find the gene.[155]

Povey: In the 1970s, people, I anyway, didn't think we'd ever find a gene by where it was. I think that you (Walter) introduced that in 1980, the reality of it. But I remember Peter Cook saying to me, 'Well, the challenge is, it's like a great big crossword puzzle to which there's only one solution', and it kept him up all night, definitely, with enthusiasm. That was what drove him.

Bodmer: Just a historical comment there because I got very involved as a graduate student, or just after, in studying the interaction between linkage and selection and the whole phenomenon of linkage disequilibrium. And I remember

[153] The Falklands War between Britain and Argentina, concerning the disputed territory of the Falklands Islands broke out in April 1982. See, for example, Commons (1982).

[154] See Bodmer (1981), in particular page 675.

[155] See Tsui *et al.* (1985); Tsui *et al.* (1989).

Figure 14: Professor Tim Bishop

discussing this with (R A) Fisher who was my supervisor and, basically, his view, which was interesting at the time, was that there would never be a high enough density of polymorphic genes for linkage disequilibrium to matter. He realised it would matter if you had enough polymorphisms but at that time researchers only had the blood groups and they thought that polymorphisms would be far and few between.

Professor Tim Bishop: I went to the University of Utah, Salt Lake City, in 1977 as a young postdoc. In 1978, within the biology department, we would take our PhD students and early postdocs up to Snowbird for a two-day meeting.[156] The idea was that then they had the opportunity to both present work themselves but also to bring in others. They brought in some great names to speak to them. They were forced to stay up in the mountains for two days; it's tough, you know, but someone's got to do it. Anyway, I went to Utah to use the Mormon genealogy to try and work out ways to identify genes predisposing to cancer. So at this meeting, there was Mark Skolnick based in Utah, Ron Davis, Ray

[156] Snowbird is a ski resort near Alta, Utah; http://www.snowbird.com/about/history/ (visited 13 November 2014).

White, and David Botstein all came that evening.[157] One of our students, I can't remember who it was, gave a talk about hereditary breast cancer because we were actually trying to get funding at that stage to do linkage mapping for breast cancer. In fact, we got our first award in 1979 to do that. Ray White spoke about recombinant DNA technology work, and so the question was: How could you use this new technology to try and find genes for breast cancer? The next day we discussed it further and subsequently described approaches to construct a linkage map following Kan and Dozy's initial observation for human beta globin.[158]

Bodmer: We said it in one paragraph a little before in the *Lancet* and they reproduced Mendelian genetics in a long paper in the *American Journal of Human Genetics* in 1980.[159]

Bishop: Yes, but we looked at the issues about actually constructing the map, and using that map. Actually, the estimates we came up with at that stage, that you'd require something like 400 markers to map the genome actually turned out to be reasonably close.

Bodmer: I think we'd said 300 in our note in the *Lancet* and we had a good idea of how to do linkage; you didn't have to tell people how to do it again. I remember at the 1986 Cold Spring Harbor symposium, I've forgotten who it was, started the symposium by explaining Mendelian genetics to people.[160]

Bakker: There was this group in Utah: Mark Skolnick; Ray White; and the students probably at that time, David Barker, Web Cavanee, Mireille Schäfer, they were starting to make clones.[161] They also found some polymorphic markers

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[157] Mark Skolnick was based at the University of Utah's biophysics department from 1973 (later called the Department of Medical Informatics), where he developed familial genetics databases; Raymond White was based at the Massachusetts Institute of Technology in 1978, and, from 1980, at the Department of Human Genetics in the University of Utah, of which he became Professor and Co-chair; see http://content.lib.utah.edu:81/cgi-bin/showfile.exe?CISOROOT=/uupahsc&CISOPTR=2928&filename=2892.pdf; Ronald Davis was Assistant Professor in Stanford University's Department of Biochemistry from 1972, later becoming Professor, http://gruber.yale.edu/genetics/ronald-davis; David Botstein was based at the Massachusetts Institute of Technology; see his remarks on the 1978 Alta meeting in Gitschier (2006) (all websites visited 28 January 2015). See also Gesteland and Leppert (1992).

[158] See note 124.

[159] See Solomon and Bodmer (1979), final paragraph, and Botstein *et al.* (1980).

[160] Lander and Botstein (1986).

[161] White *et al.* (1982).

and they were publishing that at a human genetics meeting in Jerusalem where Peter Pearson also went with the result of our probes in 1981, which was published from the Oslo meeting but he also presented an abstract in Jerusalem.[162] He discussed with these people from Utah and said, 'We should start to make a course for preparing these RFLPs and training people in clinical genetics to use RFLPs for linkage and show how to put them on the map.' So we had this course in 1982 in our lab in Leiden, organized by Peter Pearson and myself, and we had as other teachers Ray White, Web Cavanee, David Barker, Mark Skolnick, and Mireille Schäfer.[163] There were 20 participants from all over Europe: Jan Mohr, Tobias Gedde-Dahl, Marianne Schwartz, and many others. They all were in this course and learnt how to prepare and use these probes. We also gave out the probes that we already made before for people to use and to start doing linkage for genetic mapping. So that was a very interesting collaboration between Utah and Leiden at that time.

Harper: Can I bring people back for a minute or two to the workshops because the character of the workshops was pretty radically changed by the advent of DNA polymorphisms, and the numbers of polymorphisms built up astronomically. I know this caused huge changes for the people involved in informatics and statistical analysis. Have people who were involved got any impressions in terms of the kind of general, not just the structure, but the atmosphere of those workshops, from the time of the Oslo meeting, in 1981, over the succeeding 10 years?

Solomon: They were always exciting and always fun. I think for the people who were very much hands-on with producing the next map, the workload became overwhelming. Possibly that's one reason why they stopped, you just could not manage it all in 24 hours a day, so it was very, very intensive.

Bodmer: The big change was the amount of data and therefore the systematic introduction of computing, and I know Chris Rawlings would have comments on that, which really started just about after that time. Although, initially, it was mainly just to use them as word processors; it was the development of the need to have your proper databases in an organized way that was pushed by the amount of data being produced at that time. That was before the sequencing.

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[162] Cavalli-Sforza *et al.* (1982); Berg (ed.) (1982).

[163] Details of the postgraduate course 'Restriction Fragment Length Polymorphisms and Human Genetics' at Leiden, July 1982, including a photograph of laboratory work, and a sample of the laboratory manual, are available in Jones and Tansey (eds) (2014); pages 11–13, 91–4.

Harper: This whole question of databases, at the beginning there really wasn't that much data in the first and second workshop but how did the beginning of the databases relate to the workshops? How did that come about?

Craig: To start off with, there were rather haphazard data collections on diskettes that were sent through the post, which you updated and sent back. I think the turning point was the introduction of 'Edit 9.5' at the interim meeting in Yale, in 1988. This was the first attempt to have a coordinated database, which was a progenitor basically of GDB (Genome Database), but this was at the interim meeting 9.5 before HGM10, which, again, was at Yale.[164] I think that was probably the main turning point from my recollection. That was 1989, it was quite late.

Bodmer: The HLA workshop in 1977, in Oxford, made a huge use of computers. Some of us were really quite used to the need for large-scale computing. That's what we introduced, Julia Bodmer and I, when we went to the ICRF in 1979.[165]

Craig: But I think GDB was the first really useful relational database as far as I can recollect and I think that we're touching on that afterwards.

Bakker: At that time you needed to have some very good computer people in the lab who understood linkage and who understood computers, and one of these guys was a clinical geneticist from Rotterdam, Lodewijk Sandkuijl, who did massive linkage work for the whole of the Netherlands.[166] He came to all the different groups and did all the linkage work and that was very handy.

Ferguson-Smith: One measure of the activity and place of RFLPs comes by looking at the number of assignments made at the various workshops. Suddenly, from 633 autosomal gene assignments in Helsinki (1985), you go up to 1,146 in New Haven four years later. At the time of New Haven, I've got a note here that 5,100 additional DNA markers had been assigned, so that's an incredible amount of data that can be used to build maps of every chromosome.

Bakker: Yes, all the VNTRs (variable number tandem repeats) came in and later all the STRs (short tandem repeats), yes.

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[164] See Ruddle and Kidd (1988).

[165] Lady Julia Bodmer (1934–2001) was a geneticist who collaborated with her husband Professor Sir Walter Bodmer in HLA research. Their archives are available at Oxford's Bodleian Library; http://blogs.bodleian.ox.ac.uk/savingoxfordmedicine/2014/05/12/the-bodmer-archive/ (visited 14 November 2014).

[166] See, for example, Freimer, Heutink and Wijmenga (2003).

van Heyningen: A very brief interjection: in 1979 we had a gene mapping meeting in Edinburgh and I very much remember Frank Ruddle, I think he was giving one of the plenary lectures, and he said, 'By the time I retire – and that was due to be in 2003 – all the genes will be known and mapped.'[167] And I thought he was being incredibly optimistic but, of course, he was right.

Craig: Just to recap on Edit 9.5, which was at the interim Yale meeting, it was largely Ken Kidd who was certainly behind setting the whole thing up in informatics.[168] It was not wonderful but it was the first real attempt to do that, and that was 1988.

Bodmer: If you look at this, I think it was in one of the workshop summaries by McKusick; I don't know if people can see that?[169] It's an exponential curve in assignments that starts taking off between 1982 and 1984. I think it was that that stimulated the real need to have a more systematic way of dealing with the data. The gene mappers were well behind a lot of other people who were using computing extensively, including the HLA community.

Solomon: Another way of relating this huge increase in data to the workshops was that, as somebody so nicely described – Ian I think – at the first one there was 'chromosome 1' and then 'all other autosomes', and I can't give you dates and times but it certainly came down to, there were committees for 1 to 3, and 4 to 6, and then there was a committee for each chromosome, and then larger and larger numbers of people on each chromosome, and ultimately it became a piece of DNA.

Harper: From the individual workshops, the number of committees, the list gets longer and longer, as seen in the reports. By the London workshop in 1991, there was indeed one for every chromosome, quite apart from mitochondrial, comparative neoplasia, and several other things too. Perhaps because I'm a clinician, one of the things that I think was quite a challenge was keeping the disease side linked with what you might call the more basic marker-related side, because it had soon reached a point where you didn't actually need the diseases any more to make the map but a large point of the whole exercise was in relation

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167 Frank Ruddle's plenary lecture was not published in the HGM5 publication, as explained by Evans (1979); see page 2.

168 See note 164.

169 See Figure 1, 'Growth of information on chromosome assignments' in McKusick (1991), which illustrates the steep rise in gene loci mapped between the early 1980s and 1990, page 13.

to the main diseases. I can well remember, I was on the clinical committee with Victor McKusick and Jean Frézal – and actually Jean is someone whom I think we shouldn't forget.[170] His GENATLAS was very good indeed apart from the fact that originally it was only in French.[171] Then he got it translated into English, but it was always rather overshadowed by Victor's OMIM.[172] GENATLAS was a big contribution, and I was very pleased that the clinical side always stayed in the map, and actually it was helpful for everyone that it did so because the diseases themselves turned up so many unusual molecular phenomena that without them it would have been a bit of a sterile thing if it hadn't had any diseases at all involved.

Bodmer: I'm just surprised you say that, Peter, since the emphasis was so much, as Ellen and I pointed out, and others did, on using the linkage to find genes for diseases.[173] At least there were a few people around who straddled that quite strongly who weren't even clinicians.

Harper: No, I don't think I did say that, Walter. What I was saying was the diseases were no longer necessary. Once we'd got abundant DNA polymorphisms, you didn't actually need the diseases.

Bodmer: You didn't need the diseases for mapping, you needed the mapping for the diseases.

Harper: Exactly. Absolutely.

Bakker: That was very important at the HGM9 workshop in Paris, in 1987, that all these different chromosome groups had to produce a map at the end of the workshop. So the leaders of these groups had a number of people assigned, mainly PhD students, and I was one of them, to collect information from all

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[170] Jean Frézal (1922–2007) was a French geneticist based at the Hôpital Necker, Paris, where he developed medical genetics research and clinical services. He also developed the GENATLAS database; see, for example, Professor Peter Harper's interview with him, freely available at http://www.genmedhist.info/interviews/Frezal (visited 17 December 2014). He participated in HGM1; see McKusick and Frézal (1974).

[171] GENATLAS was a database created for compiling the data from the chromosome committees' reports for HGM9 in 1987; see Frézal (1987).

[172] Online Mendelian Inheritance in Man (OMIM) is a database that was founded by Victor McKusick, at Johns Hopkins University, as a catalogue of Mendelian-inherited traits and disorders, first published in print as McKusick (1966). The database is now available as an online resource; see http://omim.org/about (visited 17 November 2014).

[173] See comments from Professors Sue Malcolm, Veronica van Heyningen, and Malcolm Ferguson-Smith on pages 42–6.

the posters. We were sent around to note the locations and the distances, and at the end we produced a map on paper. All these pieces were glued to each other. It was not so much really in the computer but it was all on stretches of paper and I know that we had for the X chromosome a very dense map at that time.

Ferguson-Smith: Single Chromosome Workshops were taking over in the 1990s, within two or three years. As I said before, there were 24 different single chromosome mapping workshops that had been established and had met in the period of three years.[174]

Craig: 1989 was the first one, X chromosome, December 1989.

Harper: We'll come back to the Single Chromosome Workshops.

van Heyningen: I've got in front of me this little perspective from *Trends in Genetics*, June 1986. David Porteous and myself writing 'Cystic fibrosis: from linked markers to the gene'.[175] I see one of the methodologies that we are already talking about there is pulsed field gel electrophoresis and that, of course, is one of the things, and yeast artificial chromosomes, which helped us to bridge the gap in terms of size.

Harper: The evolution of the technology is hugely important and, in fact, Tilli Tansey suggested it might merit having a workshop, or a Witness Seminar, specifically on technologies in genetics because in a way they did determine to a huge extent what was feasible.

van Heyningen: Yes. You must get Ed Southern.[176] He invented pulsed field gel electrophoresis as well, I think.

Bodmer: No, that was invented by Charles Cantor.[177]

van Heyningen: Oh, Ed Southern developed one cheap machine then, the Waltzer.[178]

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[174] The proceedings from the Single Chromosome Workshops are published mostly in the journal *Cytogenetics and Cell Genetics,* but also one in *Genomics* and two in the *Annals of Human Genetics;* for a breakdown see Ferguson-Smith (1998).

[175] van Heyningen and Porteous (1986).

[176] See note 89.

[177] Schwartz and Cantor (1984).

[178] Southern *et al.* (1987). Professor Sir Edwin Southern discusses the informal title of the electrophoresis apparatus he devised with his colleagues as the 'Waltzer' in Southern (2005).

Craig: Just to go back to the beginning really and the somatic cell hybrids, and Frank Ruddle who died last year.[179] So in memory of him, it's worth mentioning that, in fact, he had a whole factory. He had 40 to 50 people working in the Kline Biology Tower [in Yale] by about the middle of the 1970s or late 1970s doing somatic cell genetics. It's no wonder that the field has a lot of papers by him and his group.[180]

Harper: Did Frank Ruddle ever write a historical or autobiographical account of the gene mapping work? We've got Victor McKusick's account but I'm not aware of one that Frank Ruddle wrote.[181] It's a pity if he didn't because he would have given a very valuable and rather different perspective on things. Anyone got any idea on that?

Craig: He moved on to study *HOX* genes in his latter career.

Harper: Yes, but he didn't as far as you know write a kind of retrospective paper on his gene mapping work?

Craig: I'm not aware.

Malcolm: No, but it might be relevant here. I don't know where the McKusick archive is but, of course, he took photographs of everybody and everything. So that could be very valuable.

Harper: Yes, indeed it is. I can tell you that. So could Malcolm. But, yes indeed, all his records are at Hopkins and they are properly archived and most of them have already been sorted.[182]

We now get onto the area of linkage analysis, informatics, computing, which many of us either on the clinical or the lab end tended to regard as a sort of necessary evil. I think there's a real danger in documenting the history of this that it gets made more subsidiary than it deserves to be. So Tim Bishop and Chris Rawlings are going to try and cover this area and anybody else can contribute.

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[179] See biography on page 107.

[180] Ruddle (1998); Ruddle and Kidd (1989).

[181] McKusick (1988). For Ruddle, see note 28 for a brief historical account that he presented on gene mapping.

[182] 'The Victor Almon McKusick Collection' of personal papers is available at the Alan Mason Chesney Medical Archives of the Johns Hopkins Medical Institutions; http://www.medicalarchives.jhmi.edu/papers/mckusick.html (visited 17 November 2014).

Bishop: Let's start with the linkage analysis. As Sue and Walter have already said, much of the basis for linkage analysis was formulated either through the work of Fisher or Haldane,[183] while made feasible through the work of Newton Morton. His 1955 paper was the paper that defined the kind of statistical approach to conducting linkage mapping, in particular to assert the finding that a linkage had been found.[184] It was the first approach that took into account the fact that you would have a map or a large number of markers, that you'd be doing multiple testing and there would be an issue about the correlation, linkage disequilibrium, between markers. A lot of that was defined in advance of the consideration of these workshops, as was the method of actually defining the lod score if you like. So the procedures were in place. For implementation they required better statistical probabilistic software, and so software was produced – I think Jurg Ott's LIPED programme, or the Elston–Stewart algorithm, or the PAP (Pedigree Analysis Package) programme a little later.[185] There was a series of algorithms like that which were produced and which worked on the kind of computers that were available in the early 1980s, and were really quite successful in terms of taking these approaches forward. We spent a lot of time discussing the robustness of linkage analysis, while we were very concerned as to whether linkage analysis would work in the presence of significant heterogeneity, for example if there were multiple genes. In fact, it turned out that none of those things were so important at these early stages. Recognizing traits with a clear Mendelian inheritance gave enough power to make the methods actually quite robust. We spent a lot of time worrying about this, as statisticians do, but the approach really worked very well with the benefit of the fact that heterogeneity was not actually as great as we had worried about. It meant that there was a steady increase in linkage power and approaches, etc., and it really was, statistically, impressively successful.

It's interesting going back and looking through the papers, that the kind of issues that were a concern were probably opposite to the way that Maj was suggesting. For instance, a lot of the early work was motivated by how to include chiasma mapping into the approaches, to optimize the approach to

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[183] See notes 15 and 17.

[184] For Newton Morton see note 22, and for the background to the development of the statistical technique of sequential analysis during covert war operations in Britain, see Peter Harper's 2005 interview with Newton Morton; http://www.genmedhist.info/interviews/Morton (visited 18 November 2014); page 8.

[185] Ott (1976); Elston and Stewart (1971); Hasstedt and Cartwright (1979).

linkage. Actually we were very worried that the approaches would not be powerful enough, and you had to invoke other information to make the most of the co-inheritance. In fact, the modelling was not so critical, it turns out. But it was certainly the focus of much of the earlier considerations, as was the development of mapping functions. So, statistically, the issues were not that great, certainly not as great as we thought they were going to be. Although, as Peter says about many people taking linkage analysis to be a 'necessary evil' for these workshops, there were groups of us that met together regularly. The main leader of this was Bronya Keats, who was originally in Hawaii and then moved to LSU (Louisiana State University).[186] Bronya was very much the person who encouraged the sharing of information by geneticists to promote cooperation and collaboration, and to bring linkage analysis to the level that it did. I often see discussions about extensive meta-analyses and the comments about how well these had been developed. But, in fact, I think it's the geneticists that did this first of all, when, by agreeing that you would share information in the form of a standard lod table, this was the basis for putting all that information into the public arena. So you could combine with other studies, take your data to the Gene Mapping Workshops and combine information from multiple studies, and come up with statements about linkage and linkage groups.

Towards the late 1980s/early 1990s, the discussion was changed in terms of not being a matter of how to identify linkage groups, it was how to identify marker order and gene order, and the fine-scale mapping approaches that were rather different and had quite subtle problems of their own. Overall then, the linkage analysis probably wasn't as much of a 'necessary evil' as expected but, of course, that changed when you change from major gene inheritance through to polygenic inheritance, and multifactorial diseases where in fact the complications become much more serious. It's clear that we probably still don't have a very good handle on those.

Moving on to informatics. Actually, as I wasn't really involved in the informatics until the late 1980s, I think 1987 was the first time I was involved, I can't say anything about it before that. I was in the States at that time and was involved with the Utah group, which was the group that in the States was largely driving the creation of genetic information and databases. They had a very enthusiastic colleague, Peter Cartwright, who worked with Ray White, who was developing

[186] Bronya Keats was Assistant Professor at the Department of Biometry and Genetics at Louisiana State University (1982–1986) and Associate Professor (1986–1991); see http://www.medschool.lsuhsc.edu/genetics/faculty_detail.aspx?name=keats_bronya (visited 18 November 2014).

databases in Sybase for storing genetic information, including information on different types of markers: their locations, their polymorphisms, their mapping status, etc. Peter and Fran Lewitter and, of course, then led by Peter Pearson in Baltimore, together with Ken Kidd, were the ones who really developed GDB that we got to know and love.[187] Bert will be able to fill in more on this,[188] but also Ken Kidd had a system, which was based on Lotus Notes, that was available for sharing information that worked well with the system that Bronya Keats had put in place.[189] She simply stored the information in a home location, put together all these linkage results and then produced summary statements for each of the chromosome committees. I think Chris can comment on how that was translated into the UK version at HGM9.5 and 10.

Professor Chris Rawlings: I got involved towards late 1988/1989, when it had been agreed, or certain members of the people in this room had volunteered, to run the next pair of workshops, 10.5 and 11 in the UK.[190] And this happened at an interesting time, as we've already mentioned, when the need for the computing support had become clear and I think there was a general concern that the tools that had been built for the Yale meeting weren't going to scale up to the way that was going to be needed for the London meetings. At that time, as Tim has said, there was already this move to initiate a bigger development of a relational database using professional software engineering techniques, which was being driven by the people in Baltimore at Johns Hopkins University. But there was also, at the time, a degree of uncertainty as to how that database was going to support the workshops because it clearly needed a lot of developmental work, and it wasn't going to be ready. There was a need for an intermediate solution that would

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[187] Frances Lewitter contributed to HGM9.5, in 1988, as a representative of BBN Laboratories, Cambridge, Massachusetts, reporting on the Informatics Committee; Cartwright and Lewitter (1988). See, for example, Pearson (1991). For Peter Pearson, see also note 95, and, for Ken Kidd, note 164.

[188] Professor Bert Bakker wrote, 'This was later: Peter Pearson moved from Leiden to Baltimore to become Director of the GDB in 1989, so the first data in GDB were entered and curated manually by the editors.' Note on draft transcript, 4 March 2015. A copy of the 1990 'User Guide to GDB and OMIM. Version 1.0', which was part of the package that the official GDB editors and curators received, published by the Howard Hughes Medical Institute/Johns Hopkins University, was provided by Bert Bakker and it will be deposited in the archives of this meeting at the Wellcome Library, London, Archives and Manuscripts, GC/253.

[189] Lotus Notes was software developed by IBM in the mid-1980s; see http://www.ibm.com/developerworks/lotus/library/ls-NDHistory/ (visited 18 December 2014).

[190] HGM10.5 was convened in Oxford, and HGM11 in London. For the Informatics Committee report, see Rawlings and Lucier (1990).

Figure 15: Professor Chris Rawlings

support the intermediate workshop that was going to be held in Oxford that Ian (Craig) was leading. So the team that I led took on the responsibility for providing the intermediate solution, which still capitalized on the Lotus Notes application that Ken Kidd had pioneered, but we made sure that it was coordinated with the chromosome committees, and the data were gathered and presented to the then early version of the Genome Database that was in Oxford. There were quite a lot of political tussles in the background as to who was going to build this database, what it was going to be implemented in and all the technical complexities, and who was controlling the whole thing – that's perhaps more for a conversation over a beer later.

The outcome was, or the desire was, that for the meeting in Oxford in St John's College to have the first version of the Genome Database populated with the preliminary data from the chromosome committees, for them to work on in study bedrooms in one of the accommodation blocks, and so we set about making sure that that could happen. The UK team provided a lot of the infrastructure, both the network and the computing power. We were hunting around the whole of the UK trying to find where we could get suitable work stations for everybody because each chromosome committee required two PCs and we needed a server, and we needed to get all this stuff ready and in place in

St John's College, which had no internet or ethernet connections [laughter]. It was quite early days to do some of this, and I often describe it a bit like running a rock concert, as you had to bring a team of roadies in to get all this stuff in place. We benefitted from Hewlett Packard, which I had some links with, and contacts there who were able to loan us all the PCs for nothing, but this was no small logistical exercise to get this in and out in the required time, and there was a fair amount of blood, sweat, and tears involved in this operation, as Ian will remember.

Then we had to repeat the whole exercise again for HGM11, which was held in the New Connaught Rooms in London, not far from Lincoln's Inn Fields where ICRF was based and where my department was.[191] As well as having the infrastructure development, that year was when we needed to make sure that the final printed version was automatically generated from the database and so the work was much more oriented towards writing the software that would produce hard copy, camera ready copy for Karger to print the proceedings of the meeting.[192] I think the meeting finished in somewhere around July or August time and we wanted to get the proceedings out early the following year, and so there was a lot of optimizing the database queries, writing the software that would generate the mark-up language version of the book, producing the camera ready copy, checking it with the chromosome committees, editing the whole thing as an editorial team and then delivering to Karger in time to get the thing out of the door quickly. In the end it was a scrabble but we got it out in a timely fashion with very few problems in the end.

For the rest of the informatics development we had a very different sort of architecture then – the Genome Database went back to its home fully populated with the best available maps that were curated at the London meeting and then the whole infrastructure changed when we moved to more single chromosome committees and then to an extent my involvement drifted off and I went on to other things. By then the whole concept of community databases and sharing of information was moving into the whole genome sequencing era, and we see a huge change in culture within the research community about the importance of data and the importance of sharing it in support of research for the public good.

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[191] The New Connaught Rooms is a Central London venue, now the Grand Connaught Rooms; http://www.connaughtrooms.co.uk/ (visited 20 November 2014).

[192] See Probert and Rawlings (1991), and Rawlings (1991).

Solomon: I'd just like to say that the Connaught Rooms were not networked at that time either [laughter], and getting that infrastructure in place was an absolutely gargantuan task, a real nightmare. I think that also made us reconsider how this sort of thing could possibly go forward.

Bodmer: Just a question to Chris: was the GDB actually used for workshop 11?

Rawlings: Yes.

Bodmer: So it was the database that was developed over on the other side? But it was an adequate version? I'd just like to add a few general comments that are not so much on the science of it but what went on behind the scenes.[193] The informatics operation was really, for its time, a huge enterprise and I'm not sure whether it was you (Chris) who said, 'Oh what a pity they didn't get the volume up by December 31.[194] I think it was a miracle that those two 1,000-page volumes were produced with all that huge amount of information by April 1992 after a meeting that had been in August. It was an amazing task for its time. I think it's hard to imagine and I just have a few things I note here: a computer server had 2 GB on its disk. [Laughter] I bought a memory stick the other day with 128 GB on it, and I'm getting a computer today that has a terabyte. The resources that one had for working at this scale, at that time, were incredibly less than they are now. So it's hard to imagine just how difficult it was to get these things going. The other thing, though, is that there was a huge amount of politics – one argument I remember a lot about was Sybase versus

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[193] Professor Sir Walter Bodmer was Chair of HGM11, Professor Ellen Solomon was Co-chair. Other members of the UK Executive Committee for organizing the workshop who contributed to this Witness Seminar were: Tim Bishop, Ian Craig, Malcolm Ferguson-Smith, Peter Harper, Sue Povey, Chris Rawlings, and Veronica van Heyningen. The other HGM11 UK Executive Committee members were Martin Bobrow, Kay Davies, John Edwards, Peter Goodfellow, John Johnson, Michael Probert, Bette Robson, Nigel Spurr, and Bob Williamson. See Solomon and Rawlings (eds) (1991), page v.

[194] Professor Chris Rawlings wrote, 'I don't think it was me who made this comment at the time, but in our meeting Walter may have been seeking my acknowledgement that the comment had been made. My recollection was that one of the HGM committee chairs had made the comment that it would have been nice to have had the proceedings of HGM11 published by the end of the year. This may have been the original plan. It would indeed have been nice but the technical and organizational challenges needed to produce this huge two-volume report as camera ready copy were significant.' Note on draft transcript, 4 March 2015.

Oracle; it was a huge argument.[195] It was politically motivated according to who was using Sybase and who was using Oracle and there were also enormous problems getting the funding. I mean at that time you'll notice that it says that ICRF sponsored that meeting, and it jolly well did. I think it cost nearly three quarters of a million pounds, it was a huge enterprise. It's interesting that the grants don't mention the MRC and the Wellcome Trust.[196] They did provide some money but neither of them had really got going. Well, by that time maybe the MRC had got going a bit.

I'll have to remind you of earlier times: I remember going to a meeting organized by Victor McKusick and Charles Scriver at the headquarters of the Howard Hughes Medical Institute, a beautiful villa on the coast in Florida. At that time, Don Fredrickson was the director. That was a very early, specific discussion about the idea of doing the Human Genome Project. This was in early 1986 at the latest. Then there was the Cold Spring Harbor meeting that Jim Watson organized, and I gave the opening talk where there were lots of discussions about doing it.[197] Later that year, there was a meeting at the NIH so actually the impetus for starting to think seriously about doing the Human Genome

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[195] Professor Chris Rawlings wrote, 'When the planning for HGM11 started at ICRF, the expectation was that the database that would support the workshops and associated work of the HGM committees would be built using the Oracle relational database platform. This reflected the expertise and long-standing commitment to Oracle by the ICRF clinical research database team. When the Genome Database (GDB) Project, funded by the Howard Hughes Medical Institute at the Johns Hopkins University, undertook to develop a reference database for the human genome map to complement the OMIM® catalogue of Human Genes and Genetic Disorders, they chose the Sybase database system. At that time Sybase had been identified as the database system of choice for human genome projects. Furthermore, competitive software licensing deals were available to US researchers from Sybase as a result of an agreement brokered by the National Science Foundation. As the GDB and ICRF teams began working together, it took a while for the mutual benefits to become apparent of adopting a common database platform to deliver both the data content needed for GDB from HGM11 and the data curation interfaces needed for the workshops. After much discussion, the ICRF team conceded that the available resourcing and rate of progress already made on the GDB database design made it more sensible to adopt Sybase for this project. For the informatics at HGM11, see Rawlings *et al.* (1991).

[196] In the Introduction to the published volume for HGM11, Professor Sir Walter Bodmer acknowledged funding from the Imperial Cancer Research Fund, Medical Research Council, and the Wellcome Trust, although none of these organizations were included in the list of 'granting agencies'; Solomon and Rawlings (eds) (1991), pages v and 1.

[197] The symposium was entitled 'Molecular Biology of Homo Sapiens'; see a summary of the conference on Cold Spring Harbor Laboratory's website at http://symposium.cshlp.org/site/misc/topic51.xhtml (visited 18 November 2014). See also Watson (1986), and Bodmer (1986).

Project, as it came to be called, had started five years before the 1991 meeting, and I remember Sydney Brenner and I having to go to Dai Rees, the then head of the MRC, to persuade him that this was something they should be thinking about.[198] At that time, the Wellcome Trust had hardly got involved at all. So, in fact, we'd appointed Hans Lehrach at the ICRF, in 1987, to deal with this sort of thing. One has to remember, it was a project that was being criticized for being 'big science', taking money away from everyone else, that it wasn't going to be useful. Somehow that didn't quite include the gene mapping but it certainly included the Human Genome Project. So it was extremely political, and and there were questions of whether we would continue to get money from Howard Hughes, and the Wellcome Trust didn't want to support HUGO (Human Genome Organization),[199] and I think it was actually very difficult but, in the end, that meeting in 1991 was really a watershed. It was a major meeting but it was also the transition between the old style of getting together in nice cosy groups and what became a highly politicized Human Genome Project.

Harper: Walter, I'm going to shift, we're going to come back to that in a little bit.

Bodmer: I think it's highly relevant to the whole discussion of the issue of the significance of that meeting and the difficulties at that time of really getting something like this adequately supported.

Craig: I've got a couple of comments about both the interim meetings 9.5 and 10.5, and what a miracle it was to get everything up and running in Oxford with Chris and his team. But I should just mention the fact that at St John's College, the bursar there, Dr Tony Boyce, was so enthusiastic about the whole thing that I think they paid for the networking of the different rooms, which was a huge contribution, so that every committee could have its own access

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[198] See Friedberg (2010) for Sydney Brenner and Walter Bodmer's collaboration on lobbying for the UK's participation in the Human Genome Project in the mid-to-late 1980s, pages 236–9. Sydney Brenner (b. 1927) was a Nobel Laureate in 2002; see http://www.nobelprize.org/nobel_prizes/medicine/laureates/2002/brenner-facts.html (visited 4 February 2015).

[199] The Human Genome Organization (HUGO) was founded in 1988 as the international coordinating body for research and collaboration between scientists on the human genome, a so-called 'UN[United Nations] for the human genome'; see, for example, McKusick (1989), quotation from page 386. Of this seminar's participants, Professor Sir Walter Bodmer and Professor Malcolm Ferguson-Smith were members of HUGO's first Executive Committee, see page 385, and Bodmer (1990a). See also HUGO's website for further details of its previous and current work, http://www.hugo-international.org/index.php (visited 25 November 2014).

Figure 16: Professor Michael Morgan

to the database. So it worked in both ways, absolutely. Just one point, in 9.5 where the Edit system was tried for the first time, so much time was spent worrying about the computing and everything else, they forgot about the rooms for the people who were actually going to the meeting, and the first thing that happened at the first session was a handout of light bulbs because there were no light bulbs, and, as far as I can remember, there was no furniture in the rooms apart from a bed.

Professor Michael Morgan: I just want to make one brief comment at this stage, on the fog surrounding decision-making at the Wellcome Trust with respect to genomics and funding this particular workshop. I don't think there was anybody, or very few people, on the Board of Trustees then, apart from David Weatherall, who really had any idea what this was all about, and the fact that Walter actually squeezed, I remember, a quite significant sum of money ...[200]

Bodmer: £250,000. [Laughter]

Morgan: [laughs] Not bad, Walter. That's all for the moment.

Harper: Okay, while we're still on the subject of computing and linkage analysis. Bert?

[200] For Professor Sir David Weatherall, see note 151.

Bakker: Around 1988, when all this computing business was a problem, there was a group of people who started to work on a project and on a grant from the EU, and Sue Povey was involved in that with a lot of people. Nigel Spurr was the guy who started that project, EUROGEM (European Gene Mapping Project).[201] Because there was the plan to make a 5 centimorgan-spaced map of all human chromosomes, they asked for funding from the European Union (EU) and in 1991 this project started and they got money from the EU to buy huge UNIX machines, actually ULTRIX it was, a type of UNIX, so that every centre could do their own linkage map for chromosomes.[202] There were different groups involved and after a few years there was this paper with maps, 5 centimorgan maps of all chromosomes.[203] The same project went on and on and made meiotic breakpoint maps.[204] The basis for this all was the CEPH (Centre d'Étude du Polymorphisme Humain) families on one side and the Utah families, of course, and on the other side the markers from the States and from Dausset and Weissenbach that were all put in these.[205] And that was the basis for the sequencing project later.

Bodmer: Could I just add one thing to that because, although it was a little later, I think perhaps around about that time, Nigel Spurr was asked by me to set up a probe bank.[206] The whole aim of the probe bank was to make nationally-available probes that could be used for these mapping purposes, and I think that may have fed into the European project that you're talking about. Nigel, in case people don't remember him, sadly died a year or two back. He did his

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[201] In 1988 and 1989, at the time of HGM9.5/10, Dr Nigel Spurr was based at the ICRF's Clare Hall laboratories in Hertfordshire, England. See also Professor Sir Walter Bodmer's comments on page 82. For EUROGEM, see Spurr *et al.* (1994). Ferguson-Smith (1991) describes the then forthcoming EUROGEM project as 'consisting of two resource centers and a network of research laboratories from member states. These laboratories will undertake genetic mapping studies and contribute to a central database', quoted from page 64.

[202] For UNIX, the IBM software programme, see, for example, Kernigham and Morgan (1982).

[203] Spurr *et al.* (1994).

[204] Cox *et al.* (1996).

[205] The Centre d'Étude du Polymorphisme Humain (since 1993 the Fondation Jean Dausset-CEPH) was founded in 1984 by Professor Jean Dausset (1916–2009), an immunohaematologist and a Nobel Laureate in 1980; http://www.cephb.fr/en/presentation_historique.php (visited 19 November 2014). See also pages 81–2.

[206] The ICRF-funded probe bank was tied to the launch of the UK's Human Genome Project in 1989. See, for example, Ferguson-Smith (1991), page 62, and Alwen (1990).

PhD with me and then got involved in a lot of the mapping work that was done at the ICRF; he was extremely productive. Then he went to Leeds for a while, I can't quite remember when that was, but we sent him up and that was the first involvement really of the Medical Research Council in a serious way in supporting the whole mapping enterprise because we felt that making available those probes in an appropriate way was a key step towards getting good maps.

Bishop: Nigel came to Leeds in 1997, and then subsequently he moved to the pharmaceutical industry.

Ferguson-Smith: I just want to add that the EUROGEM was set up by the Human Genome Advisory Group of the EU Commission in which they took advantage of the probe resource centre that Nigel Spurr and Walter were involved in. And the other branch, of course, as you've just mentioned, was CEPH and their idea was that Nigel Spurr's group would supply these probes to a series of 22 collaborating centres. It was originally 23 in Europe to do Southern blots on filters produced by CEPH from 69 different families.

Bakker: We started this with Southern blots, yes.

Ferguson-Smith: This was the European project, which was built up to counter what was happening in North America. It was really established to provide an independent European initiative on the Human Genome Project that would work in collaboration with the USA on human genome research. It was thought that all the development and potential intellectual property shouldn't be left to the United States.

Bakker: Well, it's very good because each of these laboratories had their own chromosome and they were really responsible for that to make the map.

Ferguson-Smith: That's correct, and they were also funded. Each of these labs was given a technician, funds to support their work, and computing equipment. Again, Bronwen Loder at the EU was involved in this and I happened to be responsible for her and for looking after the coordination. Out of that grew the Single Chromosome Workshops, something which I rather regret we don't have time to talk about.

Harper: Well, we will have time, Malcolm, if we move on to other things.

Povey: Just on the EUROGEM, John Attwood in our group was very helpful on the computing for that.[207] For example, he noticed that when you submitted

[207] See Povey *et al.* (1994) and note 201.

results to the CEPH, it knocked out the results of the previous submission [laughter], and we had to ring the people in Paris and they said, 'Oh we hear you're having trouble with this', and John explained and then immediately an email came to everybody saying, 'Stop doing it, there's a terrible bug in the system!' But it was a good collaboration, a very good collaboration. It really spread the technology, and it spread the collaboration, which lasted a long time.

Bodmer: Just a very quick comment on the background to the European setting. The obvious centre that should have done a lot of the European coordination would have been the EMBO lab in Heidelberg. I remember at that time Hans Lehrach was there. The person who was in charge of the EMBO lab, Lennart Phillipson, had absolutely no interest in it. I knew Lennart well, and I liked him. I think it was actually a major mistake because if, in fact, he had taken it on and said, 'Look, we will act as a coordinator to have a really decent genome project in Europe', that would have been very hard to turn down. It was a mistake in my view. That's why Hans Lehrach came to the ICRF and stayed there for a few years doing these things.[208]

Harper: I'm going to suggest we move on slightly now, and next on the programme we've got a rather different, but I think no less important, topic, which is nomenclature. This comes back to you again, Sue. Maybe you could tell us a bit about the background and progress, and your involvement?

Povey: Well, my involvement was really much later.

Harper: Okay, tell us about the early stage.

Povey: I hear now that even in that first conference there was some discussion of terminology. Indeed, in the second one, I think Harry Harris offered to draft some guidelines.[209] They set up a committee to have a meeting between the main meetings in order to produce guidelines for a nomenclature of genes and alleles and of proteins and loci. And this was produced, and something I remember myself but I can't remember exactly whether it was HGM3 or HGM4, but there was a presentation by Eloise (Giblett) where she produced the work of this group and established the principles really on which the naming of genes is still based.[210] Somebody criticized something, and that there was some criticism

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[208] See, for example, Francis *et al.* (1994).

[209] Professor Harry Harris was a member of the Committee on Nomenclature at HGM3, which recorded that he would prepare nomenclature guidelines for human genetic markers; see Giblett (1975).

[210] See Giblett (1976), page 65.

is so characteristic of nomenclature, it's always so controversial and people get so het up about it. Their gene is like their baby and everyone always agrees that one gene should only have one name but they are sure it should be theirs. In the end tears came into Eloise's eyes on the stage, I remember, and she said, 'Well, we thought we'd done something, perhaps we hadn't done anything at all.' The sight of her being about to cry made the whole conference vote unanimously to accept it.

Harper: It was the third workshop, Sue, in Baltimore, and she was also deputed to be in charge of terminology at the second. In the first workshop, perhaps surprisingly, it was Victor McKusick and Jean Frézal but it moved on from that and then on to Phyllis McAlpine.[211]

Povey: So anyway, that was interesting as a successful strategy. Also, in the naming of the genes, and, of course, one of the principles that was held to was: 'if there's a community out there with particular genes and they've already been named, we don't interfere with that.' So there was a specific statement that they wouldn't interfere with the HLA genes, and they wouldn't interfere with the blood group genes, they would concentrate at the moment on enzymes because that seemed to be the thing that most needed doing at the time. And the committee wanted people to have italics for the gene and non-italics for the protein. Because they were dealing with enzymes, they wanted the short form of the name, then called the symbol, to be not more than four letters, and to have some relationship to the name of the enzyme but not necessarily the EC (Enzyme Commission) name. And they would allow some flexibility in things that had already been named. Most of that has continued, although, of course, it became increasingly difficult to have the function and it became impossible to have only four letters in the symbol. Then, after that, Tom Shows, I think, really took over, after Elo (Eloise Giblett) and that group of people. It gradually moved to being Shows and McAlpine, and then it became McAlpine and Shows.[212] And at every meeting I think there was a room where you had to go and you couldn't go any further until you'd got the right name. [Laughter] You have to be quite fierce doing nomenclature.

Bodmer: I'd been involved in the HLA nomenclature for years, and the principles by which one had HLA nomenclature we felt were quite sound. As I recall, actually, a lot of those principles, not so much what the blood groupers

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[211] McKusick and Frézal (1974). For Phyllis McAlpine, see Cox, Povey and Show (1999).

[212] See, for example, Shows and McAlpine (1982) and McAlpine *et al.* (1991).

did, were then incorporated into what eventually transpired. Of course, HLA nomenclature dealt particularly with a set of related genes and with the problem of how to deal with polymorphisms, but I think that the HGM nomenclature group which eventually evolved has done an extremely valuable job. It's absolutely essential to have a common language. Even as a mathematician, one of the most important things is nomenclature – it's actually the notation that you use. Without that, you get into a real mess. So the nomenclature committee turned out to be extremely valuable.

Malcolm: I also remember, Tom Shows or Phyllis McAlpine would sit towards the front, and it was like the Commission for the Doctrine of the Faith [laughter], and they would give their approval, they would give a nod, an imprimatur.

Povey: Naming genes is a really good way of making enemies. [Laughter] I'm sure Phyllis had some, and I think she worked herself into the ground. One of the things she said to me was that you have to have good people. If you have anyone helping you, it has to be someone with a PhD, and that was absolutely right, but, mostly, Phyllis actually made the decisions herself. We just discovered that the person has to have a PhD or else they are not capable of arguing with these people who quite reasonably say, 'I've worked on this thing for 20 years and you only heard of it 15 minutes ago, how can you possibly tell me what to call it?' My staff had to go on courses on how to deal with aggressive telephone calls when I got involved in nomenclature. But this is all years later, because we're speaking of the years long before I took over, because Phyllis was 1990 to 1996 – I'd been helping her for a bit but she was very much in charge. She was definitely the last person who knew the name of every known human gene. And in those days we didn't argue so much about what is a gene. I see there's no argument about what a gene is in these workshops. I think that's got more complex.

There's obviously lots of other nomenclature, DNA nomenclature, all sorts of things but I only know about genes. The other thing we did, we never claimed, and Phyllis never claimed domination over proteins because you can sometimes get away with, really people that hate you as long as they're allowed to call the protein what they like. [Laughter]

van Heyningen: There were also always problems about bringing genes over from other species, and there were discussions about whether it was ethical to call a gene 'lunatic fringe' if somebody then had a child with a disease who had a mutation. I found it quite difficult to make my colleagues understand that they couldn't use hyphens and that they had to use the right format.

Harper: Maybe that's a good point to go on to comparative mapping. I think, Malcolm, you could say a bit about this, it's something that shouldn't be left out.

Ferguson-Smith: I'm just trying to remember when comparative mapping was first discussed at the workshops.[213] I remember that Jenny Graves was involved with gene mapping in marsupials in 1985,[214] and John Edwards too because he introduced his Oxford grid at the workshops, which was an important contribution to comparative maps between mouse and man.[215] The important outcome was the realization after a while that genomes were highly conserved. I don't remember really too much about the discussions at the workshops on comparative genomics because I was always at another session.

Harper: The first time comparative mapping had a committee, according to my notes, was the Los Angeles, 1983 meeting, where it's down with Roderick, which would be Tom Roderick, as the chair.[216]

Ferguson-Smith: Yes, this was mostly mouse and human, I guess.

Harper: Then it appeared again at the Helsinki meeting in 1985, and indeed again at the Paris meeting.[217] I think it stayed in after that.

Ferguson-Smith: Yes, it did.

Harper: Tell us a bit about it anyway.

Ferguson-Smith: Well, basically it was really looking at linkage groups between the different species and mouse and human figured prominently in this. I can't think of other species that were as important. Bert, can you think of any?

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[213] Professor Malcolm Ferguson-Smith wrote: 'Comparative mapping was first reported at Baltimore in 1975 when several genes were localized to corresponding chromosomes in human, mouse, and several primates. Over the next ten years the chromosomal location of an increasing number of linkage groups were mapped between human and various primates, mouse, rat, Chinese hamster, cat, dog, rabbit, cattle, sheep, pig, etc.' Note on draft transcript, 3 June 2014.

[214] Dobrovic and Graves (1985).

[215] Buckle *et al.* (1984). For a review of the 'Oxford grid', see Edwards (1991). For John Edwards, see also note 55.

[216] Roderick, Lalley and Davisson (1984).

[217] See Lalley and McKusick (1985).

Bakker: Also for some of the great apes, yes, the primates were also put next to it and there was a kind of map with linkage groups, what is conserved and what not.[218]

Ferguson-Smith: Yes, and I can recall that Jean de Grouchy had some early comparative gene maps between human and rabbit, and there were others that I can't remember.[219] Of course, chromosome painting did not appear until the 1990s, and widespread homology maps until 1994. [220]

Bakker: Yes, later, much later.

Ferguson-Smith: Much, much later. So that's really when my lab became involved.

Harper: Can I ask, were the Harwell people directly involved with the workshops or was it via John Edwards mainly that they were represented?[221] Were people like Mary Lyon and Tony Searle involved directly in the Gene Mapping Workshops?

Craig: Not that I can recall. I think John used to go over to Harwell; there were regular visits every month or so. He was the ambassador, basically, and the enthusiast, and the driving force of it, and it actually turned out to be extremely useful and informative, the 'Oxford grid'.[222]

Povey: I meant to say on nomenclature, that now, and, in effect, for a long time, the human and mouse names for genes have been almost identical. And, indeed, there's a sort of vertebrate genome now and mostly it's the same names following the human ones. But I notice that the very first time it was mentioned at a Human Gene Mapping Workshop was in Winnipeg, it was clear that what we called *PGM1* was in the mouse called *PGM-2*,[223] and when I looked it up yesterday, I see mouse people are still calling it *Pgm2*. They've not given in yet.

Ferguson-Smith: But the mouse use lower case?

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[218] Professor Bert Bakker wrote: 'In our group, the lab of Peter Pearson, Jim Garver and Anna Estop worked on this topic.' Note on draft transcript, 22 August 2014. See, for example, Estop *et al.* (1983).

[219] Soulie and de Grouchy (1982).

[220] For chromosome painting, see Cremer *et al.* (1988). Professor Malcolm Ferguson-Smith wrote, 'Homology maps produced by cross-species chromosome painting first appeared in the 1990s. Notable publications were: Scherthan *et al.* (1994) and Yang *et al.* (1995)' Note on draft transcript, 3 June 2014.

[221] Harwell Medical Research Council laboratories, Oxfordshire, UK.

[222] See note 215.

[223] Pearson and Roderick (1978), page 158.

Povey: Well, yes, but I mean it is not the equivalent gene. The *PGM1*s are not the equivalent genes in the human and the mouse. They're still not right to this day because neither side would give in, because they were both looking at phosphoglucomutase, and both of them found a common polymorphism but, actually, there are many protein bands in *PGM1* and *PGM2*, and the ones that are actually orthologous are not the ones that were expected. I was interested that my successors in the HUGO Human Gene Nomenclature Committee had not managed to solve that one.

Harper: Perhaps now we should come to the final London meeting, and the transition and evolution into the single chromosome meetings, and then the links across with the Human Genome Project. So I don't know who wants to start? Perhaps Ellen – I think I'm right in saying that you had a lot of hard work at the London meeting, didn't you?

Solomon: Yes, I would say. I think we've covered it to a large extent. I agree with Walter: fraught with politics, fraught with technical difficulties. Chris will remember, we had to hire and call in an IT team to get involved in the wiring and the networking of the Connaught Rooms, who also benefitted from this. It was huge, and, you know, the workshop was massively successful but 'not to be repeated', I think, would be the message from it.

Povey: I think the computing, from the Committee-chair point of view, the computing was absolutely perfect; it never went down at all.

Solomon: Yes, but unless we were going to buy the Connaught Rooms, it wasn't going to be there again, and, in retrospect, and nowadays, you would have a dedicated place where you could run a meeting like that, and we now do, but at that time we had to move into some sort of other mechanism.

Bodmer: First of all, I think what has been the successor in the practice of HGM11 are the HUGO meetings, which we're not going to get into. In a way, my impression is that to some extent they have components that are different, they're just straight scientific meetings. We did have a component, of certain plenary lectures, and, certainly, I remember that I asked Mary Warnock to give a lecture on bioethical aspects, so that there was a mixture of the workshop component and an element of scientific meeting.[224] During the

[224] Baroness Warnock (b. 1924) is a philosopher who particularly influenced UK public policy on reproductive medicine through her report on human fertilization and embryology; see Warnock (1985). Wilson (2011) examines her role in the emergence of the field of bioethics in the 1980s.

time of the NIH meeting in July 1986 Craig Venter came up with his business of sequencing, I forget what it was called, the bits of cDNA (complementary DNA). It was a huge controversy.[225] It was actually an idea that Sydney Brenner had put forward and Sydney Brenner was with us there,[226] and he was incensed at that and we had quite a lot of discussions about that area, which started off the whole debate really of what are the rights and wrongs of trying to patent DNA sequences. That was a precursor of Craig Venter's ostensibly independent venture to sequence the human genome, which to my mind never really was independent because he depended on all the mapping information that had been produced by others. That was actually a significant feature of that workshop, the discussion at that time.[227] Maybe others have a memory of what went on as well?

van Heyningen: Was there a meeting, was it organized by the MRC? Because I remember going there and that's where I remember hearing Sydney Brenner saying, 'Why don't we just sequence the coding bits of the DNA?' Do you remember that? It was at the London Zoo.

Ferguson-Smith: This became MRC policy at an early stage in the UK Human Genome Project, is that right?

Bodmer: I think Sydney Brenner would have emphasized sequencing cDNAs, which, in a way, is what would now be called, more-or-less, exome sequencing. He, rightly, at the time – given the technology – focused on the value that would come from sequencing cDNAs. I don't think he thought of that as an alternative to eventually doing the whole sequence. I remember a meeting at the NIH, which I think was some time in the late autumn of 1986,[228] the whole question of how to do it, whether just to sequence it all, whether to do maps, whether to throw it into a big pot and not worry about where things were, all

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[225] Craig Venter is well known for his role in the creation of synthetic DNA, or cDNA, 'expressed sequence tags': Adams *et al.* (1991). For the controversy over applications to patent these gene fragments, see, for example, Eisenberg (1992), and for the gene patenting and a subsequent biotechnology controversy involving 'expressed sequence tags', see Crowther (1999), pages 118–20. See also Venter (2013), pages 83–95.

[226] At HGM10.5, Sydney Brenner was a representative of the Medical Research Council's Molecular Genetics Unit; see participants' list in Craig and Rawlings (eds) (1990).

[227] Brenner (1990).

[228] See Cook-Deegan (1991).

these questions came up, and all the people who were later important in the major sequencing technologies each had their little bit of say, including Wally Gilbert.[229]

Solomon: I'd like to add an anecdote about HGM11. A plenary speaker pulled out with a day's notice and I rang Richard Dawkins and asked would he consider stepping into a plenary talk at this meeting, and he said, 'Ellen, are you kidding? Me, speaking to a conference full of geneticists? Never!'[230] [Laughter]

Bodmer: Talking about Richard Dawkins, it was Glenys Thomson and I who actually taught him a little bit about linkage disequilibrium, which he even acknowledged in the preface to his first book.[231]

Craig: Just since we're on anecdotes about HGM11, I can remember in the final sessions, I was chairing, and the news came through that Gorbachev had just been released by Yeltsin.[232] It was quite an important announcement and highly significant news at the time.

Povey: It reduced the press coverage of the meeting.

Bodmer: You might remember the foundation of HUGO was actually in 1988 and one shouldn't forget the importance of HUGO in this whole story. Victor McKusick was the first President and I was the second, and that was basically why we offered, in a sense, to have that meeting in London. We were seeking representatives of the genome community in different parts of the country and people may remember the name Mirzabekov – he was actually a notable molecular biologist in Russia, in Moscow, who had very early ideas on the sorts of things that are done now.[233] If I recall, he actually came to the London

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[229] Walter Gilbert (b. 1932) was a Nobel Laureate in Chemistry in 1980 for his role in the development of DNA sequencing; http://www.nobelprize.org/nobel_prizes/chemistry/laureates/1980/gilbert-facts.html (visited 20 November 2014). See Gilbert (1987).

[230] Richard Dawkins is an author, philosopher, and zoologist, renowned for discussing atheism as a popular philosopher and author in, for example, *The God Delusion,* Dawkins (2006); see also the author's website at https://richarddawkins.net/richarddawkins/ (visited 20 November 2014).

[231] Dawkins (1989), see 'Preface to 1976 edition', page vii.

[232] In 1991, during an attempted coup, Mikhail Gorbachev, the head of the Soviet Union, was placed under house arrest at his holiday home in Crimea for three days, and was released on 22 August 1991. See, for example, Dejevsky and Clark (1991).

[233] Andrey Mirzabekov (1937–2003); see the Azerbaijan National Academy of Science's website, http://science.gov.az/forms/pochetnyie-chlenyi/160 (visited 5 January 2015).

meeting – I think he came to the London meeting.[234] I certainly remember contacting him and saying, 'How is everything with all the turmoil there?' He said, 'Oh it's alright, there'll be no problem.' It was very soon after that that I went to, I think, a meeting in Russia at that time, and actually saw the White House from where Yeltsin had said his success had been. I think this international aspect was very important. I'm trying to remember the name of a very good Japanese molecular biologist from Kyoto University. I think it was Matsubara, he was one of the early Vice Presidents of HUGO.[235] Yes, he was a very important figure because dealing with the Japanese was a delicate matter. You couldn't tell them what to do, there had to be a consensus and Matsubara was actually extremely helpful in getting the Japanese to be involved and behind the Genome Project.

Morgan: There is a famous letter from Jim Watson to Matsubara.

Bodmer: I wouldn't know, but if you look in the Jim Watson archive you might find it I suppose. What would it have said?

Morgan: It would have said something along the lines, 'It's about time that the Japanese put some money into human genome sequencing and join the Human Genome Project.'[236]

Bodmer: That probably would have been after, later. When did Jim Watson become head of the genome research project at NIH?[237]

Morgan: 1988.

Bodmer: Oh was it that early?

Harper: Before we leave the London meeting and go on to the specific chromosome meetings, can someone give an idea, at least for me, on the timescale: how did this link, around 1991, across with the French Généthon and the whole genome map? Had that started at all at that stage, or was it a

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[234] Andrey Mirzabekov is not listed in the participants for Human Gene Mapping 11.

[235] Kenichi Matsubara was a member of the Founding Council of HUGO, 7 September 1988, and was elected an officer, see http://www.hugo-international.org/abt_history.php (visited 6 February 2015).

[236] See 'Letter from James D. Watson to Kenichi Matsubara', 12 July 1989, available in The Victor A. McKusick Papers, US National Library of Medicine, at http://profiles.nlm.nih.gov/ps/retrieve/ResourceMetadata/JQBBKQ (visited 6 February 2015).

[237] For a biography of Dr James Watson, see the Cold Spring Harbor Laboratory website; http://www.cshl.edu/Faculty/james-d-watson.html (visited 27 January 2015).

few years later?[238] I'm trying to get a picture as to the state of mapping of the different chromosomes overall at this meeting, which was the last time before the Genome Project when they were all considered together at the same meeting.[239]

Malcolm: It's only a partial answer to your question but at the London meeting the yeast artificial chromosomes (YACs) were the flavour of the month, and so on, and I remember somebody, and I'm pretty sure it was David Ledbetter, and I think it was chromosome 17 ... [240]

Bodmer: In 1990, in my introduction to HGM10.5, in Oxford, I said that the development of molecular techniques should lead to a complete union of the aims of the Human Gene Mapping Workshops and the Genome Project.[241] That was the aim, and the thought was that, actually, the two would merge and that HUGO as an organization would somehow oversee in a cooperative manner what would happen with the Genome Project. And, of course, that never happened. It was too political, too much money was involved, and the scientists themselves were not allowed to keep control of it.[242]

Harper: Walter, tell us a bit more then about this transition. I mean the London HGM meeting was the last of the old style but it had already in a sense begun to change. How did the change happen?

Bodmer: As I just mentioned, someone may remember: when did the Wellcome Trust start getting involved, maybe Michael knows, in the Genome Project?

Morgan: How long have you got? [Laughter]

Bodmer: No, just give me a date.

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[238] See, for example, Weissenbach *et al.* (1992).

[239] At HGM11, in 1991, there were separate committees for each of the autosomes, and for the X and Y chromosomes. See Solomon and Rawlings (eds) (1991), pages vi–vii. The introduction stated that: 'At HGM11, as well as at subsequent other meetings and discussions, it was agreed that the Human Gene Mapping Workshop community should work together with those involved in physical mapping, under the overall umbrella of the Human Genome Organisation, HUGO. In future, communication and discussion of chromosome-specific data will be organized through the Single Chromosome Workshops'; Solomon and Bodmer (1991).

[240] Solomon and Ledbetter (1991).

[241] Bodmer (1990b).

[242] For a personal account of working on the Human Genome Project, see Sulston and Ferry (2002). See also Cookson (1994) for the politics of gene mapping, and conflicts between academic and commercial interests prior to the HGP, pages 31–45.

Morgan: Basically, it was following a conversation between David Weatherall and myself …

Bodmer: When?

Morgan: Well, I'm trying to give you a meeting and then you're going to give me a date.

Harper: Take the microphone away from Walter and give it to Michael. [Laughter]

Morgan: International Congress of Human Genetics, Philadelphia or Washington, 1991?

Bodmer: It was in Washington in 1991.

Morgan: Yes, thereafter we set up the Genetics Interest Group.[243]

Bodmer: Well, let me just comment because that date is important, right, because that date reflects the time when a big bang first came into doing a lot of sequencing and when the project was lost from the hands of the involved community of the mappers, and that was the transition really from what the Gene Mapping Workshops were, to the Genome Project as such. So it was taken, in a way, out of the hands of the people who might have thought that they should be the ones to deal with this. And it was for a mixture of political, if you will, and financial reasons, and then it involved the Wellcome Trust and the NIH and it all became grand politics. That was what changed it. The difference was going from the bottom up, and then the top down.

Morgan: I couldn't disagree more. In fact, Watson was appointed as Director of the Center for Human Genome Research at NIH in 1988 and resigned in 1992 because of the EST (expressed sequence tags) fuss and the Director of the NIH wanting to patent ESTs.[244] He certainly didn't get on with a lot of people.

Bodmer: I don't think that was his fault.

Morgan: I'm not suggesting it was. [Laughter] He funded, with the Medical Research Council in the UK, a major mapping project on the nematode, which in many respects was the precursor of the technology for sequencing

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[243] Professor Michael Morgan wrote: 'The GIG I was referring to is (was) an internal Wellcome Trust Advisory Body, not the lobbying group (external).' Note on draft transcript, 5 February 2015. For the lobbying group, see http://www.geneticalliance.org.uk/history.htm (visited 25 November 2014).

[244] See Professor Sir Walter Bodmer's comments on pages 71–2.

the human genome.[245] And Watson approached the MRC at Christmas 1991 because a Mr Bourke, who was an entrepreneur in the States, wanted to set up a private process to sequence the human genome and he was recruiting Bob Waterston and John Sulston who, at that stage, knew more about large-scale sequencing than anybody else.[246] And he came and spoke with Dai Rees, the secretary of the Medical Research Council, Aaron Klug, who was the director of LMB (Laboratory of Molecular Biology) at that time, and eventually to Bridget Ogilvie, the Director of the Wellcome Trust, about the possibility of raising enough cash to keep John Sulston in the UK.[247] I could go on for a lot longer but I'll pause there. That's how the Wellcome Trust got seriously involved. So in 1992, we invited John to make an approach for funding and by the end of 1992 we were able to open the initial format of the Sanger Centre at Hinxton.[248]

Bodmer: That is top down.

Morgan: It was John Sulston and Bob Waterston.

Bodmer: Top down still involves scientists but it doesn't involve a community. I'm not criticizing it, I think it was inevitable that it went that way, but it was a differently natured thing, it went through a smaller number of people, strong advocates that were needed, very strong influence from the funding agencies, without which nothing could be done. I think it was probably inevitable that it went that way. My comment wasn't meant to be a criticism, it was a statement of fact of how things change and probably had to change.

Morgan: The way in which the Human Genome Project was run was a direct result of three bottom-up meetings held in Bermuda, where representatives of the scientific community got together and worked out the rules of the game.

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[245] See, for example, Waterston, Sulston and Coulson (1997).

[246] From 1993 to 2003, Robert Waterston was Director of Washington University's Genome Sequencing Centre, and Professor/Chairman of the Department of Genetics; see http://depts.washington.edu/givemed/prof-chair/holders/robert-waterston/ (visited 6 January 2015). Waterston and John Sulston collaborated on the sequencing of the nematode genome and the human genome. Sulston was the Founding Director of the Wellcome Trust Sanger Institute, Hinxton, Cambridge (UK), leading the organization until 2000. An overview of his work at the Institute is available at http://www.sanger.ac.uk/about/people/biographies/jsulston.html (visited 6 January 2015). Professor Sir John Sulston became a Nobel Laureate in 2002.

[247] 'Cash' refers to infrastructural support and personnel, not solely the cost of a salary. Correspondence with Professor Michael Morgan, 5 February 2015.

[248] For more on the history of the Wellcome Trust Sanger Institute's foundation in Hinxton, Cambridge, in 1992, see https://www.sanger.ac.uk/about/history/history.html (visited 26 November 2014).

That was definitely bottom up, not top down, which is what I'm talking about. It's true that a lot of money was thrown at it by the NIH, the DOE and the Wellcome, and others, but the drivers were the main scientists who were involved.

Bodmer: That meant that the 'top' listened to good advice. [Laughter]

Harper: Right, I'm going to ask that we switch now to the Single Chromosome Workshops because that was also a transition of a sort. So how did that transition occur? And I think, Ian, am I not right that the X Chromosome Workshop was at least either the first, or one of the very first Single Chromosome Workshops, and how did that take on from the previous HGM meetings?

Craig: I wasn't at the first X Chromosome Workshop.

Harper: You weren't?

Craig: It was in Houston the year before the London meeting.[249] I, with Kay Davies, organized the second X chromosome meeting but really that followed on, essentially, from the first.[250] I've got a couple of comments, talking about the first X chromosome meeting in terms of developments, but the relationship to the normal HGM meetings is basically the team who looked after the X chromosome at the workshops ran the single chromosome meetings, including Caskey, Ballabio, people like that.

Harper: Yes, what year was that, may I ask?

Craig: 1989. Oh, hang on, yes, the first X chromosome meeting was 1989, December 14 to 16. And the Second X Chromosome Workshop was January 1991; that was also before HGM11 as it turns out. But, certainly, by the time of the Second X Chromosome Workshop, we were talking about liaising with the GDB data and that was a complete mesh with what had already been established and information was transacted between the two.[251] The Houston meeting was organized by David Nelson, Andrea Ballabio, and Tom Caskey.[252] I think it was there that the first talk on sequencing came into the workshops.[253]

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[249] Cook-Deegan *et al.* (1990).

[250] Davies and Craig (1991).

[251] For GDB, see page 50.

[252] Baylor College of Medicine, Houston, Texas.

[253] Cook-Deegan *et al.* (1990), page 652.

Tom Caskey was presenting about the experience of sequencing around the *HPRT* using the first commercially available machines, the LKB/Pharmacia machine. And, we've heard the name before, Craig Venter was there describing his bold plan to sequence the Xq terminal region in three years at an estimated cost of $3.5 per base, which is kind of interesting in retrospect.[254] The new machines on the market were allowing this to be done by labs, generally, which had sufficient money to invest: Applied Biosystems, ABI370, and the LKB/Pharmacia machines particularly.[255] At the Oxford meeting, I remember we were talking about how the chromosomes should be divided up. Essentially, we had four subgroups dividing the chromosome into four pieces and so there were really four Single Chromosome Workshops within the Second X Chromosome Workshop. It set up a kind of networking system for YAC libraries and such like and for somatic cell hybrids with translocations.[256] It was really interactive with the workshops. I don't think there was a sudden, 'let's go separately'. Both of these happened before HGM11, and so what was done in the early single chromosome meetings went into HGM11.

Ferguson-Smith: In 1990, the European Union supported the idea of Single Chromosome Workshops. Then, because the first were successful, I think the advisory committee of the Human Genome Analysis Programme in the EU contracted the organization of Single Chromosome Workshops to HUGO, and that was to involve not only people in Europe but people further abroad, and they would provide basic funds for meetings, and also for travel to the meetings for those people who didn't have a human genome project in their national programme. So the EU provided this core support and I think that's how they took off. This was under the HUGO London coordination and the contract was made to HUGO London to organize them. That's how Bronwen Loder

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[254] See note 225.

[255] Professor Ian Craig confirmed that these machines were launched in 1987 and 1989, respectively. Note on draft transcript, 3 March 2015. Applied Biosystems was founded in 1981, gaining the rights to automated DNA sequencing in 1983; see http://www.lifetechnologies.com/uk/en/home/about-us/news-gallery/company-fact-sheet/company-history.html (visited 6 January 2015). The Applied Biosystems 370A Prototye DNA Gene Sequencer, 1987, is exhibited at the Science Museum, and can also be viewed online at: http://www.sciencemuseum.org.uk/online_science/explore_our_collections/objects/index/smxg-61227 (visited 4 March 2015).

[256] Davies and Craig (1991), page 843.

and I got involved. I think Bronwen initially was at the ICRF in 1990 and then she was funded later by the EU when she was based with me at Cambridge.[257]

Bodmer: She had been possibly still funded by the EU, and I think we employed her at the ICRF. There was always a problem with HUGO as to whether it could be an employment organization.

Ferguson-Smith: Ah, yes.

Bodmer: So I'm just guessing that, actually, what happened is that ICRF provided the employment framework for things that were funded for HUGO activities if you will.

Ferguson-Smith: Well, anyway, she was based in my department in Cambridge eventually.

Craig: Just a clarification: the funding for the first X Chromosome Workshop was from the NIH and US Department of Energy, and the second one was the MRC and also some money from NIH for travel and such like. Well, that's what the published report of the meeting indicates. Peter Goodfellow is not here but he was at the first X Chromosome Workshop and I did make a note of one thing that he was reported to have said, which was that 'the future mapping integration efforts hinge on the success of the new Genome DataBase at Johns Hopkins, and its technical objectives being met on time for HGM10.5 and 11', which they were.[258]

Harper: Is anybody in a position to say anything about the whole genome map? We haven't got anybody here from France but I feel that, in a lot of accounts,

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[257] Professor Malcolm Ferguson-Smith wrote, 'Bronwen Loder was seconded from the MRC around 1988 to assist with an ad hoc Working Party set up by the Coordinating Committee on Medical and Health Research of the European Commission. The Working Party was charged to formulate a European Programme of Research on the human genome entitled "Predictive Medicine". After their first meeting it was changed to "Human Genome Analysis". Funding of €15 million was approved by the European Parliament in 1990. This resulted in the European Human Genetic Mapping (EUROGEM) project, which ran from 1991 to 1993 with an Advisory Committee (CAN-HUG) chaired for the first year by Peter Pearson and thereafter by me, with Bronwen's assistance. Bronwen's job was as an administrative assistant and much of her work involved the day-to-day organization of the Single Genome Workshops (SGWs), almost all of which she attended to monitor the arrangements (including funding aspects) and to advise on the CAN-HUG guidelines. The project was continued for the following five years under BIOMED 1 who contracted out the project to HUGO Outstation Cambridge via HUGO (London). Bronwen was based in the Cambridge University Department of Pathology that I was responsible for, funded by BIOMED 1. Bronwen's involvement with the project lasted 10 years and she retired when it finished in 1998.' Note on draft transcript, 8 February 2015.

[258] Cook-Deegan *et al.* (1990), pages 653–4.

their work gets, not left out but it gets slightly downplayed, and would anybody like to say something about the overall genome map as it evolved? I'm thinking of Généthon.[259]

Ferguson-Smith: That was funded wasn't it by a television appeal initially and Jean Weissenbach, as I recall, was one of the key people in that. And Daniel Cohen perhaps?

Harper: Yes, indeed.

Bodmer: Wasn't that to do with CEPH?

Ferguson-Smith: Oh yes, using CEPH families, absolutely.

Bodmer: So the whole basis, I mean do people know that CEPH is Centre d'Étude du Polymorphisme Humain, which was founded by Jean Dausset.[260] He used to run an art gallery and a woman who he knew very well who had an extremely valuable set of paintings auctioned them and it's that money that actually set up CEPH and he had the idea of having this collaborative family study, which involved the Utah people as well. It was CEPH that provided a lot of the basic family data that led to conventional mapping using DNA markers to give you an actual map. I take it that's what Généthon was largely about, was it?

Ferguson-Smith: Yes. Everybody was using the CEPH families, very much later too.

Povey: Really we need to remember the date of the Weissenbach map with the 5,000 dinucleotide repeats. When were they available? I think it was 1994.

Bakker: There was a smaller one published in 1992, a smaller version.[261]

Povey: Yes, my impression was that it was really after the HGM meetings.

Bakker: Yes, so 1992 was a basic map with less markers, then in 1994 it was a *Nature* genetics paper with many markers, over 5,000 or so.[262]

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[259] 'Généthon was founded in 1990 by the Association Française contre les Myopathies (AFM-Telethon) and the Centre d'Etude du Polymorphisme Humain (CEPH). Its mission was to develop the tools needed to understand genetically inherited disorders.'; quoted from the Généthon website, http://www.genethon.fr/en/about-us/history/ (visited 5 March 2015).

[260] See note 205.

[261] See note 238.

[262] Gyapay *et al.* (1994).

Povey: So that was using CEPH for the same purpose but it was a different set of markers, which really hadn't come in at the time we're talking about, HGM11.

Bodmer: To what extent did that feed into the genome sequencing and making YAC maps that overlap and things like that?

Bakker: Yes, it did, because the Chromosome Workshops that ended up like the one in Palo Alto in Stanford University, led by Richard Myers, was the third workshop on chromosome 4 in 1993.[263] There, they had the YACs mapped but on the YACs you had also the STR (short tandem repeat) markers mapped, so you knew what was there.

Bodmer: So you could align them up?

Bakker: Align the YAC maps and the cosmids. For chromosome 4, I had 31 A4 pieces glued together for the long arm of chromosome 4, all the YACs, and the markers across. And it was based on the EUROGEM map.[264]

Bodmer: Were a lot of those markers actually assigned to their chromosome initially by somatic cell hybrids?

Bakker: No, these were all by linkage in the EUROGEM map. There were a few basic ones that were, of course, from the old data marker points.

Bodmer: But if you were using some of the marker probes that Nigel Spurr produced, a lot of those would have come from knowing where they were on the chromosome already.

Bakker: Those were the original probes, yes. And they were used as anchor points. They were a mixture of all things. Also, Utah markers were in there, and some older markers were relocated.

Bodmer: Of the somatic cell mapping, the YACs and the family data that created the statue on the basis of which then the public genome sequence was done.

Harper: I'd like now to pass things back to Michael Morgan in the first instance to look at, again, not just the transition between gene mapping and sequencing but also to ask the question: how much did the sequencing initiatives depend on the map, both physical and linkage? I've read different stories and in some

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[263] Myers and van Ommen (1994).

[264] Bakker *et al.* (1994).

the map hardly appears and the sequence seems to have been the beginning and the end of it.[265] And there are others, it's different. And it would be nice, particularly since Wellcome is undertaking a major history of the Human Genome Project in its historical documentation, it would be nice to hear first from Michael and then from others how the one either evolved into the other or what strength the links actually had.[266] So Michael, if you'd like to say a bit about that.

Morgan: Before going on to the Human Genome Project, I wanted to speak of Généthon and Jean Weissenbach simply to say that there is an equivalent process going on in France in Généthon to set up an archive of the French history in genomics.[267] As far as I'm concerned the maps were very important, physical maps and genetic maps, if for no other reason than wanting to tie the sequence into the appropriate material so to speak. So I think there was a lot of feed in and feed out. Obviously the clone maps were extremely important as the necessary tools for doing the sequencing. In terms of how did Wellcome get involved, as I say it was really as a result of the Medical Research Council not having sufficient resources to build up a major sequencing facility at LMB (Laboratory of Molecular Biology). I'm sure they had the foresight to see that that is what they wanted to do and they did have this model already of major collaboration with the NIH over mapping and eventually sequencing of the nematode.[268]

Well, the interesting thing from my perspective, as an administrator/manager, was the process by which the Wellcome Trust happened to be in a position to be involved, which was basically because a trustee of the Wellcome Trust had a father who allowed the Nuffield Foundation, he thought, to sink without a trace when the share price of Morris Motors disappeared and he was determined that that wouldn't happen to Wellcome.[269] So they'd engineered, they had to go to the High Court to do it, to get permission to sell off a chunk of Wellcome,

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265 Jordan (1993).

266 Historical records for the Human Genome Project are deposited in the Wellcome Library, Archives and Manuscripts, reference PPSUL/B/2.

267 See note 78.

268 See notes 245–6.

269 Sir Roger Gibbs was the person in question, a trustee of the Wellcome Trust and Chairman of its Board of Governors from 1989 to 1999. His father was Sir Geoffrey Gibbs, a trustee and later Chairman of the Nuffield Foundation.

the company. That gave them, for the first time, significant resources. And it was happenstance in a sense that the scene was set to enable them to come to a fairly rapid decision to spend the largest grant they'd ever made, £47 million, with a contribution from the MRC, in 1992. By early 1993 the first sequencing was going on at the Hinxton campus.[270] John Sulston was a very persuasive, shall we say, advocate of large-scale human sequencing rather than the cDNA route that's been talked about, as was Francis Collins, in particular, at the NIH.[271] I remember John and I looking for ways and means to actually enable this very large enterprise to go ahead, and at the time John felt that all he needed was about 50,000 square feet to get the job done. Eventually, I mean I don't know how big the genome campus at Hinxton now is, but it's significantly larger, shall we say. I think the turning point for the Trust was, first of all, the setting up of the workshops that took place in Bermuda and set out the principles that as soon as two kilobases of human DNA sequence was accumulated it would be released immediately on the internet, the 'no intellectual property' position would be taken rather than a protective position to make sure that the data remained freely available. That's had as much of an impact outside of genomics as probably the human genome has had within genomics. I take Walter's point that this was not in a classic sense small laboratory science, there were a lot of participants to begin with, but it became clear that this was an instance where large scale did reduce costs. It was managed mainly by Francis Collins from the NIH; there were meetings every single week by telephone, so it was not micromanaged. It was driven by the scientists, it was driven by targets and of course at some stage Craig Venter came back on the scene but that's another story.[272]

Bodmer: The Human Genome Project surely came from what the Human Gene Mapping Workshops and the HUGO community had done. That's how they knew about it. So Bridget Ogilvie was still the Director of the Wellcome Trust at that time, at the time the main decision was made. Is that right?

Morgan: Yes, absolutely.

Bodmer: Yes, and, of course, we're sitting in the Gibbs building and it was Roger Gibbs who you were talking about?

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[270] See note 246.

[271] Dr Francis Collins directed the National Human Genome Research Institute at the National Institutes for Health (NIH), USA, from 1993 to 2008. He has been the Director of the NIH since 2009; http://www.hhs.gov/about/foa/opdivs/nih.html (visited 5 February 2015).

[272] See note 225.

Morgan: No, it wasn't actually, it was David Steel.

Bodmer: My understanding was it was Roger Gibbs who actually empowered the whole business of getting the money and doing the investment but I may have got that wrong.

Morgan: You may be right, Walter.

Bodmer: It's a very important point because it's the availability of that free money without government constraint that clearly made this possible and then probably forced the MRC to play some part in it because they had been quite reluctant to take any major initiative in this direction.

Morgan: What's actually interesting, Walter, is that the decision to go ahead with Hinxton, not with Hinxton, with supporting a proposal for John (Sulston), was made before the share sale so it was a real trust, it was a real gamble. They must have known about it.

Bodmer: It sure was if they hadn't got the money. [Laughter]

Morgan: They must have known about it but they didn't have the money. They did by the time they made the decision but they didn't have the money when they told John to put in a proposal.

Bodmer: The political climate was really quite difficult because at the time Sydney Brenner and I were talking a lot about it, and I wrote a letter to the then president of the Royal Society, George Porter, saying perhaps in order to get people together on this, because they were in a sense different factions, the Royal Society could play some sort of a coordinating role. And basically they wrote back and said, 'We don't do that sort of thing because we can't get everybody to agree to it', which I think was also a shame.[273]

Morgan: The other thing that is important are the other strands that eventually came together at Hinxton. The major one was Lennart Phillipson helping with the decision for the EMBL (European Molecular Biology Laboratory) to receive a proposal to house a European Bioinformatics Institute (EBI) other than alongside the EMBL. The UK got its act together, very quickly driven by the MRC, and put in a proposal that won the bid and the EBI came to Hinxton.

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[273] Some correspondence with Sir George Porter during this period is deposited in Professor Sir Walter Bodmer's archives at the Bodleian Library, Oxford, reference MS. Bodmer. A.2.

Figure 17: Dr Susan Wallace

Bodmer: When was that? By that time he must have changed his tune about the Genome Project?

Morgan: Well, I think the main driver for that in the UK was Michael Ashburner, in 1992, and the decision was made in 1993, I think, and then the MRC decided to move the resource centre from Northwick Park to Hinxton.[274]

Dr Susan Wallace: I was the administrator for HUGO's American office starting in 1993, so I apologize I'm a little late for your meeting time-wise but I just wanted to skip back to the link between the Single Chromosome Workshops and HUGO, and I believe there was a strong relationship and there's a strong acknowledgement on the part of, certainly, members of the HUGO council that the Single Chromosome Workshops needed to be supported. I know for a fact, because I worked with Bronwen on the other side of the Atlantic on some of the Single Chromosome Workshops; she and I were in Cambridge at the chromosome 4 workshop I believe it was when there were difficulties and perhaps splinters between the group and talks about not sharing data, etc. We rang John Sulston up and said, 'You're on the Council of HUGO, John, go talk to these guys'. And he did. So I think there certainly was, over the years,

[274] Michael Ashburner FRS (b. 1942) was Professor of Biology at the University of Cambridge from 1991 to 2009.

strong support for the workshops and integration until such time as large-scale sequencing took off. That's one memory I have of the connection between the two.

Bodmer: Who was the president of HUGO then, because I must have given up after 1991 I think?

Wallace: Yes, I think it was Tom Caskey by then. He was president when I came in.[275]

Rawlings: The only thing I can think that perhaps we haven't given enough air time to is what was just briefly mentioned about the Human Gene Mapping Project Resource Centre the MRC had funded at Northwick Park, because that was also part of this transitional structure between the coordinated mapping internationally and the UK focus of that moving also to an EST and cDNA sequencing resource. And I also believe there was a linkage hotel activity as well, where again it was recognized that not everybody had the technical skills or weren't sufficiently trained in the genetics to run the software needed so that the training component was there both in bioinformatics and in linkage analysis and then there was an opportunity to provide a sequence, a small DNA sequencing resource. If I remember, if you sent in your constructs they would do that sequencing and that was run partly by Martin Bishop and Tom Freeman for a while. I can't remember who else was involved prior to that but that was quite important for a while, possibly for only three or four years before the whole, maybe for longer actually but obviously the whole Sanger Centre moving there and scaling up made a big difference to the basis for that centre. It closed at a time, I can't remember when it finally closed its doors, probably late 1990s. Other people may know it better than I do; I just thought we hadn't mentioned that enough perhaps.

Morgan: I wanted to pick up on something earlier: Walter made the comment about EMBL not really taking on a role early in this that could have been of great significance and you mentioned, Ian, about sequencing. It's coming back to your point about the technology being very important. Now the LKB/Pharmacia machine, was that something that had been developed at EMBL and they commercialized it, or have I got the wrong machine?

Craig: I think they were, I'm not absolutely sure.

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[275] Professor Thomas Caskey was President of HUGO from 1993 to 1995; see http://hugo-international.org/abt_hugopresidents.php (visited 20 January 2015).

Morgan: There were a lot of missed opportunities in Europe. The European Union never got involved in supporting large-scale sequencing.

Harper: Well I think we've given this topic a really thorough going-over actually, allowing for the folk who aren't here and on the other side of the Atlantic, and I think it's actually a pretty amazing story, how gene mapping has gone from very small, rather abstruse beginnings, and yet saying that it's always had in mind the potential for important applications in prediction and other things. But how it's developed and how really people have been able to see it in their lifetime start with the beginnings of the map and go on through to the sequence has been pretty amazing. I think people like myself who have been very peripherally involved have felt it a tremendous privilege to be even a very small part of the community. And it has been a community that has actually developed and survived despite a lot of stresses, perhaps from the inside as well as the outside. So I think it's very important to document this as fully as possible. I do hope that Wellcome's major initiative on the Genome Project doesn't forget about the mapping phase. I'm sure it won't, and I think, hopefully, those of us at this seminar will go back home and suddenly realise that we've got tucked away somewhere interesting photos, illustrative archival material, all of which, if you get in touch with Tilli's team, can then be incorporated.

Tansey: Thank you very much, Peter. Well, thank you all very much for coming this afternoon. It's been a privilege to listen to you all, and some very elucidating and entertaining stories. I'd like to pay a particular thank you to Peter, of course, for chairing this meeting so nicely as usual. He's done so many of these and I think you now, with David Weatherall, hold the record, for the most Witness Seminars chaired. So particular thanks to Peter. [Applause]

APPENDICES

Appendix 1

Photographs of participants at HGM1, Yale; *'New Haven Conference 1973: First International Workshop on Human Gene Mapping'*[276]

Plate 1.

[276] Reproduced from Ruddle et al. (eds) (1974a); pages 206–11.

Plate 1

1st row
P Meera Khan, P J McAlpine, J L Hamerton
F T Kao
J H Edwards, E B Robson, J H Renwick

2nd row
D Bergsma
L Chasin
L R Weitkamp

3rd row
K C Atwood, S Boyer
M Siniscalco
D Bootsma, E R Giblett, E H Y Chu

4th row
H J Evans, F H Allen Jr, M J Murnane, R S Kucherlapati
D Warburton, D Bootsma
L Coriell

5th row
L Langeler, C Tan
E R Giblett, C T Falk
W Bias

Plate 2.

Plate 2

1st row
P L Pearson
H van Someren, P W Allderdice
J L Hamerton, P J McAlpine

2nd row
J German
M Krim, P W Allderdice
N Van Cong

3rd row
I W Craig
E Nichols, G J Darlington, F Gilbert, G A Chase
F H Allen Jr, P J L Cook

4th row
P Meera Khan
P S Gerald, V A McKusick
C T Falk, K Hirschhorn

5th row
F A McMorris
D S Borgaonkar, MrsBorgaonkar, R S Kucherlapati
J A Tischfield, C Partridge

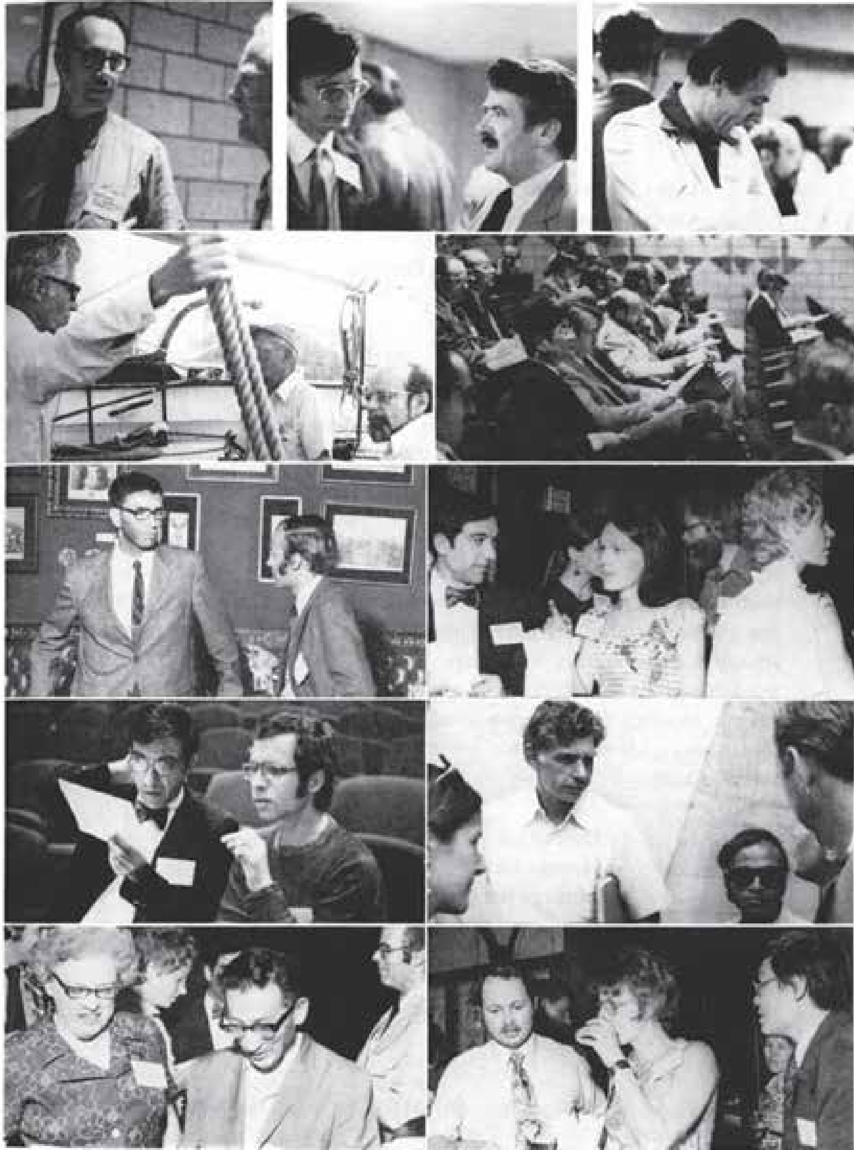

Plate 3.

Plate 3

1st row
E W Lovrein
P L Pearson, J Frézal
J H Edwards

2nd row
D M Steffensen, unidentified, H P Klinger
Participants

3rd row
H van Someren, R S Kucherlapati
G A Chase, G J Darlington, M J Murnane
L R Weitkamp, E A Nichols

4th row
G A Chase, J Ott
G J Darlington, F H Ruddle, R S Kucherlapati

5th row
E R Giblett, E A Nichols, J Mori, R Miller
T B Shows, J A Brown, P W Allderdice, C-C Lin

Appendix 2

Participants in the European Molecular Biology Organization (EMBO) workshop on 'Cell Hybridization and Somatic Cell Genetics', Oxford, 12–14 July 1973. Convened by Professor Walter Bodmer.

Key to photograph, identified where possible by Witness Seminar participants and their colleagues.

1. John Minna
2. –
3. Ruth Sager
4. –
5. Salvador Luria
6. Markus Nabholz
7. François Jacob
8. Rory Hope
9. Gordon Tomkins
10. Charles Ford
11. Julia Bodmer
12. Sue Povey
13. –
14. –
15. Alec Jeffreys
16. Peter Goodfellow
17. George Klein
18. Henry Harris
19. –
20. –
21. Chris Marshall
22. David Secher
23. –
24. Bengt Bengtsson
25. –
26. –
27. R T Johnston
28. –
29. Mike (Michael) Crumpton
30. Boris Ephrussi
31. Martin Bobrow
32. –
33. unidentified, possibly Pat Gormley
34. Bette Robson
35. Ian Craig
36. Veronica van Heyningen
37. Meera Khan
38. David Hopkinson
39. –
40. Orlando J (Jack) Miller
41. –
42. Niels Ringertz
43. Eric Sidebottom
44. –
45. Tom Brody
46. –
47. Roger Kennett
48. –
49. Anne Hagemeijer
50. Harry Harris
51. –
52. Matthew Scharff
53. Peter Cook*
54. Richard Denney
55. Walter Bodmer
56. –
57. Peter Pearson
58. –
59. –
60. Gordon Sato
61. –
62. John Watkins
63. –
64. Mary Weiss
65. Marc Fellous
66. Anne Turner (later Anne Moir)
67. Andries Westerveld
68. Nguyen Van Cong
69. Harry van Someren
70. unidentified, possibly Liesbeth van Someren

* Peter Cook from the University of Oxford, not Peter Cook of the Galton Laboratory.

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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 Genetic 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 Timothy Bishop PhD FMedSci (b. 1953) was educated at the universities of Bristol and Sheffield, in mathematics and statistics, receiving his doctorate from the latter in 1978 in probability and statistics. In 1979, he moved to the University of Utah, Salt Lake City, where he commenced his postdoctoral research on investigating the links between data in the population records of Mormon families with Utah State's cancer registration records and death certificates. Remaining in Utah, he became Assistant Professor at the Department of Medical Informatics (1979–1986) and then Associate Professor (1986–1989) and Adjunct Associate Professor (1989–1997). His research in the 1980s was facilitated by the use of recombinant DNA technology to identify genetic variation and the production of genome maps to investigate the potential for identifying breast and colorectal cancer genes. Returning to the UK in 1989, he became Senior Scientist and Head of Laboratory at the Imperial Cancer Research Fund in Leeds, running a research

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

group in genetic epidemiology and familial cancer susceptibility. This group was a key research centre that contributed to international efforts to, eventually, map and identify the genes for breast and colorectal cancer. He is currently Director of the Leeds Institute of Cancer and Pathology (2011–).

Professor Sir Walter Bodmer Kt FMedSci FRCPath FRS FSB (b. 1936) was educated at Clare College, Cambridge, UK; moving from a mathematics degree to population genetics for his doctoral research under R A Fisher, which was completed in 1959. As a postdoctoral fellow he worked with Nobel Laureate Joshua Lederberg at Stanford University's Department of Genetics, USA, while training in molecular biology. At Stanford, he became Assistant and then Associate Professor of the Department of Genetics (1962–1968), and Professor (1968–1970), during which time he contributed to the discovery of the HLA system. From 1970 he was Professor of Genetics, University of Oxford, until his appointment in 1979 as Director of Research at the Imperial Cancer Research Fund (ICRF), London. He became the first Director-General of the ICRF (1991–1996). He was appointed Principal of Hertford College, University of Oxford (1996–2005), where he also became Head of the Cancer and Immunogenetics Laboratory at the Weatherall Institute of Molecular Medicine (funded by the ICRF, latterly, in part, by Cancer Research UK). His many distinguished awards and honorary positions include a Fellowship of the Royal Society, London, 1974; election to the National Academy of Sciences, USA, in 1981; (first) presidency of the International Federation of Associations for the Advancement of Science and Technology (1992–1994), and membership of the board of patrons, St Mark's Hospital, London, since 1996 and, from 2008 to 2014, Presidency of the Galton Institute. In 2013, he was also awarded a Royal Society Royal Medal 'for seminal contributions to population genetics, gene mapping, and understanding of familial genetic disease'. He has published more than 700 papers and has also co-authored four books: Cavalli-Sforza and Bodmer (1971); Jones and Bodmer (1974); Bodmer and Cavalli-Sforza (1976); Bodmer and McKie (1994). Sir Walter is credited as being one of the first people to propose the Human Genome Project.

Professor Ian Craig
PhD (b. 1943) is Professor of Molecular Psychiatric Genetics and Head of the Molecular Genetics Section of the Social Genetic and Developmental Psychiatry Centre (SGDP), Kings College London, Institute of Psychiatry. He graduated in Biochemistry from the University of Liverpool and completed a PhD there in 1968, followed by a NATO Post-Doctoral Fellowship at the University of California, Santa Barbara. He returned to the UK with a position at the Genetics Unit at the Department of Biochemistry at Oxford University and was appointed to the titular post of Professor in Genetics there in 1996. His group was involved in one of the early positional cloning successes (a gene for X-linked blindness and mental retardation) and in the isolation and characterization of additional genes implicated in a range of human disorders. His interests in human gene mapping involved participation in the development of the Genome Database, GDB, as a Chromosome Editor and subsequently through election to the Human Genome Organisation (HUGO) Council (2000–2006) and appointment as Trustee to HUGO, London (2010). He moved to the SGDP Centre in 1998 with interests in a variety of projects concentrating on searches for genes implicated in a range of behaviours and disorders. He also has a particular interest in the contributions of the X and Y chromosomes to sex differences in behaviour. Most recently, he has collaborated in whole genome association scans for genes implicated in the aetiology and pharmacogenetics of depression.

Professor John Hilton Edwards
FRCP FRS (1928–2007) held appointments in medicine, neurology, psychiatry, and pathology, in epidemiology and clinical genetics at Birmingham University from 1953 to 1979. He was Professor of Genetics and NHS Consultant in Oxford from 1979 to 1995.

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 that developed in the late 1950s 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 human gene mapping, 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,* 6th edition (Tobias, Connor and Ferguson-Smith (2011)).

Professor Peter Goodfellow

PhD FMedSci FRS (b. 1951) studied at Oxford University, where his doctoral research was supervised by Professor Walter Bodmer. Between 1975 and 1979 he held postdoctoral fellowships at Oxford and Stanford Universities. He worked at the ICRF laboratories in Lincoln's Inn Fields in London (now part of CRUK) for 13 years, becoming Principal Scientist (1986–1992), and then Balfour Professor of Genetics at Cambridge University (1992–1996). He was a member of the German Human Genome Project Advisory Board (1995–1999) and the UK Government's Human Genetics Commission (2000–2002). From 1996 to 2006 he worked in the pharmaceutical industry as Worldwide Head of Research for SmithKline Beecham, and then as Senior Vice-President of Discovery Research at GlaxoSmithKline. He currently works for the venture capital company Abingworth, and is a board member of several companies and medical charities.

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). 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 (2006a)), 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 (www.genmedhist.org). 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 Harry Harris
FRCP FRS (1919–1994), biochemist and geneticist, qualified in medicine at Trinity College, Cambridge, served in the forces and joined the Galton Laboratory at UCL in 1947 where he pioneered the field of human biochemical genetics, became a lecturer in the Department of Biochemistry (1950–1953), Senior Lecturer (1953–1958), Reader in Biochemical Genetics (1958–1960), and Professor of Biochemistry, University of London (1960–1965). He was Honorary Director of the MRC Human Biochemical Genetics Research Unit (1961–1976), Professor of Human Genetics, University of London (1965–1976), and Harnwell Professor of Human Genetics, University of Pennsylvania (1976–1990), later Emeritus. See Harris (1959).

Professor Veronica van Heyningen
CBE DPhil FRS FRSE FMedSci (b. 1946) studied at Cambridge (BA Cantab), Northwestern, Illinois (MS), and at Oxford (DPhil) with Professor Walter Bodmer as her supervisor. She was Beit Memorial Fellow at the Genetics Laboratory, Oxford (1973–1974), then the MRC Mammalian Genome Unit (1974–1976). She worked at the MRC's Human Genetics Unit from 1977, starting as a postdoctoral scientist, and becoming Head of the Cell and Molecular Genetics Section (now Medical and Developmental Genetics) in 1992, a post in which she remained until 2012. In 1995 she was conferred

with an honorary professorship in the University of Edinburgh's Faculty of Medicine, and from 2000 to 2005 she was a member of the UK government's Human Genetics Commission, chairing its Horizon-scanning subgroup. She served as President of the European Society of Human Genetics from 2003 to 2004, and of the Genetics Society (UK) from 2009 to 2012, and was a member of the HUGO Council from 2006 to 2012. She is currently President of the Galton Institute.

Professor Maj Hultén
PhD MD FRCPath studied psychology at Stockholm University, then switched to genetics at the University of Lund, where she was inspired by Joe-Hin Tijo's role in the identification of man's 46 chromosomes, rather than 48 as previously thought, during his visit to the university.[277] She went on to study medicine, graduating from the Karolinska Institutet, Stockholm. In 1975, she moved to the UK to become the Head of the Regional Genetics Services at the East Birmingham/Heartlands Hospital, serving a population of 5.5 million, a position she held until 1997. She was awarded an honorary professorial position at Birmingham University (1989–1999) and at Warwick University (1996–2013). Since 2012, she has been Professor Emerita at the Karolinska Institutet, Stockholm. Her main research interests are the mechanisms of the origins of genetic disease and meiosis. She is also committed to the support of patient and carers' associations for genetic disease, particularly as the Chief Medical Officer for Unique; www.rarechromo.org (visited 5 March 2015).

Professor Victor McKusick
MD (1921–2008) qualified in medicine at Johns Hopkins University and completed his internship and residency in internal medicine there. He was Executive Chief of the Cardiovascular Unit at Baltimore Marine Hospital (1948–1950), while progressing through the ranks in the Johns Hopkins Department of Medicine. He also held joint professorships in epidemiology in the Johns Hopkins University School of Public Health and in biology. He founded the Division of Medical Genetics in 1957, which he headed until 1973, when he became the William Osler Professor and Chairman of the Department of Medicine, and Physician-in-Chief of Johns

[277] See Hultén (2002) and Harper (2006b).

Hopkins Hospital. He held these posts until 1985, when he was named University Professor of Medical Genetics.

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 3 February 2015).

Professor Michael Morgan

PhD (b. 1942) was Director of Research Partnerships and Ventures at the Wellcome Trust and Chief Executive of the Wellcome Trust Genome Campus in Cambridge until his retirement in 2002. He joined the Trust in 1983, and was responsible for the development of new enterprises, such as DIAMOND, the new third generation synchrotron being built in partnership with the UK government and the SNPs Consortium (a partnership of the Trust and 12 private companies). He played a major role in the international coordination of the Human Genome Project and was also responsible for scientific establishments such as the Wellcome Trust Genome Campus. Following his retirement from the Trust, he was retained as a Director of DIAMOND and Chairman of the Structural Genomics Consortium, a partnership with Canadian and Swedish public entities and GlaxoSmithKline tasked with determining the structures of human proteins of importance to human health – Novartis and Merck joined the second phase of this enterprise. From 2006 until his retirement in 2009, he was Chief Scientific Officer of Genome Canada, where he instituted a new consultative process to determine strategic priorities for Canadian investments in genomic, proteomic, and allied research programmes. Morgan has also served as a Trustee of the Institute of Cancer Research, the Scottish Crop Research Institute, and the Transatlantic Harkness Foundation. He is a graduate of Trinity College, Dublin, and obtained his PhD from Leicester University.

Professor Sue Povey

MD MA (b. 1942) graduated in natural sciences (genetics) at Cambridge in 1964 and qualified in medicine in 1967. After brief

clinical experience at University College Hospital, London, Huddersfield, and working for Save the Children Fund in Algeria, she returned to University College London to join the MRC Human Biochemical Genetics unit under Harry Harris in 1970. Having obtained an MD in 1977, she became fascinated by human gene mapping and its many different techniques and was involved in all the HGM meetings between 1975 and 1991. Her interests eventually focused on chromosome 9, for which she organized several Single Chromosome Workshops, pursuing the elusive *TSC1* gene on 9q34 (defective in some cases of tuberous sclerosis) for more than ten years until it was finally identified by international collaboration and intensive positional cloning in 1997. From 1996 till 2007 she was Chair of the HUGO Human Gene Nomenclature Committee with a team supported by the MRC, NIH, and the Wellcome Trust. Elected a Fellow of the Academy of Medical Sciences in 2001, she was Deputy Director of the MRC Unit (1989–2000), then appointed Haldane Professor of Human Genetics at UCL and Editor of the *Annals of Human Genetics* until her retirement in 2007. As Professor Emeritus of Human Genetics her interest in tuberous sclerosis continues in the curation of the *TSC1* and *TSC2* locus-specific mutation databases, and she has chaired a working group drafting ethical guidelines for such databases.

Professor Chris Rawlings PhD (b. 1954) started his bioinformatics career at the Imperial Cancer Research Fund in 1982 during which time he was the Project Manager for the computing infrastructure needed for the Human Gene Mapping Workshops (10.5 and 11). From 1991 to 1996, he led a group that researched the application of advanced logic languages to genetic mapping and protein structure bioinformatics. In 1996 he moved to SmithKline Beecham, where he was responsible for the bioinformatics platforms supporting human genetics, comparative genomics, and gene expression. From 2000 to 2004, he was the Director of Bioinformatics at Oxagen Ltd, where his group worked on the identification and validation of genes and drug targets from human genetics and genomics technologies. He moved to Rothamsted Research in 2004, where he now leads the Department of Computational and Systems Biology, which comprises over 30 staff and students engaged in research into, and application of, bioinformatics, mathematical modelling, and statistics to

problems from the agricultural sciences. His personal research interests are in the development and use of data integration systems for supporting systems biology and for candidate gene discovery from multi-omics datasets. He is a visiting Professor in the Department of Computing at Imperial College London, and was also one of the founding members and former Vice President of the International Society for Computational Biology.

Professor Frank Ruddle
PhD (1929–2013) studied zoology at the University of California, Berkeley. He conducted postdoctoral research at Guido Pontecorvo's laboratory in Glasgow from 1960 to 1961, working with John Paul. He returned to the USA and worked at Yale for the remainder of his career, becoming a professor in 1972 and helping to found the University's Human Genetics Department. In 1973 he convened the first Human Gene Mapping Workshop at Yale, New Haven (Connecticut, USA) and was joint Conference Scientific Editor for HGM1–3. He also developed the first computerized database of human gene mapping data. For an obituary see Kucherlapati and Leinwand (2013).

Professor Ellen Solomon
PhD FMedSci (b. 1943) studied biological chemistry at Harvard University. Her postdoctoral fellowship at the Institut Pasteur (1971–1973) was followed by fellowships at the University of California Medical Center (1973–1974) and at the Genetics Laboratory at Oxford's Department of Biochemistry (1974–1976). From 1976 to 1979 she was Senior Scientist at the Imperial Cancer Research Fund, London, then Principal Scientist from 1986 to 1995. At King's College London School of Medicine, from 1995 to 2009, she was Head of the Department of Medical and Molecular Genetics and of the Division of Genetics and Molecular Genetics. At King's, at present, she is Prince Phillip Professor of Human Genetics (since 2004); Research Dean of the London School of Medicine (2004–2013), and Dean for International Affairs (2008–2013). She was a member of the Executive Committee of the Human Gene Mapping Committee from 1991 to 1995, and co-organized HGM11 with Professor Sir Walter Bodmer. She was also Chairman of the Chromosome 17 Committee for HGM9.5, 10.5, and 11, and co-organized the Chromosome 17 Single-Chromosome Workshops in 1990,

1991, and 1992. In 1992 she was elected to EMBO and in 1995 to the HUGO Council. She was on the editorial board of *Cytogenetics and Cell Genetics* from 1980 to 1985, and currently serves on the editorial boards of *Human Genomics.*

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.

Dr Susan Wallace
PhD (b. 1960) is Lecturer of Population and Public Health Sciences in the Department of Health Sciences at the University of Leicester. Her research interests include the legal and policy implications of population-based and disease-based longitudinal cohort studies and biobanks; the ethical issues surrounding the collection, use, linking and sharing of research data; and research ethics review. Currently, she is a member of the Nuffield Council on Bioethics Working Party on Biological and Health Data, and of the Ethics and Governance Council of UK Biobank. She also sits on the International Cancer Genome Consortium (ICGC) Ethics and Policy Committee and the UK ICGC Prostate Project Oversight Group. She is involved in the BioSHaRE-EU (FP7) project, which focuses on the development and evaluation of tools and methods for accessing and exploiting data from biobanks and cohort studies. She chairs the University of Leicester College of Medicine and Biological Sciences Research Ethics Committee.

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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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