

GENETIC TESTING

The transcript of a Witness Seminar held by the Wellcome Trust Centre for the History of Medicine at UCL, London, on 13 July 2001

Edited by D A Christie and E M Tansey

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Key

Front cover photographs, top to bottom:

Professor Marcus Pembrey
Dr Patricia Tippet
Professor Doris Zallen
Professor Sir David Weatherall, Professor Charles Rodeck

Inside front cover photographs, top to bottom:

Professor John Woodrow
Professor Rodney Harris
Professor John Edwards (1928–2007)
Professor Sue Povey

Back cover photographs, top to bottom:

Professor Ursula Mittwoch
Professor Malcolm Ferguson-Smith
Professor Matteo Adinolfi
Professor Paul Polani (1914–2006)

Inside back cover photographs, top to bottom:

Professor Matteo Adinolfi, Professor Paul Polani (1914–2006)
Professor Paul Polani (1914–2006), Professor Rodney Harris
Professor Bernadette Modell
Mrs Cathy Holding, Professor Alan Handyside

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INTRODUCTION

Genetic testing is now such a widespread and important part of medicine that it is hard to realize that it has almost all emerged during the past 30 years, with most of the key workers responsible for the discoveries and development of the field still living and active.

This alone makes it a suitable subject for a Witness Seminar but there are others that increase its value, notably the fact that a high proportion of the critical advances took place in the UK; not just the basic scientific research, but also the initial applications in clinical practice, particularly those involving inherited disorders.

To see these topics discussed by the people who were actually involved in their creation makes fascinating reading; for myself it is tinged with regret at having been unable to attend and contribute to the seminar, but with some compensation from being able to look at the contributions more objectively than can a participant.

This Witness Seminar reminds us of the broad scientific origins of human genetics, involving not only chromosomal and molecular technologies, but blood groups, immunological and biochemical approaches, as well as the theoretical basis of genetic linkage analysis. It is the synthesis of all of these and their use in a medical context, that has made the field such a rewarding one to work in, as well as one that has had major benefits for patients and families. So has its strongly collaborative and generous nature, something that is clearly reflected throughout this volume.

The one element largely absent from this seminar is the field of clinical genetics, but the organizers were probably wise not to attempt to include this, as they have had more than ample material by staying with the scientific brief of genetic testing. I sense that strict chairmanship was required to avoid discussions that could have occupied a week, not a day, so perhaps clinical genetics will merit its own Witness Seminar in the future. Meanwhile, all those who wish to know how genetic testing originated and developed will find many of their questions answered in the following pages.

Peter Harper

University of Wales College of Medicine, Cardiff

ACKNOWLEDGEMENTS

We are particularly grateful to Professor Doris Zallen, who assisted with the organization of the meeting; she provided many of the names of individuals to be invited and decided on the topics to be discussed. We also thank Professor Marcus Pembrey for his excellent chairing of the occasion and for his help with the planning of the meeting. Dr Paddy Ricard kindly read the edited transcript for general sense and understandability. We are equally grateful to Professor Peter Harper for writing the introduction to these published proceedings. We thank Professors John Edwards, Matteo Adinolfi and Ursula Mittwoch for their assistance in compiling the glossary, Professors John Edwards, Paul Polani, Malcolm Ferguson-Smith and Doris Zallen for additional help with the text, and Mr Richard Barnett for bibliographic research. Professor Joy Delhanty kindly provided the illustrations for the text.

As with all our meetings, we depend a great deal on our colleagues at the Wellcome Trust to ensure their smooth running: the Audiovisual department, the Medical Photographic Library and Mrs Tracy Tillotson; Ms Julie Wood, who has supervised the design and production of this volume, our indexer, Ms Liza Furnival, our readers, Ms Lucy Moore, Mr Simon Reynolds and Dr Paddy Ricard. Mrs Jaqui Carter is our transcriber, and Mrs Wendy Kutner and Mrs Lois Reynolds assist us in running the meetings. Finally we thank the Wellcome Trust for supporting this programme.

Tilli Tansey

Daphne Christie

Wellcome Trust Centre for the History of Medicine at UCL

WITNESS SEMINARS: MEETINGS AND PUBLICATIONS¹

In 1990 the Wellcome Trust created a History of Twentieth Century Medicine Group, as part of the Academic Unit of the Wellcome Institute for the History of Medicine, to bring together clinicians, scientists, historians and others interested in contemporary medical history. Among a number of other initiatives the format of Witness Seminars, used by the Institute of Contemporary British History to address issues of recent political history, was adopted, to promote interaction between these different groups, to emphasize the potential of working jointly, and to encourage the creation and deposit of archival sources for present and future use. In June 1999 the Governors of the Wellcome Trust decided that it would be appropriate for the Academic Unit to enjoy a more formal academic affiliation and turned the Unit into the Wellcome Trust Centre for the History of Medicine at University College London from 1 October 2000. The Wellcome Trust continues to fund the Witness Seminar programme via its support for the Centre.

The Witness Seminar is a particularly specialized form of oral history, where several people associated with a particular set of circumstances or events are invited to come together to discuss, debate, and agree or disagree about their memories. To date, the History of Twentieth Century Medicine Group has held over 30 such meetings, most of which have been published, as listed on pages xiii–xix.

Subjects for such meetings are usually proposed by, or through, members of the Programme Committee of the Group, and once an appropriate topic has been agreed, suitable participants are identified and invited. These inevitably lead to further contacts, and more suggestions of people to invite. As the organization of the meeting progresses, a flexible outline plan for the meeting is devised, usually with assistance from the meeting's chairman, and some participants are invited to 'set the ball rolling' on particular themes, by speaking for a short period of time to initiate and stimulate further discussion.

Each meeting is fully recorded, the tapes are transcribed and the unedited transcript is immediately sent to every participant. Each is asked to check their

¹ The following text also appears in the 'Introduction' to recent volumes of *Wellcome Witnesses to Twentieth Century Medicine* published by the Wellcome Trust and the Wellcome Trust Centre for the History of Medicine at University College London.

own contributions and to provide brief biographical details. The editors turn the transcript into readable text, and participants' minor corrections and comments are incorporated into that text, while biographical and bibliographical details are added as footnotes, as are more substantial comments and additional material provided by participants. The final scripts are then sent to every contributor, accompanied by forms assigning copyright to the Wellcome Trust. Copies of all additional correspondence received during the editorial process are deposited with the records of each meeting in Archives and Manuscripts, Wellcome Library, London.

As with all our meetings, we hope that even if the precise details of some of the technical sections are not clear to the nonspecialist, the sense and significance of the events are understandable. Our aim is for the volumes that emerge from these meetings to inform those with a general interest in the history of modern medicine and medical science; to provide historians with new insights, fresh material for study, and further themes for research; and to emphasize to the participants that events of the recent past, of their own working lives, are of proper and necessary concern to historians.

Members of the Programme Committee of the History of Twentieth Century Medicine Group

The Group's activities are overseen by the Programme Committee, which includes professional historians of medicine, practising scientists and clinicians. The Programme Committee during 2002–03 comprised:

Dr Tilli Tansey – Historian of Modern Medical Science, Wellcome Trust Centre at UCL, and Chair

Sir Christopher Booth – Wellcome Trust Centre at UCL, former Director, Clinical Research Centre, Northwick Park Hospital, London

Dr Robert Bud – Head of Life and Environmental Sciences, Science Museum, London

Dr Daphne Christie – Senior Research Assistant, Wellcome Trust Centre at UCL, and Organizing Secretary

Professor Hal Cook – Director, Wellcome Trust Centre at UCL

Dr Mark Jackson – Reader, Centre for Medical History, Exeter

Professor Ian McDonald – Harveian Librarian, Royal College of Physicians, London

Dr Jon Turney – Head of the Department of Science and Technology Studies, University College London

HISTORY OF TWENTIETH CENTURY MEDICINE WITNESS SEMINARS, 1993–2003

- 1993 **Monoclonal antibodies**
Organizers: Dr E M Tansey and Dr Peter Catterall
- 1994 **The early history of renal transplantation**
Organizer: Dr Stephen Lock
- Pneumoconiosis of coal workers**
Organizer: Dr E M Tansey
- 1995 **Self and non-self: a history of autoimmunity**
Organizers: Sir Christopher Booth and Dr E M Tansey
- Ashes to ashes: the history of smoking and health**
Organizers: Dr Stephen Lock and Dr E M Tansey
- Oral contraceptives**
Organizers: Dr Lara Marks and Dr E M Tansey
- Endogenous opiates**
Organizer: Dr E M Tansey
- 1996 **Committee on Safety of Drugs**
Organizers: Dr Stephen Lock and Dr E M Tansey
- Making the body more transparent: the impact of nuclear
magnetic resonance and magnetic resonance imaging**
Organizer: Sir Christopher Booth
- 1997 **Research in General Practice**
Organizers: Dr Ian Tait and Dr E M Tansey
- Drugs in psychiatric practice**
Organizers: Dr David Healy and Dr E M Tansey
- The MRC Common Cold Unit**
Organizers: Dr David Tyrrell and Dr E M Tansey
- The first heart transplant in the UK**
Organizer: Professor Tom Treasure

- 1998 Haemophilia: recent history of clinical management**
Organizers: Professor Christine Lee and Dr E M Tansey
- Obstetric ultrasound: historical perspectives**
Organizers: Dr Malcolm Nicolson, Mr John Fleming and Dr E M Tansey
- Post penicillin antibiotics**
Organizers: Dr Robert Bud and Dr E M Tansey
- Clinical research in Britain, 1950–1980**
Organizers: Dr David Gordon and Dr E M Tansey
- 1999 Intestinal absorption**
Organizers: Sir Christopher Booth and Dr E M Tansey
- The MRC Epidemiology Unit (South Wales)**
Organizers: Dr Andy Ness and Dr E M Tansey
- Neonatal intensive care**
Organizers: Professor Osmund Reynolds and Dr E M Tansey
- British contributions to medicine in Africa after the Second World War**
Organizers: Dr Mary Dobson, Dr Maureen Malowany,
Dr Gordon Cook and Dr E M Tansey
- 2000 Childhood asthma, and beyond**
Organizers: Dr Chris O’Callaghan and Dr Daphne Christie
- Peptic ulcer: rise and fall**
Organizers: Sir Christopher Booth, Professor Roy Pounder and
Dr E M Tansey
- Maternal care**
Organizers: Dr Irvine Loudon and Dr Daphne Christie
- 2001 Leukaemia**
Organizers: Professor Sir David Weatherall, Professor John Goldman,
Sir Christopher Booth and Dr Daphne Christie
- The MRC Applied Psychology Unit**
Organizers: Dr Geoff Bunn and Dr Daphne Christie
- Genetic testing**
Organizers: Professor Doris Zallen and Dr Daphne Christie

Foot and mouth disease: the 1967 outbreak and its aftermath

Organizers: Dr Abigail Woods, Dr Daphne Christie and Dr David Aickin

2002 Environmental toxicology: the legacy of *Silent Spring*

Organizers: Dr Robert Flanagan and Dr Daphne Christie

Cystic fibrosis

Organizers: Dr James Littlewood and Dr Daphne Christie

Innovation in pain management

Organizers: Professor David Clark and Dr Daphne Christie

2003 Thrombolysis

Organizers: Mr Robert Arnott and Dr Daphne Christie

Beyond the asylum: anti-psychiatry and care in the community

Organizers: Dr Mark Jackson and Dr Daphne Christie

The Rhesus factor story

Organizers: Professor Doris Zallen and Dr Daphne Christie

PUBLISHED MEETINGS

“...Few books are so intellectually stimulating or uplifting”.

Journal of the Royal Society of Medicine (1999) **92**: 206–208
review of vols 1 and 2

“...This is oral history at its best...all the volumes make compulsive reading...they are, primarily, important historical records”.

British Medical Journal (2002) **325**: 1119 review of the series

Technology transfer in Britain: The case of monoclonal antibodies

Self and non-self: A history of autoimmunity

Endogenous opiates

The Committee on Safety of Drugs

In: Tansey E M, Catterall P P, Christie D A, Willhoft S V, Reynolds L A. (eds)
(1997) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 1. London:
The Wellcome Trust, 135pp. ISBN 1 869835 79 4

Making the human body transparent: The impact of NMR and MRI

Research in General Practice

Drugs in psychiatric practice

The MRC Common Cold Unit

In: Tansey E M, Christie D A, Reynolds L A. (eds) (1998) *Wellcome Witnesses
to Twentieth Century Medicine*. Volume 2. London: The Wellcome Trust,
282pp. ISBN 1 869835 39 5

Early heart transplant surgery in the UK

In: Tansey E M, Reynolds L A. (eds) (1999) *Wellcome Witnesses to Twentieth
Century Medicine*. Volume 3. London: The Wellcome Trust, 72pp.
ISBN 1 841290 07 6

Haemophilia: Recent history of clinical management

In: Tansey E M, Christie D A. (eds) (1999) *Wellcome Witnesses to Twentieth Century
Medicine*. Volume 4. London: The Wellcome Trust, 90pp. ISBN 1 841290 08 4

Looking at the unborn: Historical aspects of obstetric ultrasound

In: Tansey E M, Christie D A. (eds) (2000) *Wellcome Witnesses to Twentieth Century
Medicine*. Volume 5. London: The Wellcome Trust, 80pp. ISBN 1 841290 11 4

Post penicillin antibiotics: From acceptance to resistance?

In: Tansey E M, Reynolds L A. (eds) (2000) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 6. London: The Wellcome Trust, 71pp. ISBN 1 841290 12 2

Clinical research in Britain, 1950–1980

In: Reynolds L A, Tansey E M. (eds) (2000) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 7. London: The Wellcome Trust, 74pp. ISBN 1 841290 16 5

Intestinal absorption

In: Christie D A, Tansey E M. (eds) (2000) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 8. London: The Wellcome Trust, 81pp. ISBN 1 841290 17 3

Neonatal intensive care

In: Christie D A, Tansey E M. (eds) (2001) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 9. London: The Wellcome Trust Centre for the History of Medicine at UCL, 84pp. ISBN 0 854840 76 1

British contributions to medical research and education in Africa after the Second World War

In: Reynolds L A, Tansey E M. (eds) (2001) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 10. London: The Wellcome Trust Centre for the History of Medicine at UCL, 93pp. ISBN 0 854840 77 X

Childhood asthma and beyond

In: Reynolds L A, Tansey E M. (eds) (2001) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 11. London: The Wellcome Trust Centre for the History of Medicine at UCL, 74pp. ISBN 0 854840 78 8

Maternal care

In: Christie D A, Tansey E M. (eds) (2001) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 12. London: The Wellcome Trust Centre for the History of Medicine at UCL, 88pp. ISBN 0 854840 79 6

Population-based research in south Wales: The MRC Pneumoconiosis Research Unit and the MRC Epidemiology Unit

In: Ness A R, Reynolds L A, Tansey E M. (eds) (2002) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 13. London: The Wellcome Trust Centre for the History of Medicine at UCL, 74pp. ISBN 0 854840 81 8

Peptic ulcer: Rise and fall

In: Christie D A, Tansey E M. (eds) (2002) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 14. London: The Wellcome Trust Centre for the History of Medicine at UCL, 143pp. ISBN 0 854840 84 2

Leukaemia

In: Christie D A, Tansey E M. (eds) (2003) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 15. London: The Wellcome Trust Centre for the History of Medicine at UCL, 86pp. ISBN 0 85484 087 7

The MRC Applied Psychology Unit

In: Reynolds L A, Tansey E M. (eds) (2003) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 16. London: The Wellcome Trust Centre for the History of Medicine at UCL, 94pp. ISBN 0 85484 088 5

Genetic testing

In: Christie D A, Tansey E M. (eds) (2003) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 17. London: The Wellcome Trust Centre for the History of Medicine at UCL, 130pp. ISBN 0 85484 094 X

Foot and mouth disease: The 1967 outbreak and its aftermath

In: Reynolds L A, Tansey E M. (eds) (2003) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 18. London: The Wellcome Trust Centre for the History of Medicine at UCL, 114pp. ISBN 0 85484 096 6

Environmental toxicology: The legacy of *Silent Spring*

In: Christie D A, Tansey E M. (eds) (2004) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 19. London: The Wellcome Trust Centre for the History of Medicine at UCL, in press. ISBN 0 85484 091 5

Cystic fibrosis

In: Christie D A, Tansey E M. (eds) (2004) *Wellcome Witnesses to Twentieth Century Medicine*. Volume 20. London: The Wellcome Trust Centre for the History of Medicine at UCL, in press. ISBN 0 85484 086 9

Volumes 1–12 cost £5.00 plus postage, with volumes 13–18 at £10 each. Orders of four or more volumes receive a 20 per cent discount. All 18 published volumes in the series are available at the special price of £95 plus postage. To order a copy contact t.tillotson@wellcome.ac.uk or by phone: +44 (0)20 7611 8486; or fax: +44 (0)20 7611 8703.

Other publications

Technology transfer in Britain: The case of monoclonal antibodies

In: Tansey E M, Catterall P P. (1993) *Contemporary Record* 9: 409–444.

Monoclonal antibodies: A witness seminar on contemporary medical history

In: Tansey E M, Catterall P P. (1994) *Medical History* 38: 322–327.

Chronic pulmonary disease in South Wales coalmines: An eye-witness account of the MRC surveys (1937–1942)

In: P D’Arcy Hart, edited and annotated by E M Tansey. (1998) *Social History of Medicine* 11: 459–468.

Ashes to Ashes – The history of smoking and health

In: Lock S P, Reynolds L A, Tansey E M. (eds) (1998) Amsterdam: Rodopi BV, 228pp. ISBN 90420 0396 0 (Hfl 125) (hardback). Reprinted 2003.

Witnessing medical history. An interview with Dr Rosemary Biggs

In: Professor Christine Lee and Dr Charles Rizza. (interviewers) (1998) *Haemophilia* 4: 769–777.

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Participants

Professor Matteo Adinolfi	Professor Marcus Pembrey (Chair)
Mrs Diane Barnett	Professor Naomi Pfeffer
Sir Christopher Booth	Professor Paul Polani
Professor Joy Delhanty	Professor Sue Povey
Professor John Edwards	Professor Derek Roberts
Professor Malcolm Ferguson-Smith	Professor Charles Rodeck
Professor David Galton	Dr Patricia Tippet
Professor Alan Handyside	Dr David Tyrrell
Professor Rodney Harris	Professor Sir David Weatherall
Mrs Cathy Holding	Professor John Woodrow
Professor Sue Malcolm	Mrs Elisabeth Young
Professor Ursula Mittwoch	Professor Doris Zallen
Professor Bernadette Modell	

Among those attending the meeting: Dr Priscilla Alderson, Dr Mike Buttolph, Dr Pete Coventry, Mr Michael Hopkins, Lord Kennett, Professor Linda Partridge, Professor Michael Patton, Miss Melanie Pearce, Professor Hilary Rose, Ms Joanna Sumner, Mrs Carol Youngs

Apologies include: Sir Walter Bodmer, Professor David Brock, Professor Kay Davies, Professor Robert Dingwall, Professor Dian Donnai, Professor Peter Harper, Professor David Hopkinson, Professor Patricia Jacobs, Professor Sir Alec Jeffreys, Professor Richard McConnell, Dame Anne McLaren, Professor Marilyn Monk, Professor Nicholas Wald, Professor Robert Williamson

Dr Daphne Christie: The History of Twentieth Century Medicine Group was established by the Wellcome Trust in 1990, to promote interaction between scientists, clinicians, and historians who have a common interest in the history of recent medicine and medical science. To that end this group has devised a number of mechanisms to try to promote that interaction, one of which is a series of Witness Seminars, where we invite people who have been involved in particular events, or discoveries, or who have seen a lot of changes during their working lives in practice, to discuss, debate, and to share with us their reminiscences and views of how things were and how things have changed.

Professor Doris Zallen and I have organized this meeting on genetic testing, and we are very grateful to Doris for her help and for travelling from the USA to be with us today. Doris will give a brief historical introduction to the subject in a few minutes' time. A key part in these meetings is in identifying a suitable chairman, and we are indeed delighted that Professor Pembrey has agreed to chair this one, so without further ado, I will hand over to the Chairman.

Professor Marcus Pembrey: Thank you very much. Welcome everybody. This is an informal occasion, and although I am going to try to move the programme through and keep you reasonably on track, the idea is to have anecdotes and exchanges that can record 'how it was'.

In thinking about when genetic tests started and what were the early genetic tests, I thought that we needed to have some kind of a definition to show that we are not talking about a clinical diagnosis of a genetic disorder, but a test that was pretty specific, with high predictive value, for either confirming or excluding a known specific genetic disorder, or a genetic trait, like a blood group. So thinking back, the screening as I know that went on under Lionel Penrose's direction in the Royal Eastern Counties' Institution in Colchester in the 1930s, of the urines of mentally handicapped patients for phenylpyruvic acid would fit the definition of a genetic test.¹ It was a particular thing that they had in mind, as with blood grouping. The other thing I recognize is that up until the precision of clear chromosomal abnormalities and DNA changes, a lot of the tests had to take in prior probability, that is the test was useful only because of the family history, the context in which it was done. So clearly we are not just talking about genetic tests but to some extent clinical genetic services as well.

¹ See Penrose (1935a, 1935b); Harris (1973): 523–529. Further details are given in a letter from Professor Marcus Pembrey to Dr Daphne Christie, 5 August 2003, which will be deposited with the records of the meeting in Archives and Manuscripts, Wellcome Library, London.

In thinking about how things began, clearly this was dictated largely by the available material, which was blood, and so later on, after Doris has given her introduction, we will be following, as an initial introduction, those two areas that came out of blood, the blood groups and the blood diseases on the one hand, and the peripheral blood lymphocytes as a source for looking at chromosomes and chromosomal changes on the other, and then leading obviously through the programme. Does anybody have any questions about the field, the terms of reference?

Professor Doris Zallen: I have been assigned to start the ball rolling with a scientific and historical introduction. I will keep it brief because the real experts are sitting in front of me. It's often very hard for historians to pick a particular date for the start of a field, but that's not the case in genetics. Historians of science all trace the start of the field to the year 1900, with the rediscovery of Mendel's laws. As you know, Mendel explained the patterns of inheritance he observed in pea plants by hypothesizing the existence of paired factors.² This rediscovery triggered a growth in research regarding the nature of those factors – research on all kinds of organisms – that intensified through the rest of the century.

By mid-century, genetic research received an additional boost when DNA was found to be the material of these factors, now called genes, and the structure of the molecule was worked out at Cambridge.³ Then, in the 1960s, came the work that led to the understanding of the mechanism of gene function, of the triplet nature of the genetic code, and the first insight into regulation of genes in bacteria.⁴ The knowledge generated in the laboratory often spun off other programmes of research with more practical ends. For example, genetics in the USA found a home, almost immediately after the rediscovery of Mendel's work, in agricultural research stations, located in every state in the country. That firm base of support and connection with the farming community, a community which wanted specific findings from science to help their work, encouraged the development in the USA of a large research effort dealing with the development of better crop plants and farm animals, of organisms with new combinations of traits. We are seeing the end-product of that now, with genetically modified foods that are the subject of debate around the world.⁵ So much of the ground-

² Mendel (1865).

³ Watson and Crick (1953).

⁴ Jacob and Monod (1961, 1962); Crick *et al.* (1961); Nirenberg and Matthei (1961); Nirenberg and Leder (1964); Clayton and Dennis (2003).

⁵ Soulsby (1997).

breaking work in genetics was carried out by scientists in Britain, I have a very long list – I will give you a few names that I know are familiar to all of you: names like Galton, Bateson, Pearson, Haldane, Fisher, Hardy, Ford, Sheppard, Crick, Franklin, Wilkins, Brenner, Sanger. A lot of the basic work was done here.

Research in *human* genetics generally lagged well behind that of other organisms and for obvious reasons: the small number of progeny, the long generation time, and the decided unwillingness of humans to submit to planned rounds of sexual crosses at the whim of investigators. As a result, applications of genetics to medicine tended to be scarce. Yet with the advent of new tools – of cytogenetic and recombinant DNA techniques, both of which made sex unnecessary – this was to change. The increasing pace of research in human genetics has culminated in the boldest project of all, the International Human Genome Project, which in 2000 provided the first rough draft of the entire human DNA base sequence.⁶ In just one century from the start in 1900, genetics has come a long way. Even before the Human Genome Project itself, genetics had begun to enter medicine, and we have seen that with the rise in the use of genetic testing. This has led to the prediction that the 21st century will see the growth and expansion of what we now call genetic medicine, that it will be a time in which genetic testing will be routinely offered, a time in which medicine will be operating under a new genetic paradigm, and in which testing for disease prevention will be a dominant activity. Once again, scientists and physicians in Britain have had a major involvement in the evolution of genetic medicine. Garrod, Haldane, Fisher, Penrose, Harris, Lawler, Clarke, as well as many of the individuals in this room, have created the environment in which this change has taken place.

Our goal today is to track the separate developments that have crystallized into genetic medicine by examining the various foci, the various nuclei of research and application. We have the rare opportunity to benefit from your experience and your recollections. We need to find out what happened, and, beyond that, we need to try to explain how it happened. For example, was there a prevailing conceptual apparatus? Was there a set of ideas, related to polymorphisms, which guided the work? Were there particular techniques or modes of analysis that spurred the work? Were there institutional factors such as the gathering together in one place of a critical mass of people with a critical set of skills? Were there perhaps societal trends or policies that contributed to the moulding of research agendas or the translation of research findings into clinical applications?

⁶ Anon. (2001).

In line with that I will just mention the eugenics movement. The governmental policies associated with the eugenics movement in the USA, which came with such things as involuntary sterilization, have left a cloud over research in human genetics and in applications to medicine. Was there such a cloud here? Historians have said that though the eugenics movement started in Britain, it didn't lead to any real governmental policies, and so perhaps being spared the taint of eugenics has helped spur research and the development of genetic medicine in this country. Those are the factors we need to explore along with the specific events themselves. I think the discussion today may help us understand not only how we got to this point in time with genetic medicine, but may hint at some of the directions that the field is likely to take in the future.

Pembrey: Thank you very much, Doris. Your mention of the link with agriculture at the beginning reminds me that John Fraser Roberts, who was one of my mentors, started off in Edinburgh looking at the genetics of sheep and things like that.⁷ There's a nice anecdote about J B S Haldane: they didn't get on very well later on, and I had it explained that at one stage John Fraser Roberts had described a pattern on the face of a sheep that was linked to wool quality, so it was useful, and he decided to call it reverse badger face, because there was a badger-faced sheep, and this seemed to be the opposite. Apparently from then on J B S Haldane used to refer to him as old reverse badger face, and if anybody knew John he didn't like that sort of thing. Another mentor was Paul Polani and he has kindly agreed to give a historical perspective before we get into more of a free-for-all.

Professor Paul Polani: Opening on cytogenetics, I present here a sketchy and condensed view of the importance that chromosomes have had in the modern scientific developments and practical application of human genetics.⁸

So may I start with a few critical dates and names? The starting date is 1956 when Tjio and Levan revealed the number of chromosomes to be 46 in cultured somatic cells – a finding that broke the technical problem of chromosome handling, as well as the spell of magic 48.⁹ Also in 1956 number 46 was confirmed *in vivo* by the techniques that Charles Ford and John Hamerton employed on human male meiotic cells at metaphase.¹⁰ Then came 1959 with

⁷ See Polani (1992): 308.

⁸ Polani (1997).

⁹ Tjio and Levan (1956).

¹⁰ Ford and Hamerton (1956).

the discovery of chromosome anomalies, both gono- and autosomal, both numerical and structural. This search was guided by a number of clear clinical indications on where best to harvest, well before chromosome work could be applied effectively to human affairs, using the new techniques that have been alluded to by Marcus Pembrey in his introduction.¹¹

We can then skip to the early 1970s, namely to the work of Caspersson and Zech¹² with quinacrine fluorescent banding, and to this easier and more complete chromosome identification method than the autoradiography one. Chromosome identification was subsequently made more practical by G banding and reverse banding.

One can truly say that the scientific uses and practical application of chromosomology revolutionized human genetics and took it out of doldrums, that had been partly due to the influence of eugenics, partly due to technical inadequacies, especially, it was felt, of cytological methods. Medicine too had to come to grips with the practical uses of cytogenetics and genetics in the clinic, and so came to realize its fundamental contribution to basic science, level with anatomy and physiology. So the new disciplines of clinical and medical genetics were born.

Although there are many derivatives of the cytogenetic explosion, I discern at least five main lines of descent, and I will look at each of them fairly briefly. The first one was the change of the formal genetics of human sex determination, or primary sexual differentiation, already implied in our 1954/56 work on Turner syndrome females, considered quite plausibly to be XO,¹³ as well as the studies on Klinefelter syndrome males¹⁴ running in parallel and using in both cases sex chromatin as a cell marker, and colour vision/colour blindness as a genetic marker for the X chromosome. In 1959 as a result of direct X chromosome studies of these two human sex errors, the XO constitution was confirmed in females with Turner syndrome, and the XXY status of males with Klinefelter's syndrome was sorted out by the work of Jacobs and Strong, and by Ford and ourselves.¹⁵ Thus the *Drosophila* sex determination pattern, which was a dogma for humans in those days, had to be abandoned in favour of the mammalian Y chromosome as the key

¹¹ See page 3.

¹² Caspersson *et al.* (1970).

¹³ Polani *et al.* (1954, 1956).

¹⁴ Polani *et al.* (1958).

¹⁵ Ford *et al.* (1959a, 1959b, 1959c); Jacobs and Strong (1959).

sex determiner – the so-called Melandrium pattern. At the same time the reality in humans of chromosome mosaicism was objectively demonstrated.

Later, from 1990, the molecular story of Y-chromosomal control on primary sex determination was being written, to begin with largely by Gubbay, Sinclair, Lovell-Badge and Goodfellow,¹⁶ aided by the observations of Jacobs and Ross on the Y chromosome and those of Ferguson-Smith on XX males with Klinefelter syndrome¹⁷ and ourselves on XY females, often with pure gonadal dysgenesis (Swyer syndrome).¹⁸

The second leitmotif is Mary Lyon's 'inactive-X hypothesis',¹⁹ proposed in 1961, partly from XO human and murine females, partly from the study of mouse coat colour marker genes, and partly from the heterochromy of one X in XX subjects, studied especially by Ohno, and its late DNA synthesis investigated by Taylor and colleagues.²⁰ Following the pinpointing of the X inactivation (initiation) centre (XIC/Xic) and then the discovery of the influence of the inactivation control centre (Xce) which affects randomness of X chromosome inactivation, lyonization^{20a} is a good way towards its molecular resolution, particularly now that the work of Brown and Ballabio on XIST/Xist has identified a control mechanism on the X chromosome which seems to supersede the need to suppress or modulate the activity of individual X-linked genes.²¹

The third line of descent follows the fortunes of somatic-cell hybridization *in vitro*, which transformed human genetics into an experimental science by bypassing, as Pontecorvo was wont to stress, the key obstacle of sexual reproduction. Cells had been fused since 1960 by Barski first and then by Ephrussi and Sorieul,²² but what was really of interest to humans was the production of human/mouse cell hybrids by Weiss and Green in 1967,²³ which were applied to the mapping of human chromosomes. The first assignment was

¹⁶ Goodfellow and Lovell-Badge (1993); Chadwick and Goode (2002).

¹⁷ Jacobs and Ross (1966); Ferguson-Smith (1966).

¹⁸ Polani (1981): 479–484.

¹⁹ The inactive-X hypothesis asserts that only one of the two Xs in females is genetically active.

²⁰ Ohno *et al.* (1959); Lyon (1961); Morishima *et al.* (1962).

^{20a} Professor Paul Polani wrote: ‘“Lyonization” was introduced in the 1960s and used as a, let us say, rather vernacular, discoverer-friendly colloquialism synonymous with “inactive-X hypothesis” (“single active X hypothesis”).’ Letter to Dr Daphne Christie 14 August 2003.

²¹ Brown *et al.* (1991); Lyon (1992); Avner and Heard (2001); Migeon *et al.* (2002).

²² Barski *et al.* (1960); Ephrussi and Sorieul (1962).

²³ Weiss and Green (1967).

the thymidine kinase gene to an E group chromosome. This was later identified precisely, as required for mapping, as chromosome 17 by Miller in 1971:²⁴ ‘The first swallow that made summer’, as Henry Harris described the event.

The cell fusion work led not only to the mapping of genes by chromosome assignment, but also and importantly to the production of monoclonal antibodies by Köhler and Milstein in 1975; while from 1969 it led to the analysis of suppressor genes in human malignancy, especially by the work of Henry Harris.²⁵

Which brings me to the fourth line of descent from cytogenetics, namely to its contribution to the attack on malignant transformation, which technically runs in parallel, side by side, with the isolation of genes not related to neoplasia. The modern side of the chromosomes and cancer theory begins in 1960 with the demonstration by Nowell and Hungerford of the ‘Philadelphia’ marker chromosome in chronic myeloid leukaemia.²⁶ This was later found by Janet Rowley to be the result of a translocation between chromosome 9 and 22, subsequently unravelled at the molecular level with the application of the recombinant DNA methods of the ‘new genetics’.²⁷ Originally the cytogenetic analysis of solid tissue malignancies was conveniently based on the study of the 1 or 2 per cent simple mendelizing conditions with susceptibility to malignancy, perhaps some 50 syndromes in all: such as, for example, the childhood cancers, like retino- and nephroblastoma or colorectal cancers in adults. Taking retinoblastoma as an example, in 1963 a case of this tumour was described by Lele, Penrose and Stallard with a deletion in the long arm of a D-group chromosome, but the structural change was considered fortuitous.²⁸ However, Wilson reported another example in 1969, and in the same year a review by ourselves of chromosome abnormalities identified other examples of D-group deletions in retinoblastoma;²⁹ in 1971 the relevant chromosome was identified as number 13.³⁰ There followed the identification of the mutant gene (recessive at the cell level) at the site of the chromosome break and the mechanism of how it was involved in the ocular malignancy in children – with general implications for

²⁴ Miller *et al.* (1971).

²⁵ Harris *et al.* (1969); Köhler and Milstein (1975). See also Tansey and Catterall (1997).

²⁶ Nowell and Hungerford (1960a, 1960b). See also Christie and Tansey (2003): 32, 39.

²⁷ van den Berghe (1973); Nowell *et al.* (1975).

²⁸ Lele *et al.* (1963).

²⁹ Wilson *et al.* (1969); Polani (1969).

³⁰ Orye *et al.* (1971); Wilson *et al.* (1973).

malignant transformation, largely in line with Knudson's ideas on sequential hits as the origin of malignancy.

The search for chromosomal loci related to malignant transformation was accelerated through the study of natural structural chromosome errors, like translocations or deletions, which would segregate with the malignancy phenotype. In this way many specific chromosome regions involved in malignancy have been pinpointed, opening the way to their molecular analysis and gene identification.

The same approach was used for the isolation of many major genes not related to neoplasia, such as cystic fibrosis or, with a difference too, for Duchenne/Becker muscular dystrophy.³¹

Further development of cytogenetic analysis – my fifth line of descent – will depend in great part on the adoption of new techniques to increase precision and resolution power, particularly at the moment through the improvement of banding methods; the introduction of methods derived from recombinant DNA, such as, at present, the polymerase chain reaction [PCR]; and of specific DNA probes. These two techniques are often combined to produce high-resolution fluorescent *in situ* hybridization methods that are acronymed FISH, or multicolour FISH. The consequent expansion of *in situ* work, both metaphase and interphase, and not only of somatic cells but also of cells of the germ line, particularly those involved in spermatogenesis, has yielded important information, both theoretical for research and practical for application; for example, in prenatal diagnosis, in cancer research, in the investigation of infertility, and in the study of unclassified mental retardation. As examples of the latter search one may mention studies aimed at detecting subtelomeric chromosome rearrangements, namely rearrangements in the gene-rich telomeric regions of chromosomes. One notes that telomeres seem also relevant to cancer research, to research on ageing, and perhaps as counters and recorders of numbers of cell divisions.

Finally, a few words on the origins of trisomy 21, as a representative of all trisomies, which are about one-third of all recognized pregnancies in women over the age of 40. Only a small proportion of trisomy 21s are inherited in a maternal-age-independent manner through centromeric fusion translocation, as

³¹ Sarfarazi *et al.* (1983); Monaco *et al.* (1985); Riordan (1989); See also McKusick (1993); Christie and Tansey (2004a).

we showed in 1959 and 1960.³² Disregarding the 10 per cent paternal contribution to the origin of trisomy 21, maternal-age dependence of nondisjunction of chromosome 21, which lies at the origin of trisomy, seems to result either from the failure of chromosomes 21 to cross-over and recombine at meiosis, or from a mislocation of chiasma position. The result of either is an error of chromosome partitioning at the first or second meiotic divisions of the mature ovum before or at sperm penetration and fertilization. In either case, namely when no chiasmata form or when chiasmata are mislocated, we know that these recombination errors take place at the meiotic prophase, which, on the female side, is *in fetu* well before she is born, and thus long before she becomes a mother. The fact that meiotic recombination errors *in fetu* are revealed in ova matured and released at advancing maternal age might support the idea that oogenesis follows a production line system. This hypothesis was proposed by Henderson and Edwards in 1968³³ and, in essence, it says that early entry into meiosis *in fetu* corresponds to exit of the mature ovum soon after puberty, whereas late entry into meiosis *in fetu* yields ova that exit at a late maternal age, a case of first in first out, last in last out; a hypothesis which is supported by our animal experiments.³⁴

Pembrey: Thank you very much for that broad historical introduction. We are going to be coming back to cytogenetics after this historical scientific overview to tease out the players in cytogenetics, as applied to clinical genetic testing and so on. Down's syndrome is so central to that and to prenatal diagnosis and so on.

Before we get on to the specifics and to the names of the people who were involved in this, and to the groups, I think, just to give the other general broad historical perspective, David Weatherall would be prepared to say a bit on the haemoglobinopathy side, because that work very definitely, with the blood groups, led a parallel background into what then became clinical genetic testing.

Professor Sir David Weatherall: I believe it was the Churchillian view that the best extemporary speeches are made after six months' notice; I have had just six minutes, but I will do my best. In essence, the pattern of development in the haemoglobin–genetics field was similar to that just described by Paul Polani – that

³² Polani *et al.* (1960); Carter *et al.* (1960). See also Polani (1997). Professor Paul Polani wrote: 'The finding "Down syndrome with 46 chromosomes" was indeed first reported at the December 1959 New York Meeting of the Association for Research into Nervous and Mental Diseases; the same meeting at which Professor J Lejeune also discussed his work [see Polani (1962)].' Letter to Dr Daphne Christie, 14 August 2003.

³³ Henderson and Edwards (1968).

³⁴ Polani and Crolla (1991).

is, it was very much technology driven. The two important haemoglobin disorders, the thalassaemias and sickle-cell diseases, were described between 1925 and 1932 in the USA and their genetics worked out over subsequent years by workers in the USA, Africa and Italy.³⁵ In the late 1940s, Linus Pauling, following a suggestion by Bill Castle of Boston, asked one of his students, Harvey Itano, to examine the haemoglobin of patients with sickle-cell anaemia using the recently developed technique of moving-boundary electrophoresis. They found that the haemoglobin of patients with sickle-cell anaemia has a different migration in electric fields to that of normal haemoglobin, and hence the field of molecular disease was established.³⁶

Moving-boundary electrophoresis was an extremely tedious way of separating proteins, but it soon became apparent to several groups, most notably that of Smith and Conley in the USA and Herman Lehmann in the UK, that it is possible to separate proteins, at least in a crude kind of way, using filter-paper electrophoresis.³⁷ In the late 1950s Henry Kunkel, the immunologist, developed starch-slab electrophoresis, which made it possible to identify and quantify the minor haemoglobin components.³⁸ Since one of these occurred at an elevated level in the parents of patients with severe thalassaemia, it became possible to identify the carrier state for at least some forms of this condition. Indeed, it was this tedious and messy technique that was my entree to the thalassaemia field while I was serving as a medical officer in the army in Malaya. Frank Vella, a biochemist in Singapore, brought my attention to Kunkel's paper and, because I had a Ghurka child under my care with some features of thalassaemia, Frank and I spent some time – literally covered from head to foot in starch – trying to develop this technique. In the end we were able to prove that the child had thalassaemia.³⁹ Just after I moved from Singapore to the USA in 1960, Oliver Smithies developed starch-gel electrophoresis, which made it possible to identify all the minor haemoglobin components.⁴⁰ Roy Shooter and Ernie Huehns in London, and our own group in Baltimore, started to apply this technique to haemoglobin analysis, and it was an enormous help in the early days of both haemoglobin and thalassaemia research. At the same time, Max Perutz was achieving remarkable

³⁵ Cooley and Lee (1925); See also Conley (1980): 319–371; Weatherall (1980): 373–414.

³⁶ Pauling *et al.* (1949); See also Pauling (1955): 354.

³⁷ Smith and Conley (1953).

³⁸ Kunkel and Wallenius (1955).

³⁹ Weatherall and Vella (1960).

⁴⁰ Smithies (1959).

success in defining the crystal structure of haemoglobin, and Vernon Ingram had shown that the sickle mutation occurs in the β -globin chain. Vernon, together with Tony Stretton and others, had also suggested that the thalassaemias might result from a reduced rate of production of the α or β chains.⁴¹

When I returned to Baltimore for two years in 1962 I wanted to study the *in vitro* production of haemoglobin, both in normal people and in individuals with different forms of thalassaemia. I was able to label the chains *in vitro* and found that there was unequal production in the different forms of thalassaemia, but I could not get the system to be in any way quantitative, largely because there was no good way of separating the globin chains. At about this time John Clegg, a young postdoc who had been working with Neurath in Seattle, but had fallen out with him because he did not like getting out of bed early in the morning for journal clubs, arrived in Baltimore. John started to work on the synthesis of insulin, but was having as little success as I was with globin. One day over tea while discussing our mutual problems John suggested that we might try a separation approach that he had used while doing his PhD in Cambridge. This worked and we were able to quantify the rates of production of globin chains and therefore accurately define the different forms of thalassaemia, and gain some insights into what might be happening at the molecular level. This technique was also extremely valuable for studying haemoglobin synthesis during fetal development, and when we returned to Liverpool in the mid-1960s Bill Wood joined us to do work on a PhD project that analysed haemoglobin at different stages of fetal development. During this time we and others showed that there was a small amount of β -chain production from about 15 weeks of development onwards, a finding which soon led to the application of our globin-synthesis technique for prenatal diagnosis.⁴² I am sure that Bernadette Modell will have more to say about this.

Of course, in the 1960s and 1970s the nucleus was simply a black box, and all we could do was to study cytoplasmic phenomena like globin-chain synthesis and try to make some crude guesses about what might be happening at the DNA level. With the advent of DNA–RNA hybridization we realized that a tool now existed to probe to see if genes had been deleted, something that we were fairly sure was happening in some forms of α thalassaemia. Knowing what we wanted to do but not having a clue how to do it, we travelled to Glasgow to meet John Paul to design an experiment whereby we would probe for the α globin genes in

⁴¹ See, for example, Ingram (1956); Ingram and Stretton (1959); Perutz *et al.* (1960).

⁴² See, for example, Weatherall *et al.* (1965); Wood and Weatherall (1973).

babies who had been stillborn with severe α thalassaemia. John set two young scientists, Sergio Ottolenghi and Bob Williamson, to work on our material, and this led to the first direct identification of a mutation in human beings.⁴³ Soon afterwards Southern blotting was developed and a little later DNA cloning and sequencing, and we were able to apply these technologies to the molecular study of thalassaemia.⁴⁴ So by the early 1980s we had a good method for studying fetal haemopoiesis for prenatal diagnosis, most of the tools required for carrier detection of the different thalassaemias, and were getting fairly close to the molecular pathology of many of these conditions. Interestingly, this field was developed by individuals of broad backgrounds, none of whom were clinical geneticists in the sense that the term is used today. I suppose the field of blood-group genetics developed in the same way, and probably many other areas of what have become amalgamated into clinical genetics came initially from other disciplines. I will stop there, I think. You can continue any of that if you want to.

Pembrey: Yes, I think it would be good to continue, because genetic testing is identified with clinical genetic services, and it would be good to get some feel for where all the strands came from. You were up in Liverpool and Cyril Clarke had come in late from general medicine into medical genetics. There was the Galton Laboratory and then there were the cytogenetic developments and it is important for us to document where the main strands were. Was it mainly the Galton Laboratory that led into the development of clinical genetic services, or was it John Fraser Roberts and Cedric Carter at Great Ormond Street, with that very clinical end that was the main channel? I think it was a coming together of a whole group of people.

Dr David Tyrrell: There was one other strand, which was taught to me in the 1940s as a medical student. That was blood transfusion and the blood grouping, and that goes back to Landsteiner and the beginning of the century.⁴⁵ Perhaps later I can tell you how that involved me in infectious diseases, but it was a strand anyway.⁴⁶

⁴³ Ottolenghi *et al.* (1974).

⁴⁴ See Weatherall and Clegg (2001); Angastiniotis *et al.* (1986).

⁴⁵ Landsteiner (1936); Schneider (1996); Anon. (2000).

⁴⁶ The contributions made by many English scientists on the discovery of blood-group systems, their biochemical structure and their role in blood transfusions, are highlighted in a letter from Professor Matteo Adinolfi to Dr Daphne Christie, 12 August 2002. Professor Adinolfi also writes about the Coombs test and P Gorer's work that led to the discovery of the human HLA [human leukocyte antigen] system. Copies of Professor Adinolfi's correspondence will be deposited with the records of the meeting in Archives and Manuscripts, Wellcome Library, London.

Pembrey: The Clinical Genetics Society was formed in 1970,⁴⁷ and their first meeting was up in Edinburgh in October 1970. Before that time, there were already services in existence.

Professor Ursula Mittwoch: Just a small point on scientific history. Paul Polani mentioned sex chromatin, and this reminds us that cytogenetic testing began before 1956. It began with the discovery by Barr and Bertram in Canada, in 1948 or 1949, of the nucleolar satellite that would distinguish the neurons of male and female cats.⁴⁸ Later, sex difference was found in other types of nondividing cells, and also in humans. Females had a sex chromatin body or Barr body, and males lacked it. I think the first patient examined was a true hermaphrodite who also had Barr bodies.⁴⁹ It was then shown that Klinefelter syndrome patients had this Barr body, even though they were male, and Turner syndrome patients lacked it. So with this information in mind, when chromosome studies began, the early cytogeneticists were primed to look for these patients, in particular Turner syndrome and Klinefelter syndrome, and the rest is history.⁵⁰

⁴⁷ Information on the Clinical Genetics Society can be found at www.clingensoc.org/index.htm. Site accessed 10 April 2003.

⁴⁸ Barr and Bertram (1949).

⁴⁹ Moore *et al.* (1953). Professor Ursula Mittwoch wrote: 'This is the first reference of the application of the sex chromatin test in the clinic. However, the chromatin-positive patient was a "female pseudohermaphrodite" with adrenogenital syndrome.' Letter to Dr Daphne Christie, 3 September 2002.

⁵⁰ Professor Ursula Mittwoch wrote: 'Through the instigation of Lionel Penrose (Galton Professor of Eugenics, see page 100), a sex-chromatin survey was conducted among the patients of Harperbury Hospital, Shenley, Herts. This led to the discovery of a patient having both Down's Syndrome and Klinefelter syndrome, who was shown to have 48 chromosomes [Ford *et al.* (1959a)]. One of the co-authors, Orlando Jack Miller, was a young American obstetrician, who had arrived at the Galton Laboratory a few months earlier to train in the nascent discipline of human genetics. Other visitors from the USA included Arno Motulski, Alick Bearn, James Bowman, Kurt Hirschhorn, Ed Reed and Bob Krooth, as well as Marco Fraccaro and Marcello Siniscalco from Italy, Jean Frezal from France and Jan Mohr from Denmark. These and many others successfully transplanted the new medical science to many parts of the world, where it has since flourished.' Letter to Dr Daphne Christie, 3 September 2002. Professor Paul Polani wrote: 'I would also include Professor Barton Childs from Hopkins (paediatrics and genetics), c. 1954. There were, of course, in those years, numerous British visitors to the Galton. While continuing in post at Guy's, I had the great privilege of working directly under Professor L Penrose at the Galton from late 1950 to about the end of 1958. He was most interested in and helpful with our studies, Maurice Campbell and mine, on the aetiology of congenital cardiopathies, and on my ideas (which he did not always agree with) and work on Turner (and Klinefelter) syndrome and derivatives, especially on human sex determination.' Edited from a letter to Dr Daphne Christie, 14 August 2003.

Polani: Perhaps it's worth remembering that the discovery of sex chromatin was an accident. The reason why they were investigating neurons was neuron fatigue of Canadian airmen in this country, which Barr was attached to as a medical officer. In studying neuron fatigue they found a little satellite that was moving up and down into the neurons and they thought that this was significant to neuron fatigue. Then they discovered that some animals had this and other animals did not have it, and luckily a technician had kept a record of the sex of the animal.⁵¹

Professor Malcolm Ferguson-Smith: It was Bertram who kept notes of the sex of the cats and so it was good scientific practice that discovered it, rather than an accident. Fortunately Paul, and to some extent Ursula, have made some of the comments that I was going to make about the introduction to cytogenetics. I would like to say that cytogeneticists have always been slaves to technology and you will remember that the people who looked at chromosomes first in the 19th century were looking at sections of gonads, and Hanseemann and Flemming came to the conclusion that there were about 24 chromosomes.⁵² A different number wasn't found until 1912, when a Belgian, de Winiwarter, looked at gonads and found 47 in the testis and 48 in the ovary.⁵³ He thought that sex determination in humans was XO/XX, but in 1921, eight years later, Painter discovered the Y chromosome in testis. So he added one to the 47 that Winiwarter found and that came to 48. But in his paper in 1923, he said the very best mitoses had 46 chromosomes.⁵⁴ Then in 1932 I think people were interested in the possibility of chromosome abnormalities in certain situations and it was Waardenburg in 1932 who suggested that nondisjunction might occur in Down's syndrome (mongolism as it was called in those days).⁵⁵

I want to go back to Ursula Mittwoch and to say that she, in 1952, looked at the chromosomes in Down's syndrome, well before Lejeune, and she looked very carefully at diakineses.⁵⁶ I hope she is going to say something about this and put me right, because in her paper she counted 24 elements as diakineses and probably, looking back on it, they might have been 23 bivalents and one

⁵¹ Moore (1966): 7–12.

⁵² Flemming (1898); Hanseemann (1891) described in Ferguson-Smith (1961): 292–334. See also Ferguson-Smith (1993).

⁵³ de Winiwarter (1912).

⁵⁴ Painter (1923).

⁵⁵ Waardenburg (1932): 47–48.

⁵⁶ Mittwoch (1952).

univalent. Ursula, if you had had the opportunity of looking at a normal male – it was difficult to get normal males to give up bits of their testes – you would have discovered Down's syndrome many years before Lejeune. Again, being slaves of technology, the people before Tjio and Levan in 1956 had very poor material to work with. It was the use of chromosome cell cultures and the discovery that if you put the preparations by mistake into water instead of isotonic solution, then the cells swelled up and separated the chromosomes and indeed elongated the chromosomes artificially, and made them visible. Levan, of course, contributed to cytogenetics by discovering in plants that colchicine could arrest mitosis. So I think the impetus to study human chromosomes in the UK did come from Barr and Bertram's discovery. Although Paul hasn't told us, he tried to look at chromosomes in Turner syndrome in 1957, and I was trying to do it with Klinefelter syndrome at the same time.^{56a} But the preparations that I made were absolutely terrible. You could make out that there were chromosomes there but you couldn't possibly count them. I was prompted to do this by the fact that we found a patient with Klinefelter syndrome, a young man who was going into the army, and was found to have small testicles. He came for testicular biopsy, and in this testicular biopsy was a tubule full of spermatogenesis and sperm, and there were sex vesicles with the XY in these primary spermatocytes. I rushed along to Professor Pontecorvo and said, 'Everybody's saying these Klinefelters are sex-reversed females but this man has a Y chromosome'. To cut a long story short, I was directed to Charles Ford who had just been making bone marrow preparations.⁵⁷ This would be about 1956 or 1957. Charles didn't know anything about Klinefelter syndrome, but I told him about it and said, 'Look we have lots of patients here,' and he said, 'Oh well, if you can get some bone marrow from these patients you can perhaps count their chromosomes, I am working on the method but this is not quite ready yet, but I will tell you when.' So every time Mr Mack in Glasgow did a testicular biopsy on a Klinefelter individual they woke up with a little hole in their sternum from where I had taken a large chunk of bone marrow and these produced the terrible preparations that we made. Charles Ford later managed to get a Klinefelter sample from London and this was published in 1958 in *Nature*, in a paper describing the bone marrow method.⁵⁸ This Klinefelter patient had 46

^{56a} Professor Paul Polani wrote: 'In fact the work I had started at Guy's with Gordon Thomas, expert in tissue culture, was in the Autumn of 1954 [see Polani *et al.* (1956)].' Letter to Dr Daphne Christie, 14 August 2003.

⁵⁷ Ford *et al.* (1956); See also Christie and Tansey (2003): 17, 18.

⁵⁸ Ford *et al.* (1958).

chromosomes and an XX karyotype, so this was the first XX male. This is not widely known, and it is an important piece of history, and he felt that this confirmed that these patients were sex-reversed females. One of his postdocs, Pat Jacobs, came to work with Charles at the time, and she repeated this on several patients later and found XXY. So these are little bits of anecdotes which took us on.

I think that one of the most important milestones in cytogenetics, particularly in relation to testing, was the discovery in 1960 by Moorhead and Hungerford of the use of phytohaemagglutinin to stimulate lymphocytes into division.⁵⁹ In a short-term culture, in less than three days, it was possible to have a very nice looking chromosome preparation from a peripheral blood sample. This technique was so straightforward and it spread rapidly throughout the world, so that any pathology department that read the paper could do it. This meant that the search was on to find other disorders such as Down's syndrome, and Klinefelter and Turner that might have chromosomal syndromes. So a great deal of testing was done at that time.

Then, of course, John Edwards, who is here, referred tissue from an autopsy of a baby he had seen in Birmingham, and considered likely to have chromosomal abnormalities, to Charles Ford and David Harnden. An extra chromosome 18 was found, at first thought to be chromosome 17. This was before phytohaemagglutinin, which allowed blood cultures to be used, had been discovered.

Pembrey: So can I ask more widely, where were the cytogenetic tests being done in 1960 in the sense that people would say that this is a test we need for the clinical assessment of this child, or this person?

Ferguson-Smith: At places like Harwell⁶⁰ with Charles Ford and those colleagues from the Galton Laboratory who worked with him, and at the MRC Unit in Oxford.

Pembrey: So they would receive clinical samples, would they?

Ferguson-Smith: They would indeed and, of course, at the Galton Laboratory, Ursula can tell us more about that. The other places were largely departments of pathology – I would say after 1960, all round the world, certainly at Johns Hopkins. I had gone there in 1959 and started up a laboratory in its Department of Medicine, which was probably the first diagnostic laboratory in the USA for chromosome abnormalities. Then the obstetricians took it up, and then the paediatricians. So, in fact, it was such an easy technology that many people joined in, and the whole field exploded in a very satisfactory and productive way.

⁵⁹ See Moorhead *et al.* (1960).

⁶⁰ The MRC Radiobiology Unit, Atomic Energy Establishment, Harwell.

Zallen: What does it take to believe what you see? You said there had been preparations, the very best preparations, in which there were 46 chromosomes, and yet those weren't taken seriously. Can you explain that? Or is there anyone who knows why they were dismissed?

Ferguson-Smith: These were very difficult histopathological sections to look at. Painter got his preparations from the testes of executed criminals in Texas and he had to determine the number of chromosomes from serial sections.

Pembrey: I am trying to go back to testing. John, were you testing, or involved in doing clinical diagnostic tests, chromosomal tests in 1960?

Professor John Edwards: Yes, I went to the Children's Hospital of Philadelphia in 1960, after establishing tissue culture in Oxford following help from Harwell. At Philadelphia I learned the blood culture technique from Nowell and Hungerford,⁶¹ and I established their chromosome laboratory. I returned to the position I had held three years earlier in Birmingham with Professor McKeown with a joint, if informal, appointment with Professor Hubble in Paediatrics, and established the original chromosome laboratory in Birmingham. It was, I think, the only one in England north of Harwell with Charles Ford in London, Penrose at the Galton, and Polani and Hamerton at Guy's. There were leading laboratories established in Glasgow and Edinburgh. In Birmingham the flow of material was limited by resources (one technician and a rather ancient microscope), but at least there was no waiting list with reports within a week on nuclear sexing on both buccal smears and blood, and a month on biopsy material. I saw all cases before accepting, apart from buccal smears.

Polani: At Guy's we had established a research unit that had a dual track. Research on the one side and then genetic service, and that was 1960 when we were doing the first chromosomes.⁶² The work of Steele in the USA on detecting chromosomes in amniotic cells was very important. [From the floor: 1966]. The other important point was the discovery of chromosome translocations in Down's syndrome, which immediately raised the problem of being able to spot familial mongolism,⁶³ and that was important in a practical sense. Of course, the

⁶¹ Moorhead *et al.* (1960); Nowell and Hungerford (1960b).

⁶² Polani *et al.* (1979).

⁶³ Professor Joy Delhanty wrote: 'Familial mongolism due to translocations was first found at the Galton Laboratory in 1960 by Joy Delhanty, then a PhD student of Lionel Penrose.' Letter to Dr Daphne Christie, 4 September 2002. See Polani *et al.* (1960); Carter *et al.* (1960).

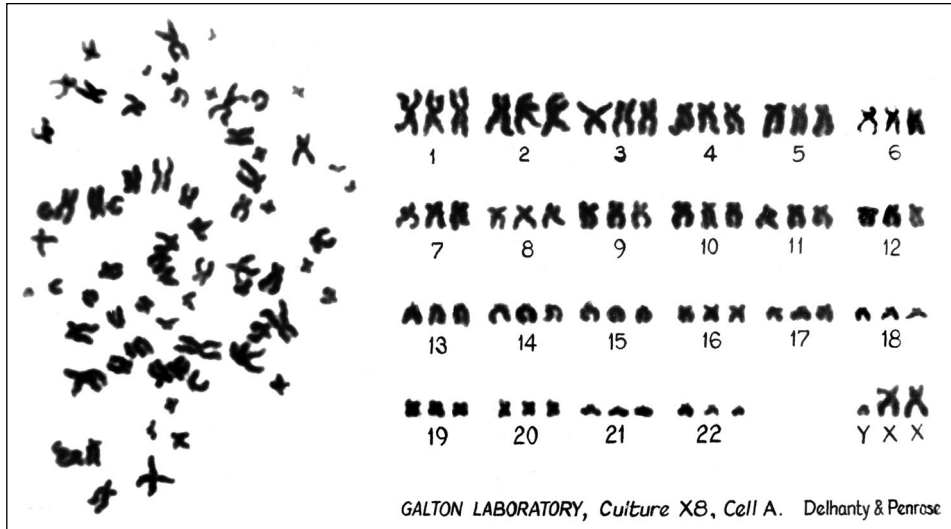


Figure 1: Triploid cells in a human embryo. Penrose and Delhanty (1961).

Photograph provided by Professor Joy Delhanty, 2003.

forerunner to the chromosomes in amniotic cells was the work of Sachs on amniotic nuclear sexing in Glasgow.⁶⁴

Mittwoch: Just a brief mention back to the Galton laboratory. The testicular biopsy of a Down's syndrome patient that Malcolm has mentioned, this was a task given to me by Penrose, and I wasn't really satisfied with the preparation and had no wish to publish it. But Penrose said, 'Yes, you must because these Down's syndrome patients might be triploid'. I could see from the preparations that they were not triploid, and so a page went into the journal that was still called *Annals of Eugenics* in those days.⁶⁵ So that was 1952.

In 1961 Penrose collected material from aborted fetuses, from University College Hospital, and Joy Delhanty found one of them to be triploid. I believe that this was the first chromosome abnormality in an aborted fetus, of which there were many more to come (see Figure 1).⁶⁶

Professor Derek Roberts: You asked for places where chromosomes were being

⁶⁴ Mittwoch (1952); Serr *et al.* (1955); Riis and Fuchs (1966): 220–228.

⁶⁵ Professor Ursula Mittwoch wrote: 'The name of the journal was changed to *Annals of Human Genetics* in 1954.' Letter to Dr Daphne Christie, 4 September 2002.

⁶⁶ Penrose and Delhanty (1961); Delhanty *et al.* (1961); Carr (1967).

examined in the early 1960s. I recall, and John Edwards will bear me out, that Alan Stevenson had already set up a unit. When he moved from Northern Ireland he came to Oxford, the MRC Population Genetics Unit, he had a chromosome laboratory there that was doing service work, albeit on a small scale. I remember it because the technician who did the work was George Clarke and when I started my department in Newcastle, George Clarke came up to help me set up the chromosome laboratory and order the apparatus.

Edwards: Can I just comment on Oxford with George Clarke in 1957? George Clarke had been trained up in Glasgow and knew how to grow cells and wash up glassware. Basically he had the techniques, which were very well established in Glasgow, of cell growth and handling glassware – a major problem at that time outside Glasgow, where tap water was pure and sterile. At that time it was quite primitive, I had to go every Wednesday and chat up some farmer not to sell his cock, because we were entirely dependent on fertile hens' eggs, which were extremely difficult to get.

That technique was developed by Lejeune in Paris, incubating bits from a skin biopsy in clotted embryo extract in test-tubes with culture media and serum. In 1958, with limited equipment – he incubated samples by strapping test-tubes to his body – he discovered the chromosomal abnormality in Down's syndrome (then termed mongolism): patients either had too few or too many chromosomes – there were 47.⁶⁷ Ford and Hamerton at Harwell, Tjio and Levan at Lund, and Hsu at Yale had defined the correct number that year.⁶⁸ At Oxford I had great help from Ford and Harnden in learning their nonphotographic techniques of analysis and referring difficult problems. These included the first cases of 18q deficiency and what we then termed 'mosaic' and 'partial' mongolism.⁶⁹

A point I wish to mention is Carr's work in Canada on spontaneous abortions.⁷⁰ He showed that about half had an extra autosome or missing sex chromosome. If this early work, fully confirmed from numerous studies, had been appreciated, affected sib-pair analysis would never have been established in the 1980s in place of the sib-pair analysis, including unaffected controls, advanced by Penrose in

⁶⁷ Lejeune *et al.* (1959).

⁶⁸ Ford and Hamerton (1956); Tjio and Levan (1956); Hsu (1956).

⁶⁹ Vollman (1969).

⁷⁰ Carr (1967).

1935.^{70a} It was clear that it is a dangerous business getting from conception to birth for largely genetic reasons.

Pembrey: We haven't got any of the three key people with regard to pharmacogenetics able to be here today, although they were invited, so we are not going to have much on pharmacogenetics at the end of the session. So we will have prenatal screening and prenatal testing after tea. One final word on cytogenetics and we can come back to this at the end if necessary.

Ferguson-Smith: Marcus, we can't leave cytogenetics without talking about banding and about molecule cytogenetics, so I will try to do this very quickly. Banding, of course, came about because Joe Gall and Mary Lou Pardue in the USA were looking at and characterizing satellite DNA, the mouse satellite DNA that was found in their DNA preparations separated by ultracentrifugation. They hybridized preparations of satellite DNA to mouse chromosomes and found that this hybridized to the paracentromeric regions of all the chromosomes. In order to do this you had to denature the chromosomes and in some of these preparations Giemsa-positive bands appeared especially near the centromere, and this banding was developed further by others, including Seabright, Dutrillaux and Adrian Sumner, to develop the R banding and trypsin banding, and various types of banding that we now know, with which we can identify every individual chromosome unambiguously. So this was a very major step that led to the further identification and detection of even smaller chromosome aberrations.⁷¹

The next step was to try to develop the *in situ* work of Pardue and Gall. The first thing that was done was to find the location of nucleolar ribosomal genes. Then early attempts to find single-copy genes were unsuccessful until recombinant technology came to the fore, when it was possible to clone sequences in plasmids and to get larger amounts of DNA material to test. That was difficult, it took a long time and those of us struggling with tritium-labelled DNA probes had to wait for three weeks and had to count lots of silver grains – it was a bit of a pain in the neck. So we were all very pleased, as Sue Malcolm will testify (she was there at the very beginning of all this), and we were very glad when fluorescent probes came along. They came along probably round about 1986 or 1987 and it was possible to biotinylate DNA probes or couple them with digoxigenin and

^{70a} See Penrose (1935c) (www.gene.ucl.ac.uk/anhungen/) site accessed 4 September 2003. Professor John Edwards wrote: 'The presence of control – the discordant sib pairs, is implicit in this article. Penrose introduced the hyphenated term "sib-pairs" in 1937.' E-mail to Dr Daphne Christie, 4 September 2003. See also page 27.

⁷¹ See, for example, Seabright (1971); Sumner (1982).

then eventually to get direct labelling of nucleotides with fluorescent dyes. This led to multicolour FISH,⁷² to the centromeric probes used for aneuploidy detection, to test for trisomies not just in cultured cells, but also in interphase nuclei, and that's been a very important development, which is much exploited nowadays. Then with chromosome sorting and with reverse painting, whole-chromosome paints could be made which would colour (hybridize) the complete chromosome along its length. From that came the complete multicolour FISH, where every chromosome in the human karyotype was given a different colour on one hybridization and could be used to look for rearrangements. In 1997, probe sets were being developed which defined the telomeres of chromosomes and that was very important, because they could be used to identify cryptic rearrangements at the ends of the chromosomes.

Finally, a word about how, if and when DNA arrays are going to take over from the FISH work. It's possible, of course, to put genomic DNAs in microarrays on slides and use the comparative genome hybridization technique to identify copy numbers of various sequences throughout the chromosome. A very nice recent application from Nottingham (just to bring us right up to date) has been a technique called MAPH [multiplex amplifiable probe hybridization], in which sequences at the telomeric ends of the chromosomes are distinguished by being different in size.⁷³ By amplifying these probes you can get a whole pattern of sequences on a gel, which can be scanned and tested for copy number. This promised to be a useful technique to determine unbalanced chromosome aberrations occurring at the ends of chromosomes. That takes us right up to the present day. I believe cytogenetics and chromosome analysis have been at the very centre of genetics, and they will continue to be so for a number of generations to come.

Pembrey: Thank you. We are going to move on to linkage now, and, if we could, try to tease out a little more of the individual contribution of people, rather than just rather politely describe the general trends. If you were involved in a particular technique and so on, and can remember anecdotally key successes or key failures, then that helps as well for the historians. I want to move on to linkage and DNA testing. We put the two together because again we need to focus on how we went from the establishment of the principles and ideas of linkage in the 1930s to the actual application of linked markers, whether they be blood groups or, subsequently, DNA markers and so on, in genetic testing in

⁷² Professor Matteo Adinolfi wrote: 'FISH has also been used to map genes and to detect deletions.' Letter to Dr Daphne Christie, 12 August 2002. See Glassman (1998).

⁷³ Hollox *et al.* (2002).

families with genetic disorders. I am just reminded of John Fraser Roberts' book of 1940 where he talks about the practical value of chromosome maps.⁷⁴ He says that at the present time all that can be said in relation to a dominant condition is that, on the average, half the offspring of the affected persons will themselves be affected. If however the manifestation occurs late in life, as in Huntington's disease – Huntington's chorea as you called it then – there is a problem because a daughter, for example, wouldn't know if she was affected before reproducing. John's book goes on to say how valuable it would be to have a marker with a cross-over value of 10 per cent, you could at least say there was a 10 per cent or a 90 per cent chance and so on. So the theoretical idea that linkage could be used to help families, for genetic prediction, was clearly established early on, but how did it happen in practice? Could we just start perhaps with the non-DNA, the earlier markers and so on, perhaps Patricia Tippett, or perhaps John, you could tell us a bit about the blood groups and the theoretical background, using genetic linkage in a predictive sort of way?

Dr Patricia Tippett: The Americans must have been the first to appreciate that blood-group antigens were good markers, because they are well-expressed and red blood cell samples are easy to get. In New York they deliberately, with two systems (MN, P), injected rabbits and then absorbed the rabbit serum with other bloods to make reagents to detect differences other than ABO. Dr Race always said that it was Sir Ronald Fisher who anticipated the use of blood groups as chromosome markers, for mapping chromosomes. When Fisher was the Galton Professor in 1935 he started a department to do blood groups. There were only three blood groups identified at this time, and ABO was the common one. He started this as the Galton Laboratory Serum Department, which then moved to Cambridge during the war. It was not until the finding of Rhesus (Rh) in 1939/1940⁷⁵ and the clinical significance of this antigen, and the development of techniques that could detect clinically significant antibodies that the whole lot blossomed. In the 1940s and 1950s, red blood cell groups were the ones that were used as markers and certainly at the MRC Blood Group Unit we used to test family members of people with various diseases that colleagues sent in to us, such as Huntington's. Unfortunately, we never found any linkage, but the first four, I think, autosomal linkages found involved a blood group.

⁷⁴ See Fraser Roberts (1940): 176–177.

⁷⁵ Landsteiner and Weiner (1940); Levine and Stetson (1939). Dr Patricia Tippett wrote: 'Landsteiner and Weiner's work gave the name Rh to the system. Levine and Stetson did not name the antigen that they described. The claim for priority caused bitter controversy.' Letter to Dr Daphne Christie, 30 May 2003. See Christie and Tansey (2004b).

Marcus Pembrey: What about the ABO and nail-patella syndrome?

Tippett: Yes, that was one of them. Also, I think, Rh and elliptocytosis.

Pembrey: That discovery was made by Renwick and Sylvia Lawler.

Ferguson-Smith: I think Jan Mohr was the first with the Lutheran blood group and secretor status.⁷⁶

Professor Sue Povey: I wonder how many of the early workers had the foresight to think that this would be really useful or whether they were motivated mostly out of academic curiosity, which is something that is less encouraged in these days. I remember that in Race and Sanger's book, the early one, there is one of the best easy explanations of how to do linkage. They say we wouldn't like blood groupers not to have the pleasure of recognizing a linkage, should they come across one.⁷⁷

Pembrey: You felt that there wasn't much of a drive to use this for genetic prediction, it was really still trying to find, to publish linkages. After all, there were so few linkages and it was even more difficult to find their chromosomal localization.

Povey: I suppose at the time that Patricia is talking about, when there were so few blood groups, the chance of finding a positive linkage with the disease was very low.

Tippett: Yes, it was very small. I think Fisher had anticipated finding linkages because in a later paper on blood groups, Race and Sanger say something about how he would have enjoyed the sort of explosion of blood groups and the increased hope of mapping. We were very naive in our expectations, even when we found Xg⁷⁸ on the X chromosome, which was already known to have many markers. At first we said that we would only be able to map the X chromosome, but we were unfortunate because only three loci were within measurable distance. However, we learned a lot about other things, especially in understanding the mechanisms of sex-chromosome aneuploidy.

⁷⁶ Professor Sue Povey wrote: 'The first autosomal linkage was found by Jan Mohr in Denmark in 1951 between the Lutheran blood group and secretor status [Mohr (1951)]. This was followed by three linkages from the Galton Laboratory by Sylvia Lawler and Jim Renwick and colleagues. These were ABO and nail-patella syndrome [Renwick and Lawler (1955)], Rhesus blood group and elliptocytosis [Goodall *et al.* (1953)] and Duffy and cataract [Renwick and Lawler (1963)]. The understanding of heterogeneity in the Rhesus/elliptocytosis linkage owed much to Newton Morton, but was also one of very many fundamental contributions by Cedric (CAB) Smith at the Galton Laboratory. Cedric's admixture test is the basis of many programmes used today and has fundamental importance in the reliability of genetic testing.' Letter to Dr Daphne Christie, 11 September 2002.

⁷⁷ Race and Sanger (1950).

⁷⁸ Mann *et al.* (1962).

Polani: What you said about John Fraser Roberts, he certainly recognized the usefulness, the clinical usefulness, of the application of linkage, although he worked mostly on association. I think probably he was, I don't know, he was one of the first, or maybe we should look at what Crow was thinking of.

Pembrey: I don't think we can leave the early period without at least talking about Julia Bell and Haldane, with the linkage between colour-blindness and haemophilia.⁷⁹ After all, that was potentially used in 1936, 1937. Does anybody know whether that was used clinically? That linkage?

Edwards: The concept was. It's a concept that has dominated all future use, but I don't think it was used at the time.

Professor Naomi Pfeffer: Could you explain what you mean by 'used clinically'?

Pembrey: Being used as a test to predict the genetic status of a family member who didn't know their genetic status. That's really it. The ABO and nail-patella linkage I guess could have been used in informative families for that purpose, although it would be fairly obvious, they wouldn't want to do it.

Zallen: I was looking some years ago in the Rockefeller Foundation archives at the logs of the officers who travelled around the world trying to find suitable and eminent scientists to fund. They were visiting R A Fisher and he was explaining something very important, what work he wanted to do. This was in 1939, and he was talking about linkage. He said, 'Suppose you see a family in which red hair always goes with madness, then you could use the red hair as the marker for predicting future problems of an individual'. So he very clearly had that on the agenda in 1935.

Tippett: The Galton Laboratory Serum Unit was set up with a Rockefeller grant administered by the MRC.⁸⁰

Edwards: In 1912 when eugenics was a highly respectable word – it was respectable until 1930 in most of Europe – Fisher was an active member of the Cambridge Eugenics Society as a postgraduate, an astrophysicist. He gave a paper and specifically pointed out, what was later pointed out by Haldane and later still by Fraser Roberts, I think, on the inferences you could get by being able to detect 'factors', as he called them then. Historically the linkage followed from the work on the white-eyed fly in 1912 and Morgan's book.⁸¹ In 1918, they had mapped 40 loci. In 1918 the term

⁷⁹ Bell and Haldane (1937); See also Tansey and Christie (1999): 7.

⁸⁰ Jones (1991): 190–194.

⁸¹ Morgan (1918); See also Morgan (1910); Peters (1959).

'linkage inequality' (and what is now called 'linkage disequilibrium'), was put forward in Ann Arbor by Robbins.⁸² Following that was Fisher's book in 1930 when he wrote on the potential for linkage equilibrium,⁸³ which is a very important concept. In the HLA [human leukocyte antigen] system, there are sets of alleles that coexist with advantage, and he put that forward as a possible cause 30 years before HLA typing was developed. Lewontin⁸⁴ never mentioned Fisher as he thought he was upper class: there was no reference to what Fisher had called linkage equilibrium and Robbins' linkage inequality. This is why I introduced the term 'allelic association' as the observation from which all these things arise.

In 1931, Bernstein in Geissen, Germany, advanced the concept of using two generations rather than three⁸⁵ and I am glad to say that with effect from last Saturday I was able to get his original document, found in a basement in Munich, on to my website.⁸⁶ I would welcome help on the translations, but the original German is very original. He was pushed out for being Jewish – from a very distinguished Jewish family – and didn't do a great deal after going to the USA in 1930. Following the demonstration that you could do linkage in two generations, and it was very difficult because of course most of the blood groups used in linkage were not codominant. Some had a very difficult kind of dominance, as in the ABO system. So he went into this and pointed out in his paper that as humans had 24 chromosomes, they were probably tetraploid or otherwise polyploid, which would make life easier. He distinguished association from linkage very clearly, particularly in usage on cows, and then this was taken up by Haldane and Hogben.

Four years later Penrose pointed out you didn't need two generations, one generation sufficed, and you didn't need parents, because although they were helpful, they were not cost effective. The important point he made was that without linkage you have discordant signs, the phenotype and a discordant genotype, and you just do a very simple test. This is the basis of the sib-pair analysis of Penrose:⁸⁷ which has been completely ignored by all later authors. It is obviously a very powerful method, and Fisher gave it tremendous support.

⁸² Robbins (1918).

⁸³ Fisher (1930).

⁸⁴ Some of his published works include Lewontin (1974, 1982); Lewontin *et al.* (1984).

⁸⁵ Bernstein (1930a).

⁸⁶ Bernstein (1930b).

⁸⁷ Penrose (1935c).

Fisher also contributed to the first paper; of his eight children several had red or reddish hair. I don't think I wish to say any more on this, except that by 1935 the basic procedures for linkage analysis were very well established, with a succinct and sufficient vocabulary. However, efficient analysis had to wait ten years for the likelihood approach of Haldane and Smith, twenty for Morton's tabulation of lod scores, thirty for its transfer to computers and almost another ten for Ott's development of a fully generalized linkage programme.⁸⁸

Pembrey: Very helpful. We now want to move to the actual application of that. I know John Woodrow with Andrew Cudworth was involved in some early analysis in diabetes.

Professor John Woodrow: John Edwards will be pleased to know that I have in my hand a photocopy of the Lionel Penrose paper on linkage to which he referred.⁸⁹ In Liverpool in the 1950s Cyril Clarke, like nearly all those who were associated with him in becoming involved in medical genetics, was a practising physician and was largely self-taught in genetics. Stimulated by Philip Sheppard,⁹⁰ whose mentor in Oxford had been E B Ford (the ecological geneticist), a research study was initiated to look for possible associations between blood groups and disease. (It is a remarkable fact that the possibility of a relationship between blood groups and disease was being investigated at the Mayo Clinic in 1917, before the ABO terminology was introduced.)⁹¹ In spite of much work in Liverpool and elsewhere and some interesting findings in respect of blood group, secretor status and peptic ulcer, few notable additions to our knowledge of disease pathogenesis emerged.⁹²

At that time genetic linkage and population association were quite separate things. If one were to find genetic linkage in family studies (and there were very few examples of this in man) one would not expect to find population

⁸⁸ See, for example, Morton (1995); Dronamara (1990). See also page 110.

⁸⁹ Penrose (1935c).

⁹⁰ Professor John Woodrow wrote: 'Professor P M Sheppard FRS came to Liverpool from Oxford in 1956 and was Head of the Department of Genetics from 1959 until his death in 1976.' Letter to Dr Daphne Christie, 14 October 2002. See Clarke (1977).

⁹¹ Buchanan and Higley (1921).

⁹² Professor John Woodrow wrote: 'The involvement with blood groups and disease led to an interest in Rh haemolytic disease of the newborn, and to the experimental and clinical studies whose success led in turn to a practical method of preventing the disease.' Letter to Dr Daphne Christie, 14 October 2002. See Christie and Tansey (2004b).

association. It is of interest that Cyril Clarke and Philip Sheppard, working in a totally different field – the genetics of mimicry in *Papilio memnon* – showed that this was determined by several tightly linked genes that were not in linkage equilibrium.⁹³ The term ‘supergene’ after Darlington and Mather was used. The discovery of the HLA polymorphism was naturally of great interest to us and also showed evidence of linkage disequilibrium. Thus, any disease susceptibility genes in the vicinity of the HLA loci on chromosome 6 might thus be expected to show both linkage and population association. As a rheumatologist I was able to take part in studies that showed strong HLA associations with several rheumatic diseases and in the case of the HLA B27-associated disorders, typing for B27 was of direct use in the clinic.⁹⁴

Andrew Cudworth⁹⁵ and I decided to investigate the possibility that there might be HLA-linked genes involved in the genetics of insulin-dependent diabetes mellitus (IDDM). We first did a population association study, and this showed an association with HLA B8 and W15. I was aware of Penrose’s paper, which was published in the *Annals of Eugenics* in 1935.⁹⁶ His introductory sentence reads: ‘The methods, originally devised by Bernstein and recently improved by Hogben and Haldane, which can be used for detecting and measuring linkage, necessitate the identification of parental genotype.’ He then goes on to describe the advantages of studying pairs of sibs. (Penrose also suggested later that in population association studies, healthy sibs could be used as controls in order to avoid the problem of stratification.) One problem with linkage studies in IDDM is that there is an appreciable chance that unaffected sibs would become affected subsequently, and we decided to study affected sibs only. Mattiuz had shown that normally there is random zygotic assortment of HLA haplotypes in families. We therefore tested the null hypothesis that this would also apply to families of diabetic sibs. If sharing of parental haplotypes was significantly greater in these sibs than expected, this would suggest the presence of an HLA-linked susceptibility genes(s) for IDDM.

⁹³ Clarke *et al.* (1968).

⁹⁴ Woodrow and Eastmond (1978); Woodrow (1979a, 1979b).

⁹⁵ Professor John Woodrow wrote: ‘Andrew Cudworth FRCP was Lecturer in the Department of Medicine at Liverpool. In 1977 he was appointed Senior Lecturer and Consultant Physician to St Bartholomew’s and Hackney Hospitals, London. In 1982 he was awarded a Personal Chair of Human Metabolism at London University, which he held until shortly before his death.’ Letter to Dr Daphne Christie, 14 October 2002. See Dickinson C J. (1984) *Munk’s Roll* 7: 129–132.

⁹⁶ Penrose (1935b).

We reported on 17 families, 15 sib pairs and two with three affected sibs.⁹⁷ There was a marked excess of sharing of parental haplotypes and this supported the population association findings in indicating the site of what is probably the major genetic factor in susceptibility to IDDM. The affected sib-pair approach has been applied to the genetic analysis of many more or less common disorders, using an increasing array of polymorphic markers and more sophisticated methods of analysis.⁹⁸ It is not as successful where disease susceptibility genes of weak effect are involved. Population association studies are still valuable and the transmission disequilibrium test is another test of association that is often used.⁹⁹

Pembrey: That's a good example of HLA being used in research to establish linkage. On the clinical side, I do think that HLA linkage was used for genetic prediction. I certainly used it, I can describe a family in the early 1980s, where I used it, where they had congenital adrenal hyperplasia, 21-hydroxylase deficiency. Rodney, did you use HLA for genetic counselling prediction in 21-hydroxylase deficiency in congenital adrenal hyperplasia in Manchester?

Professor Rodney Harris: Not really, we used the biochemistry more. I don't know whether you want me to talk about what I thought I was going to talk about.

Woodrow: To put the IDDM story in the context of the general topic of this meeting, it is known that possessing the HLA DQ8/DQ2 genotype is associated with a high risk of developing IDDM. If in addition there are present two or three of the main autoantibodies found in patients with IDDM, the risk is even higher. It has been known for some time that progressive destruction of pancreatic islet cells occurs for some years prior to the appearance of clinical symptoms. This has suggested the possibility of carrying out some form of immunomodulation to protect the islet cells in those identified as being genetically susceptible – for example, sibs of probands – thus preventing the onset of disease. Clinical trials along these lines are currently in progress.

⁹⁷ Cudworth and Woodrow (1975).

⁹⁸ Professor John Woodrow wrote: 'IDDM has been the major test-bed for the strategy of mapping susceptibility loci by large-scale analysis of affected sib pairs [Strachan and Read (1999): 459].' Letter to Dr Daphne Christie, 14 October 2002.

⁹⁹ Professor John Woodrow wrote: 'In the transmission disequilibrium test to examine whether allele A is associated with a disease, couples with one or more affected children are sought and those parents heterozygous for A are selected. The test compares the number of such parents who transmit A to the affected offspring with the number who transmit their other allele.' Note on draft transcript, 3 June 2003.

Pembrey: I can certainly describe one instance when we used HLA as a marker for genetic prediction of other family members. This was a family from the Mediterranean, they were first cousins, they were a Muslim family, and a child had been born with ambiguous genitalia, and shown to be 21-hydroxylase deficient. And then there was a comparable consanguineous marriage, that is another sister had married another one of the brothers and had only had one child who was well, and they were worried about their recurrence risk. Then there was another pairing, comparable consanguineous marriage, where they were planning to get married, but people were worried about this genetic condition, and we decided to use linkage. It was published in the *Archives of Diseases of Childhood*, in the early 1980s, about 1982, perhaps.¹⁰⁰ We certainly used HLA as a means of demonstrating that the family that had already married and had a child, they weren't carriers either of them, or at very low risk of, and therefore could carry on without any concern, and likewise the couple who wanted to get married also got the good news that they could get married. So there were sporadic examples of using linked markers to disease loci for genetic prediction in families.

Zallen: How about the secretor gene and myotonic muscular dystrophy?¹⁰¹

Edwards: We had hoped Peter Harper would be here; he had to bow out at the last minute. Anyway, with Jack Insley we had a suitable case in Birmingham, and he came down to demonstrate myotonic signs in the offending grandparent by hitting very hard using the small American patella hammer he had brought from Cardiff.

Pembrey: So this was prenatal diagnosis? Ours wasn't.

Edwards: Yes, prenatal diagnosis. It was sorted out by somebody with a very large clinical experience of this condition, who realized you had to use these small American hammers which are very good for that particular test. I am sure that it was done by all the right people. I forget the exact result, but it was published and was almost certainly the first case.¹⁰² The credit goes to the secretor expert, Dr Tippett, who did the difficult tests in London.

Tippett: We were doing a lot of tests for colleagues studying these things.¹⁰³

¹⁰⁰ Savage *et al.* (1982).

¹⁰¹ Renwick *et al.* (1971).

¹⁰² Insley *et al.* (1976).

¹⁰³ See, for example, Race and Sanger (1950); Tippett (1981).

Edwards: Could I mention a single point before we go on? The HLA association with the adrenal problem – that was picked up entirely by association studies, and not by family studies.

Pembrey: So there was a relatively limited use of non-DNA markers for prediction within families, a test as it were, until the DNA side came on. I don't know who to ask to get started, certainly haemoglobinopathies were using DNA markers, and Sue Malcolm was very involved in the early service work on this.

Weatherall: Although it had been suggested by J B S Haldane, John Edwards and Walter Bodmer, I suspect that the first intimation that one could use DNA markers clinically came from a talk that we heard in a monastery in Crete in the late 1970s. It was something of a difficult talk because the speaker, Yuet Wei Kan, had left all his slides on the aeroplane and had to *ad lib* as he went along. However, it turned out that he had been looking at the DNA of normal people and those with sickle-cell anaemia using the restriction enzyme Hpa I. He had found that the β -globin gene of normal individuals is located on a fragment approximately 7.6kb, whereas using the same enzyme it was found that the β -globin gene of patients with sickle-cell anaemia was on a larger DNA fragment, approximately 13kb. It appeared, therefore, that the sickle mutation was on a chromosome that also carried a polymorphism of DNA outside the coding area for the β chain, and further studies showed that it was a very strong association. Since the sickle-cell gene had come under strong selection, the Hpa I polymorphism had hitchhiked along with it. Shortly afterwards Y W Kan and Andrees Dozy used this linkage for prenatal diagnosis of sickle-cell disease.¹⁰⁴ Later a large number of polymorphisms were found to be in linkage disequilibrium for the different forms of thalassaemia and again this approach was used for prenatal diagnosis. Although this approach to prenatal detection of the haemoglobin disorders did not last long, since it soon became possible to identify the mutations directly, it was an important step forward and further consolidated the idea that one might be able to use polymorphisms of this type to search for genes of unknown function associated with disease.

Professor Sue Malcolm: As David has taught us, practically anything worth knowing you could learn from the globin gene, so as well as Y W Kan's announcement in Crete, Alec Jeffreys was looking at variation around the globin gene in general, not specifically in haemoglobinopathies. He published the paper in *Cell* that showed that there were quite high frequencies of RFLPs [restriction

¹⁰⁴ Kan *et al.* (1975, 1980); See also Chang and Kan (1982).

fragment length polymorphisms] all around.¹⁰⁵ That was when perhaps we made the jump from it being something specific to a gene, with some association, I should say, with coming out of the Kan thing, to the idea that these could be markers at quite high frequencies, used in general. From then it moved on very rapidly, still using RFLPs, so a number of groups were using this to map genes in a systematic genome-wide method. Lou Kunkel was one example also Jim Gusella, Bob Williamson and Peter Harper, and their various students in this country. I would say that the whole thing was given quite a boost by the fact that Gusella managed to find a linkage for Huntington's on probe number 8 and usually it is about probe 308, and I think if that had been the experience earlier on, people might have been a lot less keen to pursue it, whereas Gusella's success made people think it was all going to be rather straightforward. Well, in Duchenne's dystrophy, of course, there was a chromosome hint as well, although Bob Williamson went on record as saying that he thought it was rather a nuisance that there was a chromosome hint, because he wanted proof that you could do it without the chromosomes. But the chromosome hint there, which was X autosome translocations in females, did indeed point to exactly the right position for using the markers,¹⁰⁶ and, as I said, Kunkel's group used that and then went on from that to the positional cloning.

Povey: I just wanted to add a memory about the finding of the linkage to the chromosome 4 for Huntington's chorea. There was a very big meeting, one of the human gene mapping meetings, I think it was Los Angeles, and there were numerous posters, but the most exciting one was scrawled on a white board, as you went in, which was 'Huntington's is on chromosome 4', and it was the linkage, it was just a two-sentence poster, and that's definitely the scientific fact that most people remembered from that meeting.

Pembrey: So we have these linkages being established, but in parallel there were suggestions that genetic testing, using RFLPs and so on, might contribute towards genetic counselling. There was John Old in Oxford on haemoglobinopathies, and then there were three centres: ours at Great Ormond Street/Institute of Child Health, Manchester and Cardiff. The Department of Health [DoH] in 1984–85 funded us as a Special Medical Development, I think it was to try to introduce, to assess, these approaches in genetic counselling. Also,

¹⁰⁵ Jeffreys (1979).

¹⁰⁶ Sarfarazi *et al.* (1983); Monaco *et al.* (1985); Riordan (1989); See also McKusick (1993); Christie and Tansey (2004a).

there were studies going on in Glasgow, Cambridge and Guy's. It was just that the three DoH centres tried to look at some of the practicalities of getting these services coordinated. Are there any particular points that people want to make about those early days, particular triumphs or errors that were made?

Edwards: I would like to draw attention to the very significant paper by Dick Lindenbaum, who picked up a translocation in a girl with typical Duchenne.¹⁰⁷ This was a very significant paper, I think, and led to Lindenbaum and his colleagues, including myself, examining as many girls and women with Duchenne, or its milder variant (Becker's syndrome), as possible and, most already known to have translocations, and making sure samples were freely available to anyone competent to study them, especially Professor Southern in Edinburgh and Dr Worton in Toronto. Lindenbaum was very clear in his paper where the locus was, why it was manifest in women, and the implications for future research.^{107a} Since then there have been several hoards of X-autosomal translocations that have been picked up and which have pinpointed a locus with great efficiency and precision in several disorders.

Malcolm: I don't know whether it's worth recording that around that time, when people realized that you could use markers throughout the genome, was perhaps one of the first examples of the commercial involvement. One of the first total maps was through a company called something like Collaborative Research with Helen Donis Keller, so that was the first time when probes were not available, and somewhat secretive and not all the full details were published, and that hadn't been the case up until then. Clones and things had been exchanged fairly freely I think.

Pembrey: Peter Pearson was a good example of somebody who handed out all his probes, and he was very free and easy wasn't he? You just rang up, you asked and you got them.

Weatherall: Another interesting development around that time was the recognition that hypervariable regions may be extremely useful diagnostic DNA markers. One of the first to be properly characterized followed the work of a young PhD student of ours, Steve Goodbourne, in a region that was particularly close to

¹⁰⁷ Lindenbaum *et al.* (1979).

^{107a} Professor John Edwards wrote: 'The girl died aged 16, with a courageous and objective interest in relevant research and greatly appreciative of Lindenbaum's long letters with annotated photographs of gels and chromosomes, assuring her of the great contribution the blood and skin she had donated should offer others.' E-mail to Dr Daphne Christie, 5 September 2003.

the α -globin genes. While this work was being done another young postdoc, Steve Reeders, was working with us, attempting to find a linkage for polycystic kidney disease. When he added the markers for the α -globin hypervariable region to his study he obtained a very tight linkage, thereby pinpointing the gene for polycystic kidney disease close to the α -globin genes.¹⁰⁸ Later, collaborative work with the group in Cardiff on a patient who had both polycystic kidney disease and tuberous sclerosis, together with an appropriate deletion in the right region, led to the discovery of the genes for both these conditions.

Pembrey: Can I just talk about that family with the two diseases, because I was involved in running MSc courses in Portugal, in Oporto, during the early 1980s? When I was out there one of the geneticists there, whose name escapes me at the present time [Heloisa Santos], showed me this family and said look at that isn't that fascinating, you know, what sort of research we can do in that. I said I think it's just a coincidence, you won't get anything out of that. She then triumphantly sent me a copy of the paper with the group from Cardiff, who had picked up on it rather more sensibly, and this was a few years later.¹⁰⁹ So that was certainly a trick that I missed. [From the floor: And you were properly trained as well.] Anything else on the linkage side?

Ferguson-Smith: I would like to emphasize how excited we all were about how quickly we could transfer the information that we got from our colleagues about linkage to our patients. It was in the early 1980s, which is really when it all started, and of course, with commercialization, as Sue has said, it's become a little slower since – but it was a very exciting time.

Zallen: I have a question. I have always wondered about the 1979 paper by Solomon and Bodmer,¹¹⁰ which talks about the usefulness of linkage markers throughout the genome. The 1980 paper by Botstein and colleagues¹¹¹ is the one that is always cited in the literature, the historical literature, as being the origin of that idea. Is there any explanation for that?

Weatherall: He will be too modest to say, but I think there was one that set out the whole thing a bit before Bodmer, and that was a guy called Edwards who is sitting over in the corner.

¹⁰⁸ See Reeders *et al.* (1986).

¹⁰⁹ Anon (1994).

¹¹⁰ Solomon and Bodmer (1979).

¹¹¹ Botstein *et al.* (1980).

Pembrey: During this phase of trying to get linkage with diseases, because we could translate the findings so rapidly into service for families, the lay organizations got quite involved. I don't know if there's anybody here from LINK,^{111a} but I think it's worth recalling an early 1988 neurofibromatosis meeting. It was a meeting that Bruce Ponder was involved in – I wasn't involved in neurofibromatosis-linkage studies at all – and I know that John Edwards was there, and a number of others. A lot of Americans had come over, and at that time there was a lot of linkage work being done on neurofibromatosis 1, but there was no pooling of the negative data. So I was asked, as someone who was not working on it, to take all the relevant Americans and other workers into a room after the dinner and to get them to agree to pool all their data for exclusion mapping. Mark Skolnick was there, certainly, and after a bit of negotiation they eventually agreed to do this. Somebody took a taxi to get your [John Edwards'] exclusion map programme, you weren't there, but I know somebody had to go to Oxford in the night anyway.

Edwards: I was there, and I collected all the data, excepting from Boston. I went to Oxford because I had a computer there and I was busy that afternoon with a clinic, so I sent a taxi with the results. It was about 30 miles, just by Heathrow where they held these meetings [the Runnymede Hotel]. It was interesting, because you very cleverly got everybody, with one exception, to let me have the data.

Pembrey: Yes, that was the plan, they were trapped.

Edwards: One group from Boston refused, they never gave it, but they used it afterwards, when they had everybody's data. This was very fortunate, because the person who provided a probe to Boston was in Iowa, and was very upset at being left out. But in fact they had made a mistake with it. So if we had used the data that they refused to give, we wouldn't have found any linkage. [Laughter]

Pembrey: So what actually happened, which was very interesting for the lay organization that ran this, they said (and they, of course, had the clout), look you must all pool your data. We got people to pool the data, fortunately without the erroneous data, and it went from not knowing where it was to only two places, chromosome 17 and chromosome 10 or 11 I think it was, I am not quite sure. It went from having no published clear information, to localizing it to one of two chromosomes, and a little bit later the Boston group published, showing it was on 17, and they had said that they didn't know where it was. So I was very

^{111a} Professor Marcus Pembrey wrote: 'LINK also now more commonly known as the Neurofibromatosis Association (www.nfa-uk.org.uk)', site accessed 16 September 2003. Letter to Dr Daphne Christie, 5 August 2003.

pleased that everybody had shared all this data, but in fact they held back, and it turned out that they did have high suspicion that it was there. But you had shown with your exclusion map, without their support, that it was either there or in one other chromosome. I think that was a high spot in those early days also, with the lay organizations being involved.

Professor Charles Rodeck: I feel I should mention haemophilia, partly because it's a genetic disease not seen by geneticists because the patients are treated by haematologists, and partly because Reuben Mibashan, my colleague in haematology at King's College Hospital, sadly died recently. He very rapidly moved into linkage analysis, having initially developed a blood assay for prenatal diagnosis on fetal blood.¹¹² He enabled first-trimester fetal diagnosis and that then spread quite rapidly. Certainly the patient association, The Haemophilia Society, were very much behind that and in favour of it.¹¹³

Pembrey: Yes, the background to that first clinically used probe, DX 13, was that it came from Kay Davies's library, and I think her library paper was 1981.¹¹⁴ The collaboration with Kay was crucial in providing the DX 13 probe. I was convinced, if you could see fragile X down the microscope, it would be dead easy to see it at the DNA level. That probe was being used for studies of fragile X and Robin Winter suggested that we also look at haemophilia, and Ted Tuddenham had some families at the Royal Free and lo and behold, it was strongly linked.¹¹⁵ So, in fact, that was a very rapid move from biochemical- or coagulation-level prenatal diagnosis with all its hazards and errors, to using a pretty closely linked probe. Then, of course, the gene-specific RFLP came in very soon afterwards and that was in 1984, I think. Perhaps we could move on now from linkage and DNA diagnosis to consider biochemical genetics, because that is certainly one of the big three areas in genetic testing.

Malcolm: I think you should mention that polymerase chain reaction [PCR]. All the things that we have said so far were done before PCR, and when that [PCR] came in it immediately transformed everything: the speed; the fact that you could use it for microsatellites; and the fact that you could then use it for sequencing the actual genes, because the genes were becoming available at the time of linkage, but you couldn't use them, because it was a whole PhD project to find a mutation. So from then on, it was all different.

¹¹² See Mibashan *et al.* (1979).

¹¹³ See Tansey and Christie (1999).

¹¹⁴ Davies *et al.* (1981).

¹¹⁵ Harper *et al.* (1984); Tansey and Christie (1999): 34–35, 71–75. See also page 102.

Pembrey: No, I think that's a very good point, and I know when we come to pre-implantation genetic diagnosis, there are some great stories on the PCR side.

Weatherall: It is a shame when talking about the British end of these developments, not to remember Ted Tuddenham's contribution in work directed at finding the factor VIII gene. Ted purified some human factor VIII, not completely but enough to obtain sufficient amino-acid sequence to construct a gene probe.¹¹⁶ Of course an American company went on and found the gene, but without Tuddenham's sequence it would have been extremely difficult. I often think that this achievement is overlooked.

Pembrey: That's a very important point. So perhaps we could just talk a little bit now about the biochemical side. Before the molecular DNA diagnostic side, you had cytogenetics and you had biochemistry, our main means of genetic testing. I just wondered, Elisabeth, whether you wanted to say a bit from the Institute of Child Health lab where Des Patrick played such an important role.

Mrs Elisabeth Young: I don't think we can really start talking about biochemical genetics, unless we go right back to the beginning of the 20th century, when Sir Archibald Garrod introduced the concept of an 'inborn error of metabolism' and the idea that enzymes are responsible for carrying out specific biochemical processes.¹¹⁷ It's in the last 25 to 30 years of the 20th century, that we have seen enormous advances in the understanding of the abnormal biochemistry underlying inherited metabolic disease. The key to this expansion of knowledge has been the development of very sensitive techniques for the reliable detection of the biochemical defect at the metabolite, protein or enzyme level, and more recently, as we have been discussing, at the DNA level. More than 5000 human disorders are caused by a single human gene mutation, and in most of these metabolism must be affected at some stage of development. However, even now, a century after Garrod first reported his patients with alkaptonuria, only in about a tenth of metabolic disorders has the primary defect been established.

So how did we go about diagnosing biochemical disorders and the testing of families? In the early part of the century the specific diagnosis was often made by the detection of the abnormal metabolite or gross amounts of normal metabolite in urine. Sometimes this was a very simple procedure, and as we know they would taste the urine, for example, for sugar (I think that would be against health and safety regulations these days!). They could smell the urine of patients!

¹¹⁶ See Tuddenham *et al.* (1981).

¹¹⁷ Garrod (1909).

Some emitted an unmistakable odour, for example maple syrup in maple syrup urine disease. But in the laboratory it was the chemists who were helping with the diagnosis; they were performing laborious and painstaking analyses of these metabolites in the urine and in post-mortem material from spleen, liver, brain and so on. It was these metabolites extracted from the liver and urine that we subsequently came to use as natural substrates for the enzyme analysis. You couldn't ring up Sigma as we do these days and get the substrates sent by post overnight. Obviously as with cytogenetics and DNA technology, there have been enormous advances in biochemical technology. For example, we have moved on now to mass spectrometry from paper chromatography. With mass spectrometry we are able to analyse highly complex metabolites, and the structures of many compounds have gradually been elucidated.

We must not underestimate the contribution made by the histologists and the histochemists to our understanding of pathology of these diseases, and helping us with the diagnosis and genetic testing of children and families. Moving from light to electron microscopy gave us a completely new dimension on the effect of metabolites on the cell, and to this day, in disorders such as Batten's disease, we are still dependent on the histologists for the diagnosis of the variant subtypes.

It was in the mid-1960s that the enzymic diagnosis for many of the metabolic disorders really took off. Previously we required a biopsy of liver or the affected organ, sometimes brain, but Des Patrick, as Marcus mentioned, showed that spleen from patients with Gaucher disease was deficient in an enzyme called β -glucosidase. Des made an enormous contribution to the diagnosis of the lysosomal storage diseases in particular, by demonstrating that the sensitivity of the β -glucosidase assay could be increased at least ten-fold by the use of a synthetic colorimetric substrate.¹¹⁸ Leaback and Walker at the Institute of Orthopaedics at Stanmore and other workers synthesized a series of fluorogenic substrates that increased the sensitivity a further 100-fold. So during the 1970s, by using these substrates, the specific enzyme defect in most of the lysosomal storage disorders was elucidated and now it became possible to make the diagnosis on a blood sample, whereas before, as I said, we needed a liver, brain or spleen biopsy.

In the 1960s cell-culture techniques moved from a research environment into a routine laboratory and cultured fibroblasts were also used for diagnosis. In addition we found that assays made in cultured fibroblasts could generally be extended to cultured amniotic cells, which opened up the whole field of prenatal

¹¹⁸ Patrick (1965).

diagnosis of metabolic diseases. A pre-requisite for prenatal diagnosis is an accurate biochemical diagnosis in the index case, and we now know that similar clinical presentations may result from entirely different enzyme deficiencies. In addition the relevant enzyme could now easily be assayed in the parents. We also found that in some of the lysosomal storage disorders a few clinically normal parents had as low an enzymic activity as their affected children. They are said to have a pseudodeficiency of the enzyme. For reliable prenatal diagnosis we had to have accurate methods to be able to distinguish an affected fetus from a clinically normal fetus, irrespective of it being a heterozygote, or a homozygous normal. The measurement of the relevant metabolite in amniotic fluid supernatant has proved to be a reliable means of prenatal diagnosis in some disorders, but generally amniotic cells had to be cultured for enzyme assay.

When prenatal testing for a metabolic disorder was first offered in the 1960s and 70s, a diagnosis was not available until approximately 20 weeks' gestation. Chorionic villi sampling [CVS] for biochemical disorders began in the early 1980s and for the majority of disorders, the diagnosis could be made directly on CV material, thus alleviating the need for cell culture, and we had an answer within a matter of days and within the first trimester. In general, the definitive biochemical diagnosis in an affected child has meant that subsequent pregnancies in that family can be monitored. However, in some disorders the relevant enzyme may be tissue specific and easily available fetal material, for example CV or amniotic cells, may not be appropriate for assay. This is so in the urea cycle disorders – ornithine carbamyl transferase and carbamyl phosphate synthase deficiencies, phenylketonuria and glycogen storage disease type 1. The specific enzyme has to be assayed in liver, and it was in conjunction with Professor Rodeck in 1982 that Des Patrick in the lab at Great Ormond Street undertook the first prenatal diagnosis for an ornithine carbamyl transferase deficiency on a fetal liver biopsy at 19 weeks' gestation.¹¹⁹ It is in this sort of disorder that we have now moved on to the DNA analysis and this is obviously the method of choice for prenatal diagnosis. Once the enzyme deficiency is proven, and the mutation in the family established, mutation analysis of CV can be offered.

Of equal importance is the fact that, within a family, mutational or linkage analysis now allows the definitive determination of female carriers of the X-linked disorders, thus preventing unnecessary prenatal diagnosis in normal

¹¹⁹ Rodeck *et al.* (1982).

females. Most of the biochemical disorders are inherited in an autosomal recessive or X-linked recessive manner, they are very rare, and generally only after the birth of an affected infant is a specific genetic risk in a family recognized. Marcus spoke about mass screening programmes in neonates. We have been offering these – that's part of genetic testing as I see it – for phenylketonuria and congenital hypothyroidism. In the UK they have been offered since 1969 and for some disorders with a high incidence in certain populations, for example Tay–Sachs disease in the Ashkenazi Jews, mass screening by enzyme analysis has proven effective in determining heterozygosity. It took a while for this to take off in the UK; we tried it in the 1970s and really we had a very low take-up rate, but now people are becoming more informed and a little bit more, I suppose, liberal within that religion, we are, in fact, getting more and more to test these days. Tay–Sachs disease is unusual. In the majority of autosomal recessive disorders it is not possible to identify carriers by enzyme analysis with certainty. In a family where the mutations are known, heterozygotes can be accurately identified and certainly some individuals that were designated as carriers on enzyme analysis years ago have proved not to be carriers once mutation analysis has become available, and vice versa. So we have moved on in the last 25 to 30 years and seen these enormous advances. We now have very sensitive and varied techniques for assaying metabolites in tissues and fluid. The enzyme defect is being characterized in more and more disorders, and this, in combination with the huge advances in DNA technology, mutational and linkage analysis, means that we can now offer accurate genetic testing in more than 400 disorders. Thank you.

Pembrey: Something I particularly remember about the 1970s and 80s was the repeated attempts, driven by families wanting to know their carrier status, individual attempts to use biochemical measures for heterozygote detection, but would it be fair to say as a sort of general view here that that never came to anything really very reliable, did it? There was a lot of effort but you didn't end up with anything very useful. It never really got into the regular testing side.

Young: No, but we are being asked more and more to test the carrier these days. If you can only offer it on an enzyme test they still want you to do it.

Edwards: An enormous amount of use was made of creatine kinase in Duchenne and although there were four laboratories certainly in the UK, including Great Ormond Street, which could do this accurately, there were a number of others that couldn't and most of the people who were told they were carriers were misinformed, without any doubt. That, I think, is a fact.

Pembrey: Yes, I think that's an important thing to record.

Professor David Galton: One of the sad things about Bart's, apart from Governments trying to close us all the time, is that there is almost nothing to see of Archibald Garrod there. There's a ward called Garrod Ward and Professor Besser has got photographs of Garrod, and original urine specimens showing alkaptonuria. Garrod really was a pioneer; he was 20 years ahead of his time. When Beadle and Tatum made similar discoveries in *Neurospora*, a bread mould, they got the Nobel Prize for it; but very graciously at their presentation speech they gave full acknowledgement to Garrod, saying that all they had done was the same experiment as Garrod, not in humans, but in a much easier experimental model, the bread mould.

Sir Christopher Booth: I had a signed copy of Archibald Garrod's original 1909 edition of *Inborn Errors of Metabolism*,¹²⁰ given to Walter Fletcher who was the first Secretary of the Medical Research Council. After Joe Goldstein got the Nobel Prize, I gave it to him for his department.

Professor Matteo Adinolfi: Carrier detection of the Hunter gene was successful using the hair root test^{120a} or FISH on chromosome spreads. We were providing these tests at Guy's for many years. FISH helped to localize the site of the deletion.¹²¹

Pembrey: Hair roots – you are right, there was a hair root approach, based on X inactivation, and cell selection, you are quite right. Cardiff offered that.

Povey: It's not directly related to testing, but on biochemical genetics, I feel it's a bit sad we have entirely left out the idea of normal genetic variations – the contribution of Harry Harris, Bette Robson and David Hopkinson. Although this work only occasionally led directly to correct diagnosis – for example the discovery of adenosine deaminase deficiency (ADA) as a cause of severe combined immune deficiency¹²² – in the future the idea of polymorphism will have tremendous implications for genetic testing.

Pembrey: I agree. It's sad. There are always opportunities to have an additional one of these, I think it's difficult to choose how to focus and fully recognize how it is, and all that work of the Galton Lab.

¹²⁰ Garrod (1909). See also note 123.

^{120a} Details of the hair root test are given by Professor Matteo Adinolfi in the glossary on page 109.

¹²¹ Adinolfi and Stone (1991).

¹²² Spencer *et al.* (1968); Giblett *et al.* (1972).

Edwards: A factual comment on Archibald Garrod. His great book has had very few copies sold, and in *Biographical Memoirs of Fellows of the Royal Society*, it is not mentioned.¹²³

Pembrey: As I explained earlier we had hoped to cover pharmacogenetics, not that it's used very much in clinical practice yet, but there's always promises, promises. The key three people (one of whom had to be here, to have it as a major topic) were not able to come, so we've now gone on to consider prenatal screening and testing, and then go on naturally to pre-implantation genetic diagnosis, where Britain has made a very important contribution. That will to some extent take us to the end of high-risk specific family studies. Then we will move a little bit broader into immunogenetics and blood groups, as genetic testing that impacts on a much wider area, not only in the blood transfusion type and so on, but on transplantation and things like that. So we can move towards more multifactorial broader stuff at the end if there is time. But there are some meaty things to go through on the prenatal screening and testing side and I just wondered, Bernadette, whether you would be prepared to kick it off again. As always, haemoglobin leads, tends to lead, on these developments where we are talking about single-gene disorders and then we can bring in the cytogenetics afterwards.

Professor Bernadette Modell: You were complaining that people were not talking enough about their personal experience. So I would like to talk about personal experience with two things: screening and first-trimester prenatal diagnosis, which follows on from the developments in DNA technology, the linkage that you were talking about. The great thing about the haemoglobin disorders is that you can detect carriers accurately by using simple, conventional tests. As you were saying, you had problems using biochemical tests to detect carriers of most genetic disorders, but you could detect carriers of sickle cell because of their abnormal haemoglobin, and carriers of thalassaemia because of their small red blood cells. As the possibilities of prenatal diagnosis were beginning to open up, I used to think that it was a great pity that here we had thalassaemia and sickle-cell disorders, both extremely common, and people were desperate for some kind of prenatal diagnosis. You could detect the carriers, but

¹²³ Garrod's *Inborn Errors of Metabolism* (1909) is mentioned, albeit obliquely. See Hopkins (1939): 227. 'During 1897 [Garrod's] interest in the urinary pigments brought him in touch with a case of alkaptonuria. This fortunate happening was responsible for much of his most influential work and teaching. It was his concern with this relatively rare condition that ultimately led him to think so deeply and write so brilliantly about what he came to call "Chemical Malformations" or "Inborn Errors of Metabolism".' See Garrod (1909).

you couldn't provide prenatal diagnosis, because by definition the fetus had fetal haemoglobin but the disorders you were interested in were disorders of adult haemoglobin. Some local public health doctors in this country were very interested at the time (around 1970), and they had started discussions with the Cypriot community here about the possibilities for carrier testing, just simply for information, but those discussions stopped around 1973, I think quite advisedly, for two reasons. One is that war broke out in Cyprus with the Turkish invasion [in 1974], which diverted the attention of most Cypriots from anything to do with genetics. The other was that we went to a 'Cooley's anaemia' meeting organized by the New York Academy of Sciences, where Y W Kan presented the results of work based on a long-forgotten study, showing that early human embryos had some adult haemoglobin.¹²⁴ He had confirmed this finding and made it more precise by radioactive labelling of red blood cells obtained from fetuses. Once you knew haemoglobin A was there, you knew that in principle, you might be able to do prenatal diagnosis. To do this you would have to obtain some fetal blood, and no technique for doing this existed at the time. In fact, we were pushed into it. Charles Rodeck who is here will remember all the traumas that we went through trying to get fetal blood.¹²⁵

Talking about the involvement of patients, here is what happened to us at UCH [University College Hospital, London]. We were doing this research, because women who were at risk, rather than continue an accidental pregnancy, practically always requested a termination of pregnancy. This both showed their need and made fetal material available for study. We were therefore collaborating with Dr Blanche Alter in David Nathan's group in Boston to see if we could measure haemoglobin A in these at-risk fetuses, and so detect carriers and affected fetuses. We got to experiment number 5, when the mother of one of my patients, who happened to be a British Pakistani paediatric haematologist, asked me, 'How are you doing?'. So I said, 'Well, come into the lab and have a look', and I showed her the results. She said, 'Fine, good', and went away. Three months later she rang me up and said, 'I am pregnant and what are you going to do about it? If you won't try to make a prenatal diagnosis on this baby I will have to terminate the pregnancy, and I want you to try'. So I said, 'Ahh, we haven't really got a technique for obtaining fetal blood, as you know!'. She said, 'Well, I want you to try anyway'. So I rang up our colleagues in the USA and they started laughing, very rudely and very unkindly because they didn't appreciate our

¹²⁴ Kan (1977).

¹²⁵ Rodeck and Campbell (1978); Rodeck (1982).

problem, as I thought, until Blanche Alter said, 'Well, the same thing happened to us yesterday, too'. So we were pushed into developing new techniques, and then we had to live for some time with fetal blood sampling, which when the fetus was affected led to a mid-trimester abortion. When that happens to one in four of your patients, after a period of time it is very difficult to live with. This made it crystal clear that for us the priority in the whole field was to develop an early approach that would allow you to escape from the necessity to use red blood cells, and use some other tissue that could be obtained earlier on in pregnancy, to achieve a prenatal diagnosis. Our awareness of the importance of developing an early approach was heightened by the fact that we were dealing with thalassaemia, which is common in developing countries, and it was clear that the techniques we were using would be completely inapplicable where this disorder was most common. I have just checked with David [Weatherall], and he agrees with my impression that the first serious clinical application of the new DNA technology was to allow us to move from second- to first-trimester prenatal diagnosis. This has been immensely important because once developed, in principle, these techniques could be made available in practically any country, to practically anybody. In addition all the other approaches for prenatal diagnosis, using chromosomes, using biochemistry, using DNA, were able to piggy-back on this development to move to earlier testing.

I think it will interest the historians that we were very clear at the time that this switch from mid-trimester to first-trimester diagnosis could only happen with haemoglobinopathies, and that gave us a feeling of responsibility. This wasn't only because they were the first inherited disorders to become detectable by DNA methods. It was largely because we had such an absolutely gruesome prenatal diagnosis method, which was technically difficult and involved a high risk (about 7 per cent) of fetal loss, as well as leading to mid-trimester abortion. Everybody else was working with amniocentesis, and the risk of fetal loss attached to that was of the order of 1 per cent. When you have got a very safe technique, it's extremely difficult to move to another technique, which may theoretically be ever so much better, but with an unknown, probably higher risk. You have to take the risk of raising the risk for your patients, before it can drop again. The risk for our patients was so high anyway that we were the only people involved in prenatal diagnosis who were in a position to tackle this transition.

Since you want reminiscences, the way it all started was because we had been working with Bob Williamson at St Mary's Medical School [London], to see if he was looking in parallel at material from our prenatal diagnoses to see if he could locate linked polymorphisms. One day he rang up and said, 'We have got

it', so I went over and got a copy of the photo of the gel, took it to our obstetrician, Humphry Ward, and said, 'We are on, we should start going ahead now'. So we started working with women having first-trimester social abortions in order to obtain placental material in the first trimester. When I talked to our obstetricians (not Charles), they said, 'It's been tried before; it doesn't work and there's too much risk'. I said, 'But you don't realize how little material you need'. Obstetricians think in big terms and they deal with big pregnancies. So I went away and designed a tool, and put it in our obstetrician's hand and said, 'That's the kind of thing I want you to look at'. 'Oh,' he said, looking at it critically, 'That won't do at all'. He went off and started working with Portex¹²⁶ to design an instrument that would do the job. The result was a simple catheter that could produce a sample of chorionic villus material on which a DNA diagnosis could be made. John Old (in David's laboratory) did the first three cases and we were very lucky this time. The key question was not whether you could diagnose an affected fetus in time for a first-trimester abortion, but was whether you could make a diagnosis of unaffected fetus and the pregnancy would continue normally. The *Lancet* paper, published on 25 December 1982, described the first pregnancies in which that happened.¹²⁷ By April 1983 the Pope had made a public announcement that it doesn't matter at what stage of pregnancy you do a prenatal diagnosis, it's still not acceptable.¹²⁸ Of course that wasn't the end of the story. We were still stuck with a DNA-linkage method, which, as David was reminding me, was a very difficult technique to work with. It was when PCR came along that people really started coming from places like Pakistan to learn how to do it.

I have talked about fetal sampling, rather than screening, because there's no point in screening people unless you have got something to offer, and this illustrates the succession of steps in moving from the hopeless to the undesirable to acceptable techniques. I certainly felt like Hercules [Atlas] who got stuck with holding up the sky, and when he finally managed to dump it on somebody else, it was the most enormous relief. That was the way our whole team felt when we knew that we could move from second to first-trimester diagnosis. Second-trimester diagnosis was a terrible method for everybody involved, not only for the patients.

Pembrey: The story of patient pressure, we are going to hear that again as we talk about pre-implantation genetic diagnosis [PGD]. But Charles, perhaps from the

¹²⁶ For further information see www.portex.com. Site accessed 25 April 2003.

¹²⁷ Old *et al.* (1982).

¹²⁸ See, for example, www.catholic-forum.com/saints/pope0264ht.htm. Site accessed 18 June 2003.

fetal sampling side of things, going back to all the things you could do with genetic diagnosis, you could do haemophilia and others with fetal blood, again was there a lot of patient pressure? How did it work? Would you have the same pressure?

Rodeck: Undoubtedly, that has been the story of prenatal diagnosis all along really. People faced with high risk of fetal disease or abnormality wanting to have a test, hoping that they will get a diagnosis that the baby is normal, or lack of a diagnosis if you like, but have made up their minds that if it's affected, they will terminate. So there has always been a great deal of pressure and we found that having developed a fetoscopic technique for successful fetal blood sampling and other substances too, fetal liver as was mentioned, and fetal skin, we were on a sort of conveyor belt. There were six or eight of these cases a week, many of them from Cyprus and Italy, and the results in general were very good. I wouldn't put our fetal loss rate quite as high as the one Bernadette mentioned, but you know it was a satisfactory technique that was working at the time and, of course, that meant you looked very hard before you moved away from it. But the problem was always the second-trimester termination, which means, people may not all realize that in this room, that the mothers who are facing this already had felt fetal movements. So I think one of the very crucial things about first-trimester diagnosis, even if you get the result in the early second trimester, is that the woman has not felt fetal movements and that her friends and neighbours didn't know about it and so forth. So in general we moved very rapidly to first-trimester diagnosis as well.

Pembrey: What was the timing? In 1982 (the paper that Bernadette refers to) where were we in terms of chromosome analysis of CVS at that time?

Rodeck: The thing that I think stimulated the West was the paper on CVS from China in the 1960s from the Anshan Steelworks, where there were no named authors in true Maoist tradition, but the whole hospital, probably including all the porters, were co-authors.¹²⁹ They produced this paper, which, of course, was used for sex selection. In the meantime there were several groups of us in London already looking at CVS, but there was another paper from the Eastern Bloc by a Hungarian who had been working in Moscow called Kazy and he submitted a paper to *Prenatal Diagnosis* in 1981, which Malcolm had to rewrite and which contained a few diagnostic cases.¹³⁰ I met Zoltan Kazy in a taxi once and he was extremely grumpy because he always felt that people in the West didn't recognize his achievement and, of course, he disappeared, probably to the Gulag unfortunately.

¹²⁹ Teaching Hospital of Anshan Iron and Steel Company. (1975).

¹³⁰ Kazy *et al.* (1980).

Malcolm Ferguson-Smith: I had a letter from him last week.

Rodeck: Oh excellent, was it postmarked Gulag?

Ferguson-Smith: He is back from the Gulag. He still feels disgruntled and has a review article. Now if you could help me with his address, because my secretary, who is very good at opening my letters, threw away the envelope with the address on it.

Rodeck: I am afraid I can't.

Ferguson-Smith: His paper was published in 1982 in *Prenatal Diagnosis*.¹³¹ Bob reviewed that paper, I think, and his own paper came out in the *Lancet* shortly thereafter, that paper about CVS and haemoglobinopathies.

Modell: You sent me that paper to review too, and it was very interesting, because you said it was from behind the Iron Curtain in those days, and nobody knew what to make of it. The interesting thing was that when I was reading it I felt, oh gosh these people have got just the same problems as we have, so I thought it was a very good and realistic paper and told you so, and you published it. The question the discussion is raising now is why did this development happen when and where it did? Why did it happen for haemoglobinopathies? Why did it happen in Russia? And why did it happen in China? It happened in China because in China they hadn't got any facilities whatsoever. They did it without ultrasound, they did it blind, just by touch. I've talked to the people who did it at WHO [World Health Organization]. **[From the floor:** But all they were going to do with the villi was to sex the fetus]. Yes, they did it blind and they used the Barr body for sexing the fetus. They stopped when they found out that almost all the female pregnancies got terminated. Subsequently, it turns out that doing it blind, you can get a lot of fetal abnormalities. But they developed this approach because they hadn't got the kind of technology that we had. Exactly the same thing applied in Russia. Amniocentesis was an extremely unsatisfactory method for them, because they had to buy culture media from the West and very often it didn't work. They found out later that when a firm had a batch of medium that had nearly expired, that was the batch that went to the East. So they couldn't use tissue culture reliably for prenatal diagnosis and were forced to look for alternatives. So it's when you are really up against it that you can afford, or even are forced, to move away from the accepted conventional and safe techniques with problems, to new areas.

Weatherall: Bernadette's account of the development of prenatal diagnosis of the haemoglobin disorders makes it sound as though it was all calm and easygoing.

¹³¹ Kazy *et al.* (1982).

In fact, it was anything but! We felt that David Nathan in the USA and Bernadette Modell in London were badgering us to take our globin-synthesis technique beyond its limits and that to demonstrate, reliably, 2 per cent of β -globin chain in a fetus at 15–20 weeks was really pushing its limits. I know that Y W Kan, who was one of the earliest to try, had many sleepless nights waiting for the outcome of pregnancies in which he had used this approach and I remember the hours we spent clearing up the globin-synthesis plots of some of the first cases that were analysed by us following prenatal diagnosis in London. I think we would have preferred more work to be done to improve the technique before applying it to patients, but Bernadette's extraordinary drive and enthusiasm would simply not let this happen; without her push, which was motivated entirely on behalf of the patients and parents, we would probably have gone on improving the technology for a further ten years; in the event, it worked remarkably well. I seem to remember we went through the same qualms when the chorionic villi era appeared.

Modell: If you want to persuade the scientists, the great thing is the hands-on approach. I remember coming up to Oxford to see John Old with a little pot containing a set of chorionic villi and holding it up to the light and shaking it and saying, 'Look, John, that's what we are talking about', and I saw his eyes go, 'Ooh! I think I could handle that'.

Adinolfi: I would like to mention, very briefly, a new approach about performing prenatal diagnosis by non- or minimally invasive techniques. The test is based on a method introduced in 1971 by L B Shettles, an American obstetrician, who claimed that he could detect fetal cells (trophoblastic cellular elements) retrieved from the endocervical canal at early stages of gestation.¹³² He suggested that trophoblastic cells are first shed into the uterine cavity and then in the endocervical canal where they could readily be found. Several years later Charles Rodeck and I decided to see whether this phenomenon was frequent.¹³³ We collected transcervical mucus from pregnant women between five and 13 weeks of gestation, and found fetal cells in 60 to 80 per cent of samples according to the method used for their collection. In a recent paper in *Prenatal Diagnosis*, Amiel and collaborators claim they could detect fetal cells in 98 per cent of samples collected with a cytobrush.¹³⁴ So, this seems a promising noninvasive prenatal technique that can be used for analysis of fetal chromosome disorders

¹³² Shettles (1971).

¹³³ See, for example, Adinolfi and Sherlock (2001).

¹³⁴ Fejgin *et al.* (2001).

by FISH or single-gene diseases by fluorescent PCR. Unfortunately, a few years ago we discovered that this approach had been misused in South Korea for fetal sexing (with 95 per cent success) and for aborting female fetuses.

I would like to mention another approach for rapid prenatal diagnosis of numerical chromosome disorders, based on PCR, which has not been mentioned by Paul Polani. The technique, called quantitative fluorescent PCR (QF-PCR) is based on the amplification of highly polymorphic DNA sequences (short tandem repeats, STRs) specific for chromosomes 21, 18, 13, X and Y. STRs are amplified and a fluorochrome is incorporated into the PCR products, which are then tested by a DNA scanner. In only a few hours it is possible to perform prenatal diagnosis of numerical disorders.¹³⁵ QF-PCR is now used in many genetic centres in the UK, Italy, Spain, Portugal, Germany and Austria as a preliminary test before conventional cytogenetic analysis, in order to reduce the anxiety of the parents. But, when applied to test samples from pregnancies at high risk, the QF-PCR results can be accepted as definitive evidence of fetal chromosomal abnormalities and, eventually, termination of pregnancies may be performed if required.

Pembrey: Just remind me, what cells are you doing these tests on?

Adinolfi: You can use any type of fetal cells.

Pembrey: But which ones are they using in this screening test?

Adinolfi: Amniotic or chorionic cells, for example. And, as I have mentioned, trophoblastic cellular elements present in the endocervical canal of pregnant women.

Pembrey: But not maternal blood?

Adinolfi: Barbara Pertl and Diana Bianchi have used QF-PCR for the detection of fetal cells in maternal blood samples. I am sceptical about the claimed success of using this type of approach for prenatal diagnosis, since too few fetal cells are present in the maternal samples, and their isolation will be quite time consuming and expensive. It has also been claimed that fetal erythroblasts can persist for many years in maternal circulation. Were this true, fetal cells from a previous pregnancy would hamper the accuracy of the tests and produce false results!¹³⁶

Pembrey: It's very interesting; these fetal cells in maternal blood, the sort of way things have gone. Because I remember doing a lecture tour in South Africa in 1981 and saying that it's a toss up as to whether it's going to be analysis of chorionic villi

¹³⁵ Adinolfi *et al.* (2000).

¹³⁶ Adinolfi (1995).

samples that's going to really take off, or whether that's going to be superseded by extracting fetal cells from peripheral blood. So at that time there was a feeling that they were sort of level pegging. I don't know if others had that feeling.

Rodeck: We had that feeling for quite a long time. When I was a medical student there was a man at Northwick Park called Barnes, an immunologist who was looking for fetal cells in maternal blood.

Ferguson-Smith: Two comments. First of all can I ask Matteo to tell us what the effect of this screening for sexing was in Taiwan?¹³⁷ I understand that the number of pregnancies screened for gender selection was over 20 000 per annum.

Adinolfi: Fetal sexing with any method has now been forbidden by law in Taiwan.

Ferguson-Smith: But the effect on the population sex ratio at birth was extraordinary, what was it, 1:1.6?

Adinolfi: I don't know. It has been difficult to get clear data on the use and results of the noninvasive approach that was carried out in the private clinics.

Ferguson-Smith: Then, following up about fetal cells in the maternal circulation, results have been very disappointing over the last few years. I don't think there is going to be a prenatal test using nucleated red blood cells containing embryonic haemoglobin, because people have found to their cost that adult maternal cells, progenitor cells, can also produce fetal and embryonic haemoglobin. What is more promising recently are two approaches, one is the actual DNA in the serum itself, and if you can identify suitable markers you will be able to make a genetic diagnosis. The other point is going back again to trophoblast. Trophoblast seems to be much more in vogue because there are good antibodies to identify the occasional trophoblast cells in the maternal blood and that looks a much more promising mechanism. I would put my money on DNA in the circulation, derived from breakdown of placental cells, and apoptosis in fetal and placental cells.

Adinolfi: Malcolm, do you believe that fetal DNA in maternal plasma is mainly derived from trophoblastic cells that are shed during pregnancy in the maternal blood reaching the lungs and forming emboli where they are rapidly lysed?

Pembrey: I think the interesting thing in drawing that part of the discussion to a close is again in this case in Taiwan or China, it's the patient pressure in a sense, that is driving some of the people to develop these techniques.

¹³⁷ His and Adinolfi (1997).

Rodeck: Matteo has brought us up to the sunny uplands of the 21st century really, and I think you wanted to know a bit about the dark ages of the 20th century. You asked about the application of cytogenetic diagnosis using chorionic villi and this was extremely difficult. In the early 1980s as far as I am aware in London there were three groups, UCH, I was at King's, and there was St Mary's with Dulcie Coleman in cytogenetics and Bob Williamson in molecular genetics. Dulcie had been working on a method of culturing chorionic villi, which is, in fact, very difficult. The trophoblast covering the villi is very difficult to culture and it turned out that you could only get success if you digested off the covering trophoblast and cultured the mesenchymal core, or perhaps the endothelial cells of the capillaries in the core of the villus. While attempts were going on along these lines, the whole situation was transformed by Simoni in Milan¹³⁸ who developed a method for obtaining chromosomes, chromosome analysis, on metaphases from spontaneously dividing cells in the cytotrophoblast. So he also digested off the trophoblast, but then developed what is called a direct preparation, which in theory you could do in two or three hours. In practice most people would culture over night, and then perform this analysis. That meant it transformed cytogenetic diagnosis, because you not only did the test several weeks earlier than amniocentesis, you got a result in a day or two, rather than in three or four weeks, which a karyotype took in those days. So then that was quite widely adopted, but it became apparent that this tissue, the cytotrophoblast, had a high level of mosaicism, or at least high compared with amniotic fluid. So to cut a long story short, nowadays the chorionic villi are not regarded as the best tissue for a cytogenetic diagnosis on the fetus, and we have gone back to amniocentesis, particularly because we now have PCR methodology to do specific chromosomal diagnosis.

The other aspect that CVS revolutionized was biochemical disorders, because as Liz [Young] knows, many of the techniques that people like her have developed for amniotic fluid, could quite rapidly be modified for chorionic villi. So even before all the genes were cloned for these conditions, very rapid biochemical diagnosis could be done in the first trimester, on chorionic villi.

Adinolfi: Do you think the Chinese were doing chorionic biopsy or were collecting cells from the endouterine cavity, because they were not using ultrasound? It's possible they were just getting into the endocervical canal and collecting fetal cells there.

¹³⁸ Simoni *et al.* (1983).

Pembrey: We are going to move forward now into the pre-implantation stage, because this is an important area where Britain has made pioneering contributions. I am going to take Chairman's privilege to tell a story about a meeting, a workshop, that was held by Ciba, the Ciba workshops – invited workshops that have played a very important role in a number of these developments. I know the date, it was on the 7 November in 1986, it was certainly a Thursday, because I carried the Thursday's *Nature* with me. Earlier that year, in the summer, there had been a genetics meeting in Berlin and everybody was desperate to hear about the PCR. I think it was Henry Erlich from California (I think he was in Genentec then or something) but he was in a little side room. There was the plenary session in Berlin with hardly anybody there. Everybody was trying to get into this small theatre, with people relaying the information that was being said, out into the corridor to the crowd, about this amazing PCR technique. So that was in the summer, and then we had this Ciba meeting, and Bernadette was asked to speak. Bob Edwards was involved on the IVF [*in vitro* fertilization] side, and Anne McLaren, who was, I think, one of the people who brought the obstetricians, and I think Charles was there. Bernadette was asked to state whether or not there was a clinical need for this pre-implantation diagnosis, and she quite simply, in her characteristic way, asked the patients what they would most dearly like us to develop, and they said, we would like to be able to start the pregnancy knowing that we have got a healthy baby, or a baby without the genetic problem. So that was the pressure from the patients.

I was asked to talk about the genetics in general terms, but I had with me a paper in *Nature* by Henry Erlich, saying that they could do PCR and get typing of HLA genotypes on as few as 75 cells,¹³⁹ and when I said this, Bob Edwards jumped up and danced around the room, saying 75 cells, 75 cells, we are going to be able to do it! Because he had earlier said I don't think it is on, we can't give you geneticists enough cells. So that was a key moment for me, and that was in November 1986.

At that time we were just beginning the big debate that led up to the Human Fertilisation and Embryology Bill and Act in 1990.¹⁴⁰ So it was a four-year period and this was a key time in which the technology and the ideas came together. But for that bill to be carried through, everybody is agreed, I think, that prenatal, pre-implantation genetic diagnosis was the main thing that was being championed, indicating the positive side of being able to do embryo research on

¹³⁹ Saiki *et al.* (1986).

¹⁴⁰ Anon. (1990); Braude *et al.* (1990). See www.hmsa.gov.uk/acts/acts1990/Ukpga_19900037_en_1.htm. Site accessed 25 April 2003.

pre-implantation embryos. I know Alan Handyside was very involved in those early studies at Hammersmith and perhaps you could take it from there?

Professor Alan Handyside: The attempts to develop pre-implantation genetic diagnosis [PGD] involves the use of assisted reproduction and is an interesting story, because for the first time it brought human genetics and assisted reproduction together, raising challenging technical and ethical issues. Nevertheless, as you have just pointed out, it occurred in the mid- to late-1980s; against a background of an intense debate on whether or not we should legislate within the UK in favour of human embryo research.¹⁴¹ I believe it played a key role, as I will explain, in helping to persuade people that perhaps there were benefits to be gained from allowing human embryo research. In fact, when the legislation went through, one of the specific reasons for which human embryo research can be allowed is for understanding the aetiology and diagnosis of genetic defects at early stages of development. On a personal level, my involvement goes back to slightly before the Ciba meeting, to 1985. I have always credited Anne McLaren for talking about this at a meeting.¹⁴² I think she must have had privileged access to the rumours that had been going round about the success of the polymerase chain reaction, and in the audience was a young clinician, Richard Penketh, who at that time had a fellowship and was working with Dorothy Gibbs, and the senior professor at the CRC [Clinical Research Centre], Richard Watts, on inherited metabolic disorders. He had one patient that he was particularly interested in helping and used to show pictures of the affected teenage boy bound to a wheelchair for his own protection. The parents had tried to use prenatal diagnosis to avoid having another affected boy and had something like, I think, six terminations of pregnancy without success. So this was the major stimulus for the use of assisted reproduction – the hope of bringing the diagnosis back to a stage at which we could then go on and select embryos that were unaffected, transfer them back to the woman's uterus and, as Marcus said, really fulfil this dream that couples could start a pregnancy knowing that it should be normal.

This was a very interesting coincidence, because at the time I was working at the MRC Experimental Embryology and Teratology Unit. I wasn't working in this area at all, but had just, working with Martin Hooper in Edinburgh, developed the first gene knockout mouse using embryo stem cells, mouse embryonic stem

¹⁴¹ See, for example, Editorial (1985, 1989).

¹⁴² See, for example, McLaren (1985).

cells.¹⁴³ This was achieved independently by Martin Evans at Cambridge,¹⁴⁴ with whom I had worked previously. The gene that we had chosen to knock out was hypoxanthine–guanine phosphoribosyl transferase (HPRT) and the goal was to create a model of Lesch–Nyhan syndrome, which was precisely the condition that this patient of Richard's was at risk of transmitting. Towards the end of that work when we were racing really to prove that we had the knockout mouse, we approached Marilyn Monk because she had a very sensitive biochemical assay to prove that the gene, in fact, had been knocked out, and the mice had no HPRT activity. We did this by isolating individual intestinal crypts and individual hairs.¹⁴⁵ We spoke a little earlier on in terms of biochemical genetics, hair follicles were still being used to determine carrier status in Lesch–Nyhan syndrome at that time, and hence I had various discussions with Dorothy Gibbs as to whether her tests would be sensitive enough to get down to the single cell level. But clearly Marilyn Monk had, over a period of many years, refined this technique to analyse, mainly using this X-linked enzyme, the timing of X inactivation in early development. So although the HPRT knockout mouse turned out to be a failure in terms of replicating the symptoms of Lesch–Nyhan syndrome, or for providing a vehicle for testing therapeutic strategies, it was clear that we should be able to use this mouse model to develop techniques that would be necessary for pre-implantation genetic diagnosis, such as to biopsy cells from the early embryo and single-cell analysis. Ironically, although this occurred against a background in which PCR had just been discovered if you like – and that's controversial in itself as to whether Kary Mullis was, in fact, the discoverer – we used a biochemical approach initially, and so did the group in the USA, who were the only group I think in the USA that were interested at that time, and that was a collaboration between Eugene Pergament, who had been very much involved with CVS, and Yury Verlinsky, who is still one of the major players in the USA.

At this point, I would just like to give credit to the first attempt, or the first recognition that pre-implantation genetic diagnosis might be possible, to the pioneer of IVF itself, Bob Edwards. I would be interested if anybody else knows of any other precedents. In 1968, really within the context of animal embryo genetics and the commercial needs to either pre-select the sex of bovine or sheep embryos, for obvious commercial reasons, attempts had been made for many years to differentiate between X and Y bearing sperm. Bob Edwards got together with his

¹⁴³ Hooper *et al.* (1987).

¹⁴⁴ Kuehn *et al.* (1987).

¹⁴⁵ Monk *et al.* (1987).

first PhD student, Richard Gardner, to attempt this in the rabbit. This was a very fortuitous choice, because the rabbit pre-implantation embryo can get to several millimetres in size *in vitro*. The results were published in *Nature* in 1968,¹⁴⁶ in which they performed embryo biopsy, by snipping a piece of trophoctoderm with a pair of iridectomy scissors from the blastocyst and then used the presence of the Barr body to identify female embryos. After they transferred them back to recipients, they demonstrated that they had correctly sexed all of the embryos.

I went up to Cambridge in 1971 and it was through the lectures that Bob Edwards gave that I decided on a career in embryology. This was only three or four years following publication of this work. Looking back after many years at that paper they do explicitly say we are aware that it may be possible to use it in X-linked conditions and, in fact, speculate about combining chromosomal analysis with enzyme analysis to look at human disease. Interestingly, one of the offspring was anencephalic, raising worries about the biopsy process. Why biopsy of the trophoctoderm would cause any problems isn't clear, but I believe the feeling, Bob Edwards's feeling, was that there was a high level of anencephaly in this particularly strain of rabbit. So the original attempt certainly arose out of attempts to sex embryos in farm animal species and go back as far as 1968, but modern attempts really were stimulated by PCR.

So as Marcus has pointed out, as a result of Richard Penketh's interest, Anne McLaren and Richard Penketh wrote a very stimulating review about possibilities.¹⁴⁷ He then approached David Whittingham who was the director of the unit that I was at, and so because I had the model of HPRT, and was already collaborating with Marilyn Monk, we then went on to show that we could indeed sample cells at cleavage stages. We had to culture them to the appropriate stage, because Marilyn knew in detail when you would be able to ascertain the embryonic genotype from the enzyme activity. One of the problems about biochemical analysis in this period is that most of the enzyme activity is inherited in the oocyte cytoplasm and persists for a variable period of time. So you had to be sure that the maternally derived enzyme had degraded and that any enzyme activity that you picked up was, in fact, from zygotic gene expression. But she had already done many experiments in which the timing had been established, and in fact we were able not only to pick out HPRT-deficient embryos and prove this by transferring them, but also Marilyn and I went on to show that because you can see a two-fold difference, measuring this X-linked enzyme, you could sex

¹⁴⁶ Gardner and Edwards (1968).

¹⁴⁷ Penketh and McLaren (1987).

on this basis too. So this was entirely non-PCR based. Then we all got together at the Ciba Foundation meeting, and of course shared in the excitement of the publication finally describing PCR and demonstrating the possibility of analysing as few as 75 cells. At that stage we had no idea how many cells there were in the human blastocyst. It wasn't until 1989 that I did some studies that showed that indeed by the time you get to the end of the first week of development, you have hundreds of cells in the human blastocyst on different days, and indeed you might well be able to use PCR to analyse genetic defects.

So having got involved in the field, I then had to make a decision about how I took the work forward. Clearly, the knockout mouse had not proved to be a model for the human disease. Martin Hooper went on to knock out genes involved in cancer, the retinoblastoma gene and so on, and I decided to follow up on the pre-implantation genetic diagnosis and realized that what it required was to move to an obstetric department and really get involved with assisted reproduction clinics. So I approached Robert Winston, now Lord Winston, at Hammersmith Hospital about this. He was very excited about two projects, one was human embryonic stem cells, and I had been very involved during the years in the mouse, but also in PGD [pre-implantation genetic diagnosis], and it ended up that we put most of our efforts into PGD, because we didn't have the ability to culture human embryos for very long at that time. So it was, in fact, almost coincident with the Ciba meeting that I moved across to work with Robert.

We had two clear objectives to begin with. The first was to develop methods for embryo biopsy. Anne McLaren was the key figure here. She was running the Interim Licensing Authority [for human *in vitro* fertilization and embryology], and the challenge she gave us was to develop an embryo biopsy strategy that would not threaten the development of the embryos. So I set about doing this, against, as I say, a background of very intense media interest in human embryo research. Robert was very keen to interact with the media and really worked very hard to try to persuade people. Looking back on that time, it was really a nightmarish period of my life, because we literally had several film crews through every week. So we were literally being filmed during the experimental phase; as we were developing the biopsy techniques, they were being filmed, and we were being interviewed about the possibilities. But in the end this paid dividends and I kept cuttings from this period of time and collected them altogether. I had a friend who worked in the Home Office – obviously the Home Office took a lead on this legislation – who passed me their own cuttings, and after the debate in the House [of Commons], all these papers were passed to a sociologist in York

[Professor Mulkay] who studied the language used, and how the debate evolved over this period of time. So it had an academic spin-off.

The second thing that I decided very early on, is that you couldn't do this at the blastocyst stage. We weren't able to get pregnancies by transferring embryos at that stage, so we had to go for single cells biopsied from early cleavage stage embryos. We therefore had to develop PCR. So working with Ted Tuddenham's¹⁴⁸ group – the names keep recurring here – who was then at the CRC and had moved down to Hammersmith, we were finally able to use a Y-linked repetitive sequence to identify males and used this in five couples at risk of X-linked disease, having published work that showed that we could biopsy the single cells safely. The first couples were treated in September of 1989. We had no idea whether they would get pregnant at that stage. They were fertile couples, so we were optimistic from that point of view. However, we were making a large hole in the zona¹⁴⁹ and had no idea whether the embryo would be lost. We knew from animal experiments that this could destroy the embryo. In fact, in the very first case a single embryo was transferred and the couple had a biochemical pregnancy, and the pregnancy rate in the other couples was exceptionally higher. We then had a very nervous period of waiting to have the diagnosis confirmed. We counselled all of the couples that this was very early and experimental. So they went on to have the diagnosis confirmed by CVS in the majority of cases. When we had the results from several couples confirming the sex as female, I approached *Nature* to see if they would be interested in this publication. Miranda Robertson, who was at the time Assistant Editor, went off to talk to John Maddox [Editor] and really because of the background of the intense debate on human embryo research, they said that they would be very interested but wanted to make sure it was published ahead of the debate in the House of Commons. So we were literally working day and night to write the paper against these tight deadlines. The peer reviewers had already been set up, and it was probably one of the first papers to be peer reviewed by fax. It was submitted and accepted, after peer review and corrections, in only two days, because John Maddox was absolutely clear that the public should be aware of the potential benefits of embryo research.¹⁵⁰ In the week of publication he organized a press

¹⁴⁸ Handyside *et al.* (1989).

¹⁴⁹ Professor Andy Handyside wrote: 'This was the glycoprotein coat surrounding the embryo at these early stages.' Note on draft transcript, 9 July 2003.

¹⁵⁰ Handyside *et al.* (1990); See also McLaren (1989).

conference and the two women who carried the first pregnancies came along because they wanted to support the work and enable other couples to benefit following PGD. I think they were very brave and both of them were heavily pregnant with twins, but it had a significant impact on the press conference and their story was featured on the front page of the *Daily Telegraph* the following day. The following week at the end of the debate, even Margaret Thatcher went through the aye lobby and voted to allow human embryo research, which was carried by a substantial margin.

Pembrey: Cathy, if you would like to talk a little, if you have got any comments about your early work with Marilyn that led into this, and then we will move on to the chromosomal side.

Mrs Cathy Holding: I seem to have been involved in all these various aspects of genetic testing, going right back from testing for HPRT activity in hair roots and cell lines from skin biopsies to the development of an HPRT assay for use in prenatal diagnosis of Lesch–Nyhan syndrome by chorionic villus biopsy.¹⁵¹ I then moved on to Marilyn's lab, where she had developed a single-cell double microassay for the X-linked HPRT and autosomal APRT for her X-chromosome inactivation studies throughout the 1970s. Marilyn had already developed various single-cell procedures for studying gene expression in pre-implantation embryos long before people began to talk about pre-implantation diagnosis. At the time I joined her lab, we were developing single-cell assays for adenosine deaminase – the enzyme that is deficient in some forms of severe combined immunodeficiency disease (SCID).

When the discussions of the feasibility of pre-implantation diagnosis began, Marilyn knew she was already doing this in her diagnoses of HPRT levels in single embryos, and she only needed to gear her experiments across to this more clinical arena. I can remember Alan coming into Marilyn's lab in the mid-1980s to help with the blastomere biopsies, and both of them at the lab bench. Alan biopsied the single blastomeres from the embryos, and Marilyn then carried out the single-cell molecular assays. Initially they used a mouse model for Lesch–Nyhan disease and diagnosed the HPRT-deficient embryos, and later they also used Marilyn's dosage analysis of X-linked HPRT also for the sexing of pre-implantation embryos. After that, PCR hit the headlines as a really powerful technique for amplifying small-defined regions of DNA. Marilyn decided that it would be a good idea to try to use PCR to amplify single-copy genes in single

¹⁵¹ Gibbs *et al.* (1986).

cells, also for use in pre-implantation diagnosis. Alan points out that they did PCR on multiple-copy sequences on the Y chromosome for the purpose of sexing in pre-implantation diagnosis, but Marilyn could see great potential for pre-implantation diagnosis in amplifying single-copy sequences in single cells for direct analysis of genetic defects, as sexing is only relevant for sex-linked diseases. So we developed our single-cell nested-PCR technique for detection of defined sequences of DNA and showed that we could diagnose β thalassaemia by assay of a sequence of the β -globin gene in single blastomeres from the pre-implantation embryos. We were the first to show that PCR could be used on single-copy genes in single cells using nested PCR.¹⁵² Cui and colleagues also reported successful single-cell PCR using two-primer PCR on single sperm at the same time, but they needed to use a radioactive hybridization technique to see the products. We were directly able to see the products of nested PCR in an agarose gel, greatly speeding up the process for a clinical setting.

Since the research on embryos was an ethically sensitive issue (human embryo research was at that time being debated in the House of Commons), Marilyn could see the potential for using PCR for pre-fertilization diagnosis (that is, diagnosing a genetic disorder in the oocyte before fertilization by removing and analysing its first polar body, leaving the oocyte intact for *in vitro* fertilization after diagnosis is completed). We showed that it was possible to carry out the analysis of a single-copy gene, this time using a PCR strategy that detected the sickle-cell mutation in β globin, in the first polar body of a human oocyte.¹⁵³ We could deduce from the genetic status of the first polar body the genetic status of the oocyte, and thus diagnose whether the oocyte carried a sickle-cell mutation. This was an important breakthrough for the debate, because we had shown that we could do the diagnosis without having to do any research on the embryo, and we were using a human oocyte now rather than mouse-model systems. In fact, the single-cell assay we developed to detect the human sickle-cell mutation in the polar body of the human oocyte (and in any single cell) is widely used in pre-implantation diagnosis labs today.

Marilyn has played a major role in the development of techniques for the pre-implantation diagnosis of genetic disorders, initially in mouse models and, by 1990, in the polar body of the human oocyte.

¹⁵² Holding and Monk (1989).

¹⁵³ Monk and Holding (1990).

We were successful in the first instance, where so many other labs were not able to do single-cell PCR due to contamination, because we went to extreme lengths to avoid cross contamination with PCR products.¹⁵⁴ Both myself and Marilyn (in separate laboratories) then went on to do relevant quality-control experiments to evaluate carefully the accuracy and efficiency of the diagnoses – so important before offering these procedures in the clinic.

Pembrey: I certainly remember Marilyn saying, and perhaps you would like to corroborate this, but one of the things that drove her wasn't so much the patients driving her to develop these micromethods, it was her respect for animals, and not wanting to sacrifice an unnecessarily large number of animals, to take a little clip off the tail of a mouse, rather than kill it.

Holding: That's absolutely right, yes. Long before the development of the molecular procedure for pre-implantation diagnosis, Marilyn had been setting up molecular analysis of gene expression in pre-implantation development. Before she attempted this, however, she decided to work on the molecular microassays, to make these assays sensitive to the single cell, so that a great deal of information could be gained from the embryos of a single pregnant female mouse – to use one single mouse instead of hundreds, as had been used previously.

Pembrey: Joy, chromosomes were a rather different sort of story I seem to remember?

Professor Joy Delhanty: In the beginning it wasn't chromosomes. In the beginning my involvement began in parallel with Alan's work on developing the PCR method for sexing embryos. Then Richard Penketh and I were working trying to develop a non-radioactive method of *in situ* hybridization to detect the Y chromosome in an interphase nucleus. That was working quite well, but the problem was it was all taking too long, as we thought then, taking about 48 hours to detect the Y chromosome and there was quite a lot of background. So we thought, well, the PCR had won the race and that was going to take over. But then along came FISH, fluorescent *in situ* hybridization. I took on a young student called Darren Griffin, in the lab in the late 1980s, without really knowing whether FISH was going to work at all – there were just a few abstracts from meetings and things. He got that going in our lab and we were able to develop FISH to detect not only the Y chromosome, but also the X chromosome

¹⁵⁴ Mrs Cathy Holding wrote: 'It was Peter Koopman, in the Unit at the time, who suggested to me that I should totally deconstruct our Gilson pipettes and subject the parts to UV irradiation for 20 minutes each time a PCR was carried; one of the most significant pieces of advice I have ever received.' E-mail to Dr Daphne Christie, 25 June 2003.

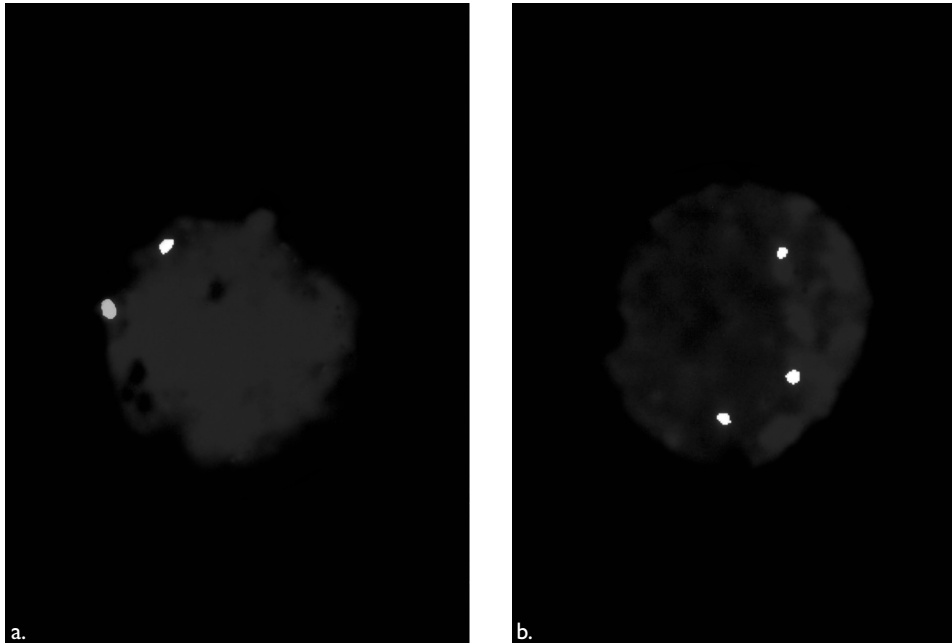


Figure 2: The use of FISH with DNA probes from the X and Y chromosomes to sex human embryos, by interphase cell analysis. a. Nucleus from a male embryo following dual FISH with biotin-labelled X chromosome probe (top signal) and digoxigenin-labelled Y probe (bottom signal). b. Nucleus from a female embryo that consistently had three X signals per nucleus after dual FISH with X and Y probes. Delhanty (1994): 1224. Photographs provided by Professor Joy Delhanty, 2003.

simultaneously (see Figure 2),¹⁵⁵ and that proved in the slightly longer run to be a more reliable method for determining the sex of the embryo, but also it gave us an indication of the copy number of the chromosomes present.¹⁵⁶ So not only could you say whether there were X and Y chromosomes present in this nucleus, but also how many there were. So it meant that you could distinguish between a normal female for instance, and one that would develop Turner's syndrome, and only have a single X, and similarly distinguish a Klinefelter XXY from a normal male. So that was an important advance. From that, we went on to develop ways of detecting other chromosome abnormalities, mainly for couples where one of them was carrying a translocation, and this was causing a lot of

¹⁵⁵ See Delhanty (1994).

¹⁵⁶ Professor Joy Delhanty wrote: 'This early work on embryo sexing also provided an insight into why so many human embryos die. It is due to chromosomal mosaicism that arises in the first few days of development.' Letter to Dr Daphne Christie, 4 September 2002.

problems. Often these people were unable to carry a pregnancy, because they were having many miscarriages, and that sort of led to an application for FISH – to be able to select healthy embryos for these couples.

One thing I would like to say is that as far as patient pressure is concerned, it's interesting that now we are able to do PGD for the dominant disorders, in particular the cancer-predisposing genes, that couples who come and ask us if we can help them. What they say is I want to get rid of this gene from my family, it is a curse. The people who are worried about PGD in terms of eugenics wouldn't like to hear that, but that's what the families say. Also for things like fragile X, they say that as well, we want to get rid of it, it's just a curse. That's an interesting reflection.

Pembrey: It's the phraseology, but in practice I guess you could turn round and say in a sense they also want to have a healthy child.

Adinolfi: A very brief note about the use of embryonic cells for the correction of selected inherited diseases. A few years ago I was talking with Bob Edwards about embryonic cells, and we came to the conclusion that there was too much emphasis on and hopes about these cells being used for therapeutic correction of genetic disorders. Embryonic cells, once differentiated, are expected to produce histocompatibility antigens, and consequently their use would be limited only to immunocompatible donors.

It has been claimed that stem cells from normal adults (such as bone marrow and brain cells) may differentiate into other types of cell. We do not know why stem cells from an adult may de-differentiate and differentiate into other types of cell producing insulin, or other proteins. This topic is still controversial, but if early results are confirmed, Bob and I thought that the direction to go would be to induce differentiation *in vitro* of adult stem cells into specific differentiated cells, which could then be transplanted into a compatible patient.

Pembrey: I understand, but I am sure we will have a witness seminar on stem-cell research, and that there will be just as much time pressure on it. Right away from the individual families at high risk and culminating with the very early pre-implantation, stand back a bit now and not forget that genetic testing has also played its role in medicine more broadly; in immunogenetics and in blood groups. And perhaps Rodney if you could say a little bit on the HLA side, and then perhaps Derek Roberts could come in and cover other areas.

Harris: Peter Medawar once said, 'We are being progressively relieved of the burdens of single instances, the tyranny of the particular. We need no longer record the fall of every apple'. This comment became very apposite to the HLA [human leukocyte

antigen] field and human histocompatibility because for some time they were enormously complicated by descriptions of a multitude of serological and cellular reagents defining putative new and overlapping antigens. In the HLA community a uniquely enlightened collaboration, in the form of a series of international workshops, defined the system and incidentally provided the model for future scientific advances, including those leading to the sequencing of the human genome. Foremost among the people who initiated and made these histocompatibility workshops succeed were Walter Bodmer and Julia Bodmer, at first in California with Rose Paine, but subsequently in the UK with Richard Batchelor and Sylvia Lawler, and many colleagues in other countries, including Jean Dausset, Roy Walford, Paul Terasaki and Jon van Rood among others. By sharing reagents and data, ‘apples’ were found to fall in recognizable patterns that vastly clarified immunology, organ transplantation and understanding of disease susceptibility.¹⁵⁷

With the help of many collaborators, including Charles Rodeck and Bernadette Modell, who are here, the confidential enquiries showed that the primary care providers, GPs, obstetricians, internists, etc., often had little knowledge of genetics, and that many non-genetic clinicians were so concerned with the management of disease in individual patients that the implication for relatives and future generations were often overlooked. Non-geneticist healthcare providers often did not correctly interpret the results of genetic tests ordered by them, and were poorly prepared to discuss the results of testing. Many were woefully unaware of ethical, legal and psychosocial implications such tests may have, and were often not in compliance with ethical and clinical guidelines, especially regarding informed consent for testing.

Fortunately Cedric Carter, with others in the Clinical Genetics Society, had established the specialty of medical genetics, and the successful application of new clinical genetic discoveries in UK was greatly assisted by trained clinical and laboratory geneticists working metaphorically ‘under one roof’. A network of genetic centres was created as a result of initiatives by the Royal College of Physicians, Royal College of Pathologists and the Department of Health. An

¹⁵⁷ Professor Rodney Harris wrote: ‘I am certain that my participation, as a junior worker, in the HLA workshops made me think about the pretty random fall of genetic apples among non-geneticist clinicians. Then, our original survey of teaching genetics to medical students [Report of a working party of the Clinical Genetics Committee of the Royal College of Physicians. (1990)] showed how ill prepared existing doctors had been for genetics and this was later confirmed by the disconcerting results of the UK National Confidential Inquiry into Genetic Counselling by Non-geneticists (CEGEN). See Harris *et al.* 1999; Modell *et al.* (2000).’ Letter to Dr Daphne Christie, 3 July 2003.

important example was the Special Medical Development allowing the introduction of molecular genetics in the NHS.¹⁵⁸ Patterns of clinical genetics services in other European countries were documented by the EU-funded Concerted Action on Genetic Services in Europe (CAGSE)¹⁵⁹ and although, in Europe, CAGSE found a nucleus of highly trained clinical geneticists, this elite was numerically incapable of delivering the expanding range of new genetic procedures. As genetic testing moves into the main stream of healthcare, physicians and others with little training in genetics increasingly administer and interpret genetic tests. Most routine antenatal genetic screening is the responsibility of obstetricians and midwives and, although the speed with which testing for genetic susceptibility for common disease will be integrated into clinical care is unknown, public awareness is rapidly increasing demands and hence the need for professionals' knowledge of genetics.

In contrast to the generally satisfactory state of clinical genetics where integrated genetic centres exist, it was apparent that there was a need for an empirical basis for assessing current genetic education for primary care and other nonclinical genetic health professionals providing most of the services. Accordingly, the EU has funded GenEd (Genetics Education: Improving non-genetics health professionals' understanding of genetic testing).¹⁶⁰ The object is to find out what is going on at the moment, what is available, what non-geneticists perceive as important and then to develop educational and training packages which fit into the special requirements for each country. GenEd will be the first empirical study to be conducted in the EU on education needs assessment and education priorities in genetics among non-genetics healthcare professionals.¹⁶¹

Pembrey: We need to round off. We have moved from specific family testing, to the broader service issues and so on, but another trend that we have got to, and it's picking up a little bit on what Susan Povey said earlier on, about the normal, looking at normal population structure, normal variation as well, not just serious genetic disease. That's also been a part; there's a history there of the use of genetic

¹⁵⁸ Harris *et al.* (1989).

¹⁵⁹ Harris (2000).

¹⁶⁰ See www.medicine.man.ac.uk/gened. Site accessed 10 July 2003.

¹⁶¹ Professor Rodney Harris wrote: 'Subsequent to the present seminar the UK Government launched the Genetics White Paper, "Our Inheritance, Our Future – realising the potential of genetics in the NHS" [www.doh.gov.uk/genetics/whitepaper.htm (site accessed 10 July 2003)]. The paper sets out the Government's commitment to developing genetic knowledge, skills and provision within the NHS by investing more than £50 million over the next three years.' Letter to Dr Daphne Christie, 3 July 2003.

tests and polymorphisms to look at populations in addition to some of the more health-related issues. I wondered, Derek, whether there are any comments you want to make on that, in this general field?

Roberts: A most useful feature of the red cell blood group is the illustration of the principles of genetics in the classroom. You asked us to go back in time: The first achievement that made many subsequent developments and applications possible was in 1557 by the man whose memorial you can see from the window here, a couple of miles down the street, when Sir Christopher Wren devised an implement consisting of a sharpened quill and a bladder attached, and it was this that allowed intravenous therapy, and it also allowed all the investigations that led to not only our blood-group knowledge, but also to many of the other genetic variants.¹⁶²

We have spoken of the pressure from patient groups, and I think this is another outstanding feature that the blood-group work shows us, that much of the development of our scientific knowledge, particularly in human genetics, has been as a result of pressure from somewhere else. I suppose the big pressure was the Franco–Prussian war, about 1870, when the numerous casualties that required surgical treatment in the field would have benefited from knowledge of the blood groups and particularly of compatible and incompatible transfusion.¹⁶³

Shortly after, about 1875, came the discovery of the serological species specificity, whereby if blood from one species was introduced into another species, agglutination developed. This animal incompatibility prompted Landsteiner in Vienna to carry out his inquiries as to whether differences in agglutination such as occurred in interspecific mixtures also occurred between individuals of the same species. This, of course, led him to discover what subsequently became known as the ABO blood groups in 1900 and the fourth, the AB group, discovered two years later.¹⁶⁴ I suppose also that the widest application of genetic testing, namely testing for the presence of a genetic character, is that of the ABO blood groups. Many of us, perhaps not so many here, a couple of decades ago, or several decades ago, wore round our necks dog tags with our blood groups, to be of use and application when we required transfusions. That type of genetic testing was applied to millions of individuals and has expanded as our knowledge of blood groups developed.

¹⁶² See Hutchinson (1976): 36–37.

¹⁶³ Ponfick (1875); Zimmerman and Howell (1932); Tansey and Christie (1999): 13; Christie and Tansey (2003): 27–29.

¹⁶⁴ See Landsteiner (1901, 1903); Rous (1948). See also Roberts D F, De Stefano G F. (1986): 4, 6.

One of the most useful applications, not only of the blood groups, but of the other human polymorphisms, has been the information it has given us on the lack of homogeneity of human populations. Namely even in an area such as Britain, if you plot the distribution of the blood-group frequencies, you see that there are pronounced regional differences in frequency, not only big regional differences and frequencies, there are also local differences, and these I think are more and more important as one finds the curious, very rare, genetic conditions that are associated with the molecular heterogeneity. These too show a remarkable lack of uniformity, and we want to know why. The differences in gene frequency between north Northumberland and Tyneside, or between the different parts of the Lake District, how have these come about? These are of relevance in a clinical situation, because, for instance, we want to know whether the curious conglomeration of unpleasant disorders that have occurred round Sellafield, are the result of some underlying population structure, or whether as a result of the presence of the British Nuclear Fuels establishment there. I think we are at the stage of exit of the polymorphisms, the classical polymorphisms, and the serological polymorphisms, they are being replaced by molecular work. There we have had the pressure from medicine, but we have also had it from another curious source, the lawyers, for forensic medicine, as forensic medicine and its applications of genetic tests, in paternity cases for instance, and the identification no longer depends on the quite precise probabilities that can be obtained from testing with a battery of polymorphic markers to be replaced by the much less time-consuming molecular tests. I don't think I have very much else to say on this, I would like to have spoken a little on a completely different topic, but anyway I have done what you asked me.

Pembrey: We've had a full sweep from academic interest in the early blood groups and so forth, right through to testing, and to delivery of genetic services, and then back again to the broader polymorphism in the population, which is going to be essential as we try to tackle complex diseases. I think as we finish, it would be quite good to get a general feel (I know people might be reluctant to do this) about the other question that Doris raised in her introduction. Was it just the individuals, or were there schools or groupings, critical masses of people in Britain over the last century, that led to the accelerated application of this genetic knowledge, or the discovery of genetic variation for genetic testing as such? I am just wondering if anybody wants to comment. Historians like schools, but I am not sure the people who were involved see it in quite that way. We probably don't see it as a school. It sounds like something terribly formal, but just a network, a zone of collaboration that was critical. Were there such foci of activity?

Woodrow: Surely there were no rigid rules here. Some years ago it was possible for a small group of interested people, using relatively unsophisticated techniques, to make useful and even important contributions. In Liverpool Cyril Clarke had many of the qualities of the best 19th-century naturalists, and he and his colleagues were not primarily geneticists. It may be that work of this kind is no longer possible and all the important work will be done in institutes of the kind that David Weatherall left Liverpool to set up in Oxford, and in those that have been established subsequently.

Ferguson-Smith: I would like to emphasize something that Rodney has just pointed to, how successful for genetics has been the development of a network of groups within the UK. That is rather special to the UK. It was made possible by each of us knowing one another, and deciding on sharing and having common interests and common meetings. It also occurred in the environment of the National Health Service, which is absolutely key, and something that is a tremendous advantage that the UK has, for example, as opposed to North America and Europe. Some of us were fighting political attempts to destroy this network in the Thatcher days and fortunately I am happy to say that in politics the pendulum has swung the other way again, and now we look like developing and strengthening the network that we have got. I think that's something special about genetic services in the UK that bears mentioning.

Adinolfi: Talking about 'schools' or 'groupings', I think that we should mention the 'critical mass' of scientists involved in the discoveries of blood-group antigens here in the UK. I am referring to the work of R R Race, Ruth Sanger, A E Mourant, W V Watkins, W T J Morgan and P L Mollison, just to mention a few. Many foreign scientists have learned genetics by visiting blood group units in the UK, like R Ceppellini and R Grubb who later discovered the relationship between the Lewis and the Secretor/non-secretor system.^{164a}

About new techniques, the detection of 'incomplete' Rh antibodies by the antiglobulin test by Coombs, Mourant and Race in 1946 solved many problems, including those associated with maternal–fetal incompatibilities.¹⁶⁵

Pembrey: Yes, I think it very much did.

^{164a} Professor Matteo Adinolfi wrote: 'Lewis and the Secretor non-secretor system of ABO antigens are blood groups. They interact with each other.' Letter to Dr Daphne Christie, 5 August 2003.

¹⁶⁵ Coombs *et al.* (1945). Professor Matteo Adinolfi wrote: 'I would like to add that although the test is now described as the 'Coombs test' the principle of the method was discovered by C Moreschi in 1908 [Moreschi (1908)].' Note on draft transcript 2 June 2003.

Booth: This is a question from a complete non-expert, but in Huntington's chorea the argument we constantly hear is do you want to genetically screen members of families; do people want to know they have got the disease long before they have developed it? That applies to a whole lot of other diseases too, but let's take Huntington's as an example.

Pembrey: There are only a few minutes left and I think that's another workshop. I would like to add that, in addition, it is probably partly because of the size of the country that this network was manageable to get together. I think the formation of the Clinical Genetics Society in 1970 was very timely and it is fair to say that there is a tradition when people are trained in genetics, if a research fellow has a project and needs cases of a relatively rare kind, there's a sort of unwritten rule, which I think still exists and always did exist, of well so and so in this unit is doing it, so we send everything there. I think the links between the clinicians and the scientists and this sort of sharing, and I know we are saying it about ourselves, is something that's been quite influential in pushing forward the clinical applications of genetic testing.

Harris: I wanted to add and reinforce what you have said and what Malcolm was saying. We haven't mentioned Cedric Carter,¹⁶⁶ I don't think, but I think we ought to, because of his founding of the Clinical Genetics Society. I was at it, and he made me Treasurer of the Society (and Sarah Bunday was the Secretary – that's the beginning). Cedric really midwived that and the Institute of Child Health had a very large part in this networking, especially when the dysmorphology thing came along. There's no question about that at all.

The other thing that comes from the relationship with the Department of Health or the DHSS as we used to know and love it,¹⁶⁷ was that Cedric, through the Department of Health, was responsible for getting the job of consultant clinical geneticist established as part of the Health Service and that allowed the network to develop. Subsequently, but again through the consultant adviser, the money came for the molecular genetic laboratory, the three molecular genetic laboratories you have mentioned before. This really has been a very important and influential aspect, to a large extent due to Cedric's Institute initiation.

Pembrey: Yes, I would endorse that.

Mrs Diane Barnett: As a non-doctor here, I hope you will allow me a couple of words. I am a representative of a national organization called Contact a Family, and

¹⁶⁶ Cedric Carter is mentioned earlier (see pages 14 and 64).

¹⁶⁷ See, for example, Abel-Smith (1988).

we act as an umbrella for many, many disorder groups.¹⁶⁸ I am wondering whether – as I know a number of the doctors here know of the disorders I am talking about, and perhaps know of the groups – whether they feel that these groupings of parents, sometimes only a very few, ten perhaps, of identified cases and some of them much larger, whether this has had an influence and helped perhaps in your work?

Pembrey: An enormous influence. Clinical research fellows, certainly speaking for the Institute of Child Health, if they latched on to a particular condition, they were interested in a particular condition, they would immediately make contact and establish a relationship with the support group. Sometimes there was more than one support group. I know in my own work that I did on Angelman syndrome; there's nothing like going to a meeting where there are a hundred children with Angelman syndrome to never not be able to diagnose it again. So I think that again has been a feature, and I tried to bring it out in that neurofibromatosis story. I think it has been a feature in Britain. We have got the Contact a Family, and then we have the Genetic Interest Group as well, that produces the appropriate political representation at the Department of Health and Government.

Rodeck: I think it is relevant to point out that the activity of prenatal screening and diagnosis is controversial in some areas and there are opponents on ethical grounds, and indeed the people who are involved in that activity have been accused of eugenics and of 'search and destroy' and that kind of thing. That is in very sharp contrast to the attitude of most of the patient support groups who, in my experience, have nearly always welcomed advances in prenatal diagnosis for the families with their particular conditions, because they see it as simply another medical facility that is made available to their members.

Povey: I was just going to reiterate about the support groups. For example, in tuberous sclerosis, the support group there really started out as a smallish group of articulate parents and that group has been responsible for genetic testing being ten years ahead of where it would be by their pressure and their support for the work.

Edwards: It has been brought up several times, but so far we have been discussing all the recent advances. I wanted to draw attention to a great non-advance over the last 20 years, which unfortunately has been associated with the potential for the Internet and that is secrecy. The journals do not insist on raw data being made available after publication. It's widely believed that there are

¹⁶⁸ More information about Contact a Family can be found at www.cafamily.org.uk/dirworks.html.

methods for analysing things with great complexity by methods nobody really understands, and we now have the multi-author paper. There are two varieties: those in which a minority of the authors understand it, and those in which none of the authors understand it. Very few of these authors could have had time to influence the paper, and I know of some who first read it in print. Peer review is incomplete, *Nature* rejects most papers without peer review and, like *Science*, often fails to answer letters pointing out factual errors in editorials. The Internet offers space to resolve the physical problems in making raw data available at publication, suitably shorn, even at the cost of some information, of any possible breach of clinical confidentiality. However only Elsevier enforces this, and, so far as I know, of the major analysis of human data, only Hinxton and Professor John Todd make access to raw data simple.^{168a} Unless those responsible, as advisers on ethics or purveyors of grants or, for ensuring blood and gold provide the maximum information, and insist on this obvious convention, the major problems of analysis and related optimal strategies in major population studies, haplotype mapping and multifactorial disorders will remain inadequately resolved for even longer.

The other point is that there has almost been no conceptual development in the last 20 years. The development has been technical. The great conceptual development took place in the 1930s, with people like Wright and Hogben and so on, but their papers are all lying about in basements and second-hand bookshops. It does seem very important requirement that 1 per cent of the cost of putting papers on the Internet should go to the great papers which are few in number, which are now virtually non-existent, because most people don't go to libraries, they go to the Internet and what's on the Internet is what exists. I think this is a very important problem, because there has really been very little conceptual advance in the last 20 years. The advances have all been made in the past and we can only make use of the great advances of the past if the raw data are made available, so that they can be analysed and considered. This is particularly important in the DNA field, because the big advance is going to be relating to environment, rather than purely to the pharmaceutical industry.

Pembrey: I think that is a very good point and a message to the Wellcome History of Medicine Group, that in addition to recording our sometimes rambling reminiscences and details of how we saw genetic testing develop, they

^{168a} Copies of correspondence received during the planning of the meeting and the editorial process are deposited with the records of the meeting in Archives and Manuscripts, Wellcome Library, London.

may perhaps look to researching the maintenance of raw data, rather than just anecdotes and the issue of material disappearing after publication as the paper copies get lost.¹⁶⁹ I think it is an area where perhaps, John [Edwards], you might want to put a project to the History of Medicine people at the Wellcome on this. But it is certainly relevant to historians as well as to scientists trying to progress. I should like to thank everybody very much for what has been a long afternoon, for being so attentive and contributing so well to this Witness Seminar. Thank you very much.

Christie: I would like to add my particular thanks to Marcus Pembrey for his excellent chairing of the meeting, and also to Doris Zallen for travelling from the USA to be with us today.

¹⁶⁹ Professor John Edwards wrote: 'These great achievements, when the few leaders in the general field of population genetics and applied genetics were writing extensively, defining, developing and using the basic nomenclature on which we should depend, and clarifying the boundaries of 'what was known', and 'what was knowable' within the technical and calculating resources available are largely unread by that majority of libraries that make the past inaccessible to browsing, or worse, sell to make space for the excessive and rapidly increasing number of periodicals that are on the web and deserve, but do not get, a short shelf life, if indeed with electronic access they need any shelf life.' E-mail to Dr Daphne Christie, 5 September 2003.

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Biographical notes

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FRCP (b. 1928) was Professor of Developmental Immunology in the Paediatric Research Unit at Guy's Hospital Medical School, London, from 1965 to 1994. Since his retirement he has been working at the Galton Laboratory and Department of Obstetrics and Gynaecology, University College London.

Mrs Diane Barnett

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Professor George Beadle

(1903–89) was Professor of Biology at the University of Chicago (1961–75), Emeritus since 1975, and shared the 1958 Nobel Prize for Physiology or Medicine with Dr Edward Tatum (1909–75). See Sourkes T L. (1967) *Nobel Prize Winners in Medicine or Physiology 1901–1965*. New York: Abelard-Schuman, 352–367.

Dr Julia Bell

FRCP (1879–1979) was a medical student under Karl Pearson in the Galton Laboratory at University College London from 1914 to 1920 and a Medical Research Council research assistant from 1920 to 1965. In 1944 she was made an Honorary Research Associate at University College London. See Wolstenholme G. (ed.) (1984) Julia Bell. *Munk's Roll* 7: 31–32.

Sir Walter Bodmer

Kt FRCPATH FRS (b. 1936) was Professor in the Department of Genetics, Stanford University, Stanford (1962–70), Professor of Genetics at Oxford University (1970–79), Director of Research (1979–91) and Director-General (1991–96) of the Imperial Cancer Research Fund.

Sir Christopher Booth

Kt FRCP (b. 1924) trained as a gastroenterologist and was Professor of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, London from 1966 to 1977 and Director of the Medical Research Council's Clinical Research Centre, Northwick Park Hospital, Harrow from 1978–1988, and Harveian Librarian at the Royal College of Physicians from 1989 to

1997. He was the first Convenor of the Wellcome Trust's History of Twentieth Century Medicine Group from 1990 to 1996.

Professor Cedric Carter

FRCP (1917–84) was Director of the MRC Genetics Unit from 1964 to 1982. He founded the UK Clinical Genetics Society in 1972 and, with John Fraser Roberts, established the first genetic counselling clinic in Britain at the Hospital for Sick Children, Great Ormond Street, London, in 1957. See Wolstenholme G. (ed.) (1989) Cedric Oswald Carter. *Munk's Roll* 8: 78–80.

Professor William [Bill] Castle

(1897–1990) was Professor of Medicine in the Harvard Medical School, Boston, from 1937 to 1968 and studied the pathogenesis of pernicious anaemia. See Jandl J H. (1995) William B Castle. *Biographical Memoirs. National Academy of Sciences* 67: 15–40.

Professor Sir Cyril Clarke

KBE CBE FRCP FRCOG FRS (1907–2000) was Emeritus Professor and Honorary Nuffield Research Fellow in the Department of Genetics at University of Liverpool from 1966 to 1976. See Weatherall D. (2002) Sir Cyril Astley Clarke FRS. *Biographical Memoirs of Fellows of the Royal Society* 48: 69–86.

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HonFRCP FRS (b. 1936) was on the Medical Research Council Senior Scientific Staff from 1979 to 2001 and has been Professor of Molecular Medicine at University of Oxford since 1996.

Professor Dulcie Coleman

FRCPATH (b. 1932) was a clinical assistant in the Department of Cytopathology and Cytogenetics at St Mary's Hospital, London, from 1964 to 1972. From 1972 to 1998 she was Head of Department, and since 1998 has been Professor Emeritus of Cell Pathology at Imperial College School of Medicine, London.

Professor Robin Coombs

FRS (b. 1921) was Professor of Immunology at the University of Cambridge from 1966 to 1988, then Professor Emeritus. He was Fellow of Corpus Christi College, Cambridge, since 1962.

Professor Jean-Baptiste Dausset

Grand Croix de la Légion d'Honneur (b. 1916) was Professor of Immunohaematology at the University of Paris from 1958 to 1977. From 1977 to 1987 he was Professor of Experimental Medicine at the Collège de France and was awarded the 1980 Nobel Prize for Physiology or Medicine.

Professor Kay Davies

CBE FMedSci FRS (b. 1951) has been Lees Professor of Anatomy and Fellow of Hertford College, University of Oxford, since 1998. In 1999 she was made Honorary Director of the Medical Research Council Functional Genetics Unit, and since 2001 has been Co-Director of the Oxford Centre for Gene Function.

Professor Joy Delhanty

FRCPath FRCOG (b. 1937) is Professor of Human Genetics in the Department of Obstetrics and Gynaecology, University College London. She worked at the Galton Laboratory, UCL, under Lionel Penrose in the pioneering days of human cytogenetics, but since the late 1980s has specialized in pre-implantation genetics.

Professor John Hilton Edwards

FRCP FRS (b. 1928) is Emeritus Professor of Genetics, University of Oxford, and has held appointments in medicine, neurology, psychiatry and pathology, in epidemiology and clinical genetics in Birmingham from 1953 to 1979 and Professor of Genetics and NHS Consultant in Oxford from 1979 to 1995. His main interest is in multifactorial disorders, linkage and comparative mapping.

Professor Martin Evans

FMedSci FRS (b. 1941) was a lecturer in the Department of Genetics, University of Cambridge (1978–91), Reader in Genetics (1991–94) and Professor of Mammalian Genetics (1994–99). Since 1999 he has been Director of the Cardiff School of Biosciences, and Professor of Mammalian Genetics at the University of Cardiff.

Professor Malcolm Ferguson-Smith

FRCP FRCPath FRSE FMedSci FRS (b. 1931) was Emeritus Professor of Pathology, University of Cambridge (1987–98), and is now Research Professor at University of Cambridge Veterinary School. He was Professor of Medical Genetics at Glasgow University (1973–87) and Director of Regional Genetic Services and Honorary Consultant in Medical Genetics (1966–98).

Sir Ronald Fisher

Kt FRS (1890–1962) was Galton Professor of Eugenics at University College London in 1933, and Arthur Balfour Professor of Genetics at the University of Cambridge from 1943 to 1957. See Yates F, Mather K. (1963) Ronald Aylmer Fisher FRS. *Biographical Memoirs of Fellows of the Royal Society* 9: 91–130.

Sir Walter Fletcher

KBE FRS (1873–1933) qualified in medicine from St Bartholomew's Hospital, London, in 1900 and became Secretary to the Medical Research Committee (later Council) from its establishment in 1914 to 1933. See Anon. (1935) Walter Morley Fletcher FRS. *Obituary Notices of Fellows of the Royal Society* 1: 153–163.

Dr Charles Ford

FRS (1912–99) was Head of the Cytogenetics Section at the Medical Research Council Radiobiology Unit, Harwell, from 1949 to 1971 and from 1971 to 1978 was a member of the Medical Research Council's External Staff at the Sir William Dunn School of Pathology, University of Oxford. See Lyon M F. (2001) Charles Edmund Ford FRS. *Biographical Memoirs of Fellows of the Royal Society* 47: 189–202.

Dr John Fraser Roberts

FRCP FRS (1899–1987) was Honorary Consultant in Medical Genetics at the Hospital for Sick Children, Great Ormond Street, London (1946–1964) where he started a genetics clinic in 1946, the first in Europe. The MRC created a Clinical Genetics Research Unit in 1957 with John as Director until 1964. See Polani P E. (1992). John Alexander Fraser Roberts FRS. *Biographical Memoirs of Fellows of the Royal Society* 38: 306–322.

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Professor Richard Gardner

FRS (b. 1943) was a research assistant in the University of Cambridge Physiological Laboratory from 1970 to 1973, and from 1973 to 1977 he lectured in developmental and reproductive biology in the Department of Zoology, University of Oxford. Since 1978 he has been the Royal Society Henry Dale Research Professor.

Sir Archibald Garrod

KCMG FRCP FRS (1857–1936) studied at Christ Church College, Oxford, and at St Bartholomew's Hospital from 1880. From 1897 he worked on alkaptonuria, albinism and cystinuria. He was Regius Professor of Physics at the University of Oxford from 1920 to 1927, and Consulting Physician to the Hospital for Sick Children, Great Ormond Street. See Hopkins F G. (1939) Archibald Edward Garrod. *Obituary Notices of Fellows of the Royal Society* 1936–1938. London: Harrison and Sons, 225–228.

Professor Joseph Goldstein

(b. 1940) has been Paul J Thomas Professor of Medicine in the Department of Molecular Genetics at the University of Texas

Southwestern Medical Center at Dallas since 1977. He shared the 1985 Nobel Prize for Physiology or Medicine with Michael Brown for their work on the genetic basis of hypercholesterolaemia.

Professor John Burdon Sanderson Haldane

FRS (1892–1964) was Professor of Genetics at University College London from 1933 to 1937, and Professor of Biometry at UCL from 1937 to 1957. See Pirie N W. (1966) John Burdon Sanderson Haldane FRS. *Biographical Memoirs of Fellows of the Royal Society* 12: 219–250.

Professor Alan Handyside

(b. 1951) is Professor of Developmental Biology in the School of Biology, University of Leeds. Influenced by Professor Robert Edwards while studying at Cambridge, who was pioneering human *in vitro* fertilization in the mid-to-late 1970s, he became interested in early mouse development. He later joined Professor Lord Robert Winston at Hammersmith Hospital, London, where the first pregnancies following assisted conception and pre-implantation genetic diagnosis were established in 1989 in a series of couples at risk of X-linked inherited disease.

Professor David Harnden

FRCPath FRSE (b. 1932) was a Scientific Member of the Medical Research Council Radiobiology Unit, Harwell, from 1957 to 1959, and a Scientific Member of the Medical Research Council Clinical and Population Cytogenetics Unit, Edinburgh, from 1959 to 1969. He was Professor of Cancer Studies at the University of Birmingham (1969–83) and Honorary Professor of Experimental Oncology at the University of Manchester (1983–97). From 1997 he has been Chairman of the South Manchester University Hospitals NHS Trust.

Professor Peter Harper

(b. 1939) is Professor of Medical Genetics at University of Wales College of Medicine, Cardiff. 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 more general medical service for Wales and has a particular interest in the historical aspects of human and medical genetics. See Harper P S. (1995) Genetic testing, common diseases and health service provision. *Lancet* 346: 1645–1646.

Professor Harry Harris

FRCP FRS (1919–94) was Director of the MRC Human Biochemical Genetics Unit from its foundation in 1961 until he left to continue work in the USA in 1976. From 1965 to 1976, he was Galton Professor of Genetics and Biometry at UCL. His extensive laboratory research into patterns of human genetic diversity in health and in disease led to the concept of normal genetically determined biochemical variation between different individuals, and prepared the ground for many genetic tests currently widely used today. See Hopkinson D A. (1996) Harry Harris FRS. *Biographical Memoirs of Fellows of the Royal Society* 42: 152–170.

Professor Sir Henry Harris

FRCP FRCPATH FRS (b. 1925) was Professor of Pathology at University of Oxford from 1963 to 1979, and Head of Department in the Sir William Dunn School of Pathology, Oxford, from 1963 to 1994. See Harris H. (1993) How tumour suppressor genes were discovered. *FASEB Journal* 10: 978–979.

Professor Rodney Harris

CBE FRCP FRCPATH (b. 1932) is Emeritus Professor of Medical Genetics at the University of Manchester having been Professor of Medical Genetics from 1980 to

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

Professor Lancelot Hogben

FRS (1895–1975) was Regius Professor of Natural History at the University of Aberdeen from 1937 to 1941 and from 1941 to 1947 was Mason Professor of Zoology at the University of Birmingham, later Professor of Medical Statistics from 1947 to 1961. See Wells G P. (1978) Lancelot Thomas Hogben FRS. *Biographical Memoirs of Fellows of the Royal Society* 24: 183–222.

Mrs Cathy Holding (Previously Headhouse-Benson.)

(b. 1957) is a research assistant currently at the Babraham Institute in Cambridge, UK. She has worked with Professor Marilyn Monk three times during the last 20 years, once at the MRC Mammalian Development Unit, and twice at the Institute of Child Health in London.

Professor Martin Hooper

FRSE FRCPE (b. 1947) was a research fellow in the Institute of Genetics, University of Glasgow, from 1973 to 1980. In 1980 he moved to the University of Edinburgh, where he has been Senior Lecturer in Experimental Pathology (1980–90), Reader in the Department of Pathology (1990–96) and Professor of Molecular Pathology since 1996.

Professor David Hopkinson

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Professor Sir Douglas Hubble

KBE FRCP (1900–81) was Professor of Paediatrics and Child Health and Director of the Institute of Child Health at the University of Birmingham from 1958 to 1968. See Wolstenholme G. (1984) Sir Douglas Vernon Hubble. *Munk's Roll* 7: 280–281.

Professor Vernon Ingram

FRS (b. 1924) has been Professor of Biochemistry since 1961 at the Massachusetts Institute of Technology, Boston, USA, and John and Dorothy Wilson Professor of Biology since 1988.

Professor Patricia Jacobs

OBE FRSE FRCPATH FRCPE FRCOG FRS (b. 1934) was a Medical Research Council scientist (1957–72), Professor in the Department of Anatomy and Reproductive Biology at the University of Hawaii School of Medicine (1988–2001), Professor and Chief of the Division of Human Genetics in the Department of Paediatrics at Cornell University Medical College (1985–87) and Director of the Wessex Regional Genetics Laboratory (1988–2001).

Professor Yuet Wai Kan

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

Professor Herman Lehmann

CBE FRCP FRCPATH FRSC FRS (1910–85) was Professor of Clinical Biochemistry at the University of Cambridge from 1967 to 1977, and Honorary Director of the Medical Research Council Abnormal Haemoglobin Unit from 1963 to 1975. See Dacie J. (1988) Herman Lehmann FRS. *Biographical*

Memoirs of Fellows of the Royal Society 34: 405–450.

Dr Mary Lyon

FRS (b. 1925) was on the scientific staff of the Medical Research Council Radiobiology Unit, Harwell, from 1955 to 1990 and Deputy Director of the Unit from 1982.

Sir John Maddox

Kt HonFRS (b. 1925) was Lecturer on Theoretical Physics at University of Manchester (1949–55), Science Correspondent of the *Guardian* (1955–64) and Editor of *Nature* (1966–73, 1980–95).

Professor Sue Malcolm

FRCPath was Professor of Molecular Genetics, at the Institute of Child Health, London, until June 2002, now Emeritus.

Professor Thomas McKeown

FRCP (1912–88) was Professor of Social Medicine at the University of Birmingham from 1945 to 1977. See Wolstenholme G. (ed.) (1989) Thomas McKeown. *Munk's Roll* 8: 311–313.

Dame Anne McLaren

DBE FRCOG FMedSci FRS (b. 1927) was the Director of the Medical Research Council's Mammalian Development Unit, University College London, from 1974 to 1992, and was Fullerian

Professor of Physiology at the Royal Institution from 1990 to 1995.

Sir Peter Medawar

OM CH CBE FRS (1915–87) was Jodrell Professor of Zoology and Comparative Anatomy at University College London from 1951 to 1962. He shared the 1960 Nobel Prize in Physiology or Medicine with Macfarlane Burnet for the discovery of immunological tolerance. Between 1962 and 1971 he was Director of the National Institute for Medical Research at Mill Hill, London, remaining on its scientific staff until 1984. See Mitchinson N A. (1990). Peter Brian Medawar FRS. *Biographical Memoirs of Fellows of the Royal Society* 35: 281–302.

Professor Reuben Mibashan

FRCP FRCPath (1927–2001) held posts in the Department of Medicine at the Cape Town University Medical School. Following research fellowships in London and Salt Lake City, he settled in the UK and was appointed Professor of Haematology at King's College School of Medicine in 1986. See Anon. (2001) R S Mibashan. *Proceedings of the Royal College of Physicians of Edinburgh* 31: 269.

Professor Ursula Mittwoch

DSc (b.1924) entered the Galton Laboratory as a PhD student in 1947. She was later offered postdoctoral appointments to work on the biochemistry of cystinuria (in collaboration with Harry Harris and Bette Robson), and on cytogenetics. During the 1960s she carried out genetic testing by demonstrating mucopolysaccharide inclusions in the lymphocytes of patient with Hurler and Hunter syndromes. Since then she has specialized in the genetics of sex determination with special reference to cell proliferation. In 1989 she retired as Emeritus Professor.

Professor Bernadette Modell

FRCP FRCOG (b. 1935) is Emeritus Professor of Community Genetics in the Department of Health Informatics and Multiprofessional Education (CHIME) at the Royal Free and University College Medical School, London.

Professor Patrick Mollison

CBE FRCP FRCPath FRCOG FRS (b. 1914) was Professor of Haematology at St Mary's Hospital Medical School, University of London, from 1962 to 1979, then Professor Emeritus and Honorary Consultant Haematologist at the London Blood Transfusion Service from 1983.

Professor Walter Morgan

CBE FRS (1900–2003) was Professor of Medicine at the Lister Institute of Preventative Medicine, University of London, from 1951 to 1968, then Professor Emeritus, and Director of the Lister Institute from 1972 to 1975. See Tippett P. (2003) Professor Walter Morgan. *Vox Sanguinis* 84: 161–162. Anon. (2003) Professor Walter Morgan. *Daily Telegraph*, 14 February 2003, page 14.

Dr Arthur Ernest Mourant

FRCP FRCPath FRS (1904–94) was Physician, and Director of the Blood Group Reference Laboratory, Lister Institute. In 1944 he discovered the predicted antibody, anti-e, helping to establish the three-factor theory of the Rhesus system. His published works include *The Distribution of the Human Blood Groups* (1954); *The ABO Blood Groups and Maps of World Distribution* (1958). See Misson G P, Bishop A C, Watkins W M. (1999) Arthur Ernest Mourant. *Biographical Memoirs of Fellows of the Royal Society* 45: 331–348.

Professor Linus Pauling

(1901–94) was Professor of Chemistry at the California Institute of Technology (1931–1963) and from 1974 was Research Professor at the Linus Pauling

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Professor Marcus Pembrey
FRCP FRCPCH FRCOG FMedSci (b. 1943) was Head of the Mothercare Unit of Paediatric Genetics at the Institute of Child Health and Consultant Clinical Geneticist at the Hospital for Sick Children, Great Ormond Street, London, from 1979 to 1998. He was Consultant Adviser in Genetics to the Chief Medical Officer, Department of Health from 1989 to 1998. After training in medical genetics at Liverpool and Guy's Hospital, he led a team that helped to introduce DNA testing into clinical genetics in the 1980s and carries out research into non-Mendelian inheritance.

Professor Lionel Sharples Penrose
FRCP FRS (1898–1972) was Resident Director of the Royal Eastern Counties Institution, Colchester, from 1930 to 1939. He was Galton Professor of Eugenics from 1945 to 1962, and of Human Genetics from 1962 to 1965, at University College London. See Harris H. (1973). Lionel Sharples Penrose FRS. *Biographical Memoirs of Fellows of the Royal Society* 19: 521–562.

Professor Naomi Pfeffer
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Professor Paul Polani
FRCP HonFRCP(Ire) FRCPCH FRCOG HonFRCPATH DCH FRS (b. 1914) is Fellow of King's College London, and Geneticist, Division of Genetics and Development at Guy's Hospital, Research Professor Emeritus, London University (1982), Prince Philip Professor of Paediatric Research at Guy's Hospital Medical School, and Director of Paediatric Research Unit there (renamed Division of Genetics and Development, King's College, London) (1960–82), Geneticist, Guy's Hospital and Medical School, and Director of South East Thames Genetics Centre (1976–82) and Honorary Paediatrician, Guy's Hospital and Medical School (1960–85).

Professor Bruce Ponder
FRCP FRCPATH FMedSci FRS (b. 1944) has been Honorary Consultant Physician at the Royal Marsden Hospital, London, since 1980, and Director of the Cancer Research UK Human Cancer Genetics Group at the University of Cambridge since 1989.

Professor Sue Povey
FMedSci (b. 1942) qualified in medicine from Cambridge/UCH in

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Dr Robert Race

CBE FRS (1907–84) was Director of the Medical Research Council Blood Group Unit from 1946 to 1973. See Clarke Sir C. (1985) Robert Russell Race. *Biographical Memoirs of Fellows of the Royal Society* 31: 455–492.

Professor Derek Roberts

FRSE (b. 1925) was Professor of Human Genetics at the University of Newcastle upon Tyne and Honorary Consultant to the Royal Victoria Infirmary, Newcastle upon Tyne, Honorary Director, Genetic Advisory Service NHS Northern Region from 1965 to 1990, Professor Emeritus since 1990.

Professor Charles Rodeck

FRCOG FRCPath FMedSci (b. 1944) is Professor of Obstetrics and Gynaecology and Head of Department at University College London, and Director of the Fetal Medicine Unit at University College London Hospitals. His research and clinical practice have been in prenatal diagnosis and the emerging discipline of fetal medicine. He established the first fetal medicine unit in the UK in 1983, the Harris Birthright Centre at King's College Hospital, and further departments of fetal medicine at Queen Charlotte's Maternity Hospital (1986), and University College Hospital (1990). He has been President of the International Society for Prenatal Diagnosis since 2002.

Dr Ruth Sanger

FRS (1918–2001) was on the Scientific Staff of the Medical Research Council Blood Group Unit from 1946 to 1983, and was Director of the Unit from 1973 to 1983. See Mollison P L. (2002) Ruth Sanger. *Transfusion* 42: 125–126.

Dr Alan Stevenson

CBE FRCP (1909–95) was the Director of the Medical Research Council Population Genetics Unit, Oxford, and Lecturer in Human Genetics at the University of Oxford from 1958 to 1974.

See Gillam S J, Macdonald I. (eds) (2001) Alan Carruth Stevenson. *Munk's Roll* 10: 469–470.

Dr Patricia Tippet

(b. 1930) was a member of the Medical Research Council Blood Group Unit from 1958 to 1995 and became Director of the Unit when Ruth Sanger retired in 1983.

Professor John Todd

(b. 1958) has been Professor of Medical Genetics and a Fellow of Gonville and Caius College, Cambridge, since 1998.

Professor Edward (Ted) Tuddenham

FRCP FRCPath (b. 1944) was Co-director of the Haemophilia Centre, The Royal Free Hospital, London, from 1978 to 1986, and Director of the Medical Research Council Haemostasis Research Group at Northwick Park Clinical Research Centre from 1987 to 1994. He has been Director of the Haemostasis Research Group, Clinical Sciences Centre, Imperial College Medical School, London, since 1994 and Honorary Consultant Haematologist at the Hammersmith Hospital, London, since 1994. He is a member of the World Federation of Hemophilia, the International Society on Thrombosis and Hemostasis, and the British Society of Haemostasis and Thrombosis.

Dr David Tyrrell

FRS (b. 1925) was a member of the scientific staff of the Medical Research Council Common Cold Unit at Salisbury from 1957, and its Director from 1982 until his retirement in 1990. His main line of research was on virus infections in humans.

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FRCOG (b. 1938) was Consultant Obstetrician and Gynaecologist at University College London, from 1972 to 2001.

Dr Winifred Watkins

FMedSci FRS (b. 1924) was Professor of Biochemistry at the University of London from 1968 to 1975. Since 1990 she has been Visiting Professor and Senior Research Fellow at the Imperial College School of Medicine, London.

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Glossary

Note the use of bold for items in glossary. The editors thank Professor John Edwards, Professor Matteo Adinolfi and Professor Ursula Mittwoch for their assistance in compiling the glossary. The following textbooks were consulted: Rieger R, Michaelis A, Green M M. (1991) *Glossary of Genetics. Classical and molecular*. 5th edn. Berlin; Heidelberg: Springer-Verlag. Klug W S, Cummings M R. (2002) *Concepts of Genetics*. New Jersey: Prentice-Hall, Inc. National Human Genome Research Institute (www.genome.gov/10002096).

Adenosine deaminase (ADA) deficiency

A severe immunodeficiency disease that results from a lack of adenosine deaminase and usually leads to death within the first few months of life. Now amenable to gene therapy.

Alkaptonuria

An **autosomal recessive disorder**, the first to be described in humans, caused by the lack of homogentisate 1,2 dioxygenase. It may result in arthritis of the spine and joints, and kidney stones.

Allele

An alternative chemical variant of a given **gene** at its locus. There may be, for that **gene**, a number of alleles.

Amniocentesis

The sampling of amniotic fluid by inserting a needle into the womb, usually at 14–16 weeks' gestation allowing diagnostic tests on the fluid, chromosomal analysis and other tests on cultured or noncultured cells. It may be safer

than **chorionic villus sampling** (CVS) but has to be done later and results usually take longer.

Anencephaly

The absence of most of the brain in the fetus: a common cause of stillbirth.

Aneuploidy

Having a variant **chromosome** number (too many or too few) that is neither the **haploid** number nor a simple multiple thereof (e.g. **Down's syndrome**, **Turner syndrome**).

Angelman syndrome

A condition characterized by severe mental deficiency, developmental delay and dwarfism, puppet-like gait and frequent inappropriate laughter.

Autosomal recessive disorder

A disorder caused by an error or mutation in a single unit of genetic information. An autosomal disorder that is recessive can be expressed in

a person only if both copies of the gene are altered. Examples include **cystic fibrosis** and **Tay–Sachs disease**.

Autosome

Any **chromosome** other than the sex **chromosome**. In humans, there are 46 **chromosomes**, 22 pairs of autosomes and either two Xs or an X and a Y.

Barr body

Densely staining nuclear mass seen in the somatic nuclei of mammalian females.

Base pair

A pair of hydrogen-bonded nitrogenous bases (one purine and one pyrimidine) that join the two strands of the double helix.

Batten's disease

A group of severe progressive neurodegenerative disorders.

Becker muscular dystrophy

See **Duchenne muscular dystrophy**.

Carrier

An unaffected person who harbours a disease gene.

CAH

See **congenital adrenal hyperplasia**.

Chiasma

The region of contact between homologous **chromosomes** during **meiosis**.

Chorionic villus sampling (CVS)

A diagnostic procedure involving removal of villi from the human chorion to obtain cells for diagnosis of **chromosomal** and some metabolic disorders in early pregnancy.

Chromatin

The readily stainable portion of a cell nucleus consisting of DNA and RNA, and various proteins.

Chromosomal mosaicism

The existence of cells with two or more chromosomal variants within one individual due to events after fertilization.

Chromosome

The self-replicating genetic structures of cells containing the DNA that bears the gene sequence. Humans have 23 pairs of chromosomes, 46 in all: 44 **autosomes** and two sex chromosomes. Each parent contributes one chromosome to each pair, so children get half of their chromosomes from their mothers and half from their fathers.

Chronic myeloid leukaemia

A form of leukaemia characterized by uncontrolled proliferation of myeloid cells in the bone marrow and in other sites, and the presence of large numbers of immature and mature granulocytic forms in

various tissues and blood. Also referred to as chronic granulocytic leukaemia.

Codominancy

Pertaining to a pair of dissimilar **alleles** that are both expressed when present together at a particular locus, the individual being a **heterozygote** at that locus.

Codon (triplet code)

A specific sequence of three consecutive **bases** that is part of the genetic code and that specifies a particular amino acid in the synthesis of protein or starts or stops such synthesis.

Colchicine

An alkaloid that blocks **mitosis**.

Congenital adrenal hyperplasia (CAH)

A form of adrenal insufficiency due to mutations in genes coding for enzymes needed by the adrenal cortex. About 95 per cent of cases of CAH are caused by absence of 21-hydroxylase, which is necessary for efficient production of cortisol and aldosterone.

CVS

See **chorionic villus sampling**.

Cystic fibrosis

An inherited **recessive disorder** characterized by chronic infections of the respiratory tract, liver disease and digestive problems.

Cytogenetics

The study of cells, and especially their **chromosomes**.

Cytotrophoblast

See **trophoblast**.

Deletion

The loss of a piece of DNA from a **chromosome** that may lead to a disease or abnormality. A synonym of the term 'deficiency'.

Diploid

The presence of the two **haploid** sets, one from each **gamete**, of **chromosomes** in a cell.

Disjunction

The separation of **chromosomes** during cell division.

Down's syndrome (trisomy 21, mongolism)

One of the most common causes of mental retardation, due to **trisomy** of chromosome 21. See Lejeune *et al.* (1959).

Duchenne muscular dystrophy

An **X-linked recessive disorder** caused by a **mutation**, usually a **deletion**, in the gene for dystrophin, a protein essential for muscle after infancy. A similar but milder condition known as **Becker muscular dystrophy** is caused by different mutations in the same gene.

Duplication

A chromosomal aberration in which a segment of **chromosome** is duplicated.

Electrophoresis

A technique used to separate a mixture of molecules by their differential migration through a gel in an electrical field.

Eugenics

The study of methods of improving genetic qualities by selective breeding.

Factor VIII (antihæmophilic globulin)

A plasma coagulation factor whose inherited deficiency is responsible for **haemophilia**.

Fluorescent *in situ* hybridization (FISH)

A process that vividly paints **chromosomes** or portions of **chromosomes** with fluorescent molecules via DNA and may be used for identifying subtle chromosomal abnormalities and in gene mapping.

Fragile site

A heritable gap or nonstaining region of a **chromosome** that can be induced to generate **chromosome** breaks.

Fragile X syndrome

A syndrome characterized by mental retardation, autistic-like behaviour and other physical abnormalities. Both males and females can be affected and their **karyotype** shows a gap (the fragile site) on the long arm of the X **chromosome**.

Gamete

Specialized reproductive cell, either sperm or ovum, with a **haploid** number of **chromosomes**.

Gene

The fundamental unit of heredity. A locus defines the position of a gene.

Genetic marker

A segment of DNA on a **chromosome** whose inheritance can be followed. A marker can be a **gene** or some segment of DNA.

Genetic screening

Testing a population group to identify a subset of individuals at high risk for having or transmitting a specific genetic disorder.

Genetic testing

Analysing an individual's genetic material to determine predisposition to a particular disorder, to confirm a diagnosis or to establish or exclude identity or paternity.

Genome

The total set of **genes** carried by an individual or cell.

Haemophilia

An **X-linked recessive disorder** in which the ability of the blood to clot is greatly reduced.

Haemopoiesis

The process of producing cellular constituents of the blood (e.g. red blood cells, platelets, white blood cells – mainly lymphocytes and granulocytes). In adults, haemopoiesis occurs almost entirely in bone marrow. In the fetus it also occurs in the yolk sac, liver, spleen and thymus.

Hair root test

A test based on the collection of a certain number of pulled hair roots, each containing a ‘clone’ of identical cells. When retrieved from a female donor, each hair root will have cells with the same **X chromosomes**, one active the other inactive. If a mother is a carrier of an X-linked disorder, like the **Hunter** mutation, one set of hair roots will contain the enzyme, the other set will be deficient.

Haploid

A cell, or occasionally an organism, having a single set of unpaired **chromosomes**. See **gamete**.

Haplotype

The set of **alleles** from closely linked loci carried by an individual and inherited as a unit until broken by recombination. See **gamete**.

Heterozygous

Possessing two different forms (**alleles**) of a particular **gene**, one from each parent.

Human leukocyte antigen (HLA)

Cell surface proteins involved in the acceptance or rejection of cells and tissues from other individuals.

Human Genome Project (formerly Human Genome Initiative)

An international research project to map each human gene and to sequence human DNA.

Huntington's disease

A degenerative brain disorder that usually appears in mid-life. Its symptoms include involuntary movement of the face and limbs, mood swings and dementia. It is generally fatal within 20 years.

Karyotype

The chromosomal complement of an individual, including the number of **chromosomes** and any abnormalities.

Klinefelter syndrome

An endocrine condition in males caused by the presence of an extra X **chromosome** (47, XXY), characterized by small testes, absence of germ cells and low testosterone level.

Lesch–Nyhan syndrome

An inborn error of purine metabolism resulting in severe neurological problems, renal stones and self mutilation.

Linkage

The inherited association of certain genes due to their being localized in the same **chromosome** or nucleic acid molecule.

Lod score

A statistical method used to determine the relative odds of two loci being linked or unlinked.

Lutheran blood group

A blood group inherited independently of the ABO, MN and Rh systems.

Lyon hypothesis

The random inactivation of the maternal or paternal X **chromosome** in somatic cells of mammalian females early in development. All daughter cells will have the same X **chromosome** inactivated, producing a mosaic pattern of expression of **genes** on the X **chromosome**.

Meiosis

The process of two consecutive cell divisions with only a single round of **chromosome** duplication. Meiosis results in four rather than two daughter cells, each with a **haploid** set of **chromosomes**, although ova only become **haploid** for maternal **chromosomes** after fertilization. At meiosis the paternal and maternal **chromosomes** cross over, and most **chromosomes** are mixed in terms of parentage.

Metaphase

A stage in **mitosis** or **meiosis** during which the **chromosomes** are aligned along the equatorial plane, the ideal time for their laboratory examination.

Mitosis

The process of nuclear division followed by cell division and preceded by **chromosome** duplication and separation. Mitosis results in two daughter cells that are genetically identical to each other.

Murine

Mammals of the genus *Mus*; includes rodents (e.g. mice), but not hamsters or guinea-pigs.

Mutation

An alteration in DNA or **chromosome** structure that can cause a disorder or inherited susceptibility to a disorder.

Nail-patella syndrome

A rare genetic disorder with abnormalities of the fingernails and some bones, especially the knee-cap.

Neurofibromatosis

A progressive disorder in which tumours form on nervous tissue. These can be severely disfiguring and can result in loss of vision, epilepsy, bone deformities, and learning disabilities

Nucleotide

A structural component, or building block, of DNA and RNA.

A nucleotide consists of a base (adenine, guanine, thymine, or cytosine in DNA; adenine, guanine, uracil, or cytosine in RNA), a sugar molecule (deoxyribose in DNA and ribose in RNA) and a phosphate group. Long chains of nucleotides make up nucleic acids (DNA or RNA).

PCR

See **polymerase chain reaction**.

Phenotype

The observable features of an organism that results from the interaction of genes and the environment.

Phenylketonuria (PKU)

A recessive disorder in humans associated with the inability to metabolize phenylalanine, usually

due to absence of phenylalanine hydroxylase, which results in the accumulation of phenylalanine in the blood and impairs early neuronal development. The condition can be controlled by diet.

Phytohaemagglutinin

A substance produced by a plant that agglutinates red blood cells. Some, including scarlet runner and American black-eye beans, also induce cell division in **lymphocytes**, the basis of all **chromosome** analyses conducted on blood.

PKU

See **phenylketonuria**.

Polar body

Very small cells produced by grossly unequal division of the ovum, allowing one of the four potential daughter cells to have almost all the cytoplasm – the others die.

Polycystic kidney disease

A group of conditions characterized by fluid-filled sacs that slowly develop in both kidneys, eventually resulting in malfunction.

Polymerase chain reaction (PCR)

A fast, inexpensive technique for making an unlimited number of copies of any piece of DNA.

Polymorphism

Now frequently used as a synonym for 'variant' by molecular geneticists to cover one or more **genes**, or other structures, at the same place or locus.

Quantitative fluorescent-polymerase chain reaction (QF-PCR)

A highly specific analytical form of PCR. The QF-PCR assay can be used for the rapid prenatal diagnosis of **chromosome** disorders and the detection of some single-gene defects.

Restriction enzyme (Restriction endonuclease)

A bacterial enzyme that recognizes specific nucleotide sequences in a DNA molecule and cleaves or nicks the DNA at that site. Also known as a restriction endonuclease.

Restriction fragment length polymorphisms (RFLPs)

Variation in the length of DNA fragments generated by a **restriction endonuclease**. These variations are caused by enzymes that cut, or do not cut, specific sequences of DNA.

Retinoblastoma

A cancer of the retina of the eye. Usually presenting in childhood: about half are inherited, the remainder new mutations.

RFLP

See **restriction fragment length polymorphisms**.

Severe combined immunodeficiency disease (SCID)

A primary immune deficiency, the defining characteristic being a severe defect in both the T- and B-lymphocyte systems. This usually results in the onset of one or more serious infections within the first few months of life.

Sickle-cell disease

A hereditary form of severe anaemia due to changes in the structure of haemoglobin, which causes the red blood cells to become sickle shaped in conditions of lowered oxygen. The sickle-shaped cells block blood vessels and cut off the blood supply.

Somatic cells

All cells other than the germ cells and the **gametes** they produce.

Spermatogenesis

Mitotic and meiotic cell divisions leading to the production of sperm cells (spermatozoa).

Swyer syndrome

The condition of complete gonadal dysgenesis, where the gonads (testes or ovaries) do not form in the usual way. It occurs during the first few weeks of pregnancy. Girls with Swyer syndrome have XY (usual male) genes.

Tay–Sachs disease

A fatal degenerative disease of the nervous system due to a deficiency of hexosaminidase A, causing mental deficiency, paralysis and blindness; found primarily but not exclusively among Ashkenazi Jews. **Autosomal recessive.**

Telomere

The ends of a **chromosome** involved in chromosomal stability.

Thalassaemia

Recessively inherited disorder in which there is an abnormality in either of the haemoglobin genes.

Transcription

Transfer of genetic information from DNA by the synthesis of an RNA molecule copied from a DNA template.

Translocation

The breakage and removal of a large segment of DNA from one chromosome, followed by the segment's attachment to a different chromosome.

Triplet code

See **codon**.

Trisomy

The condition in which a cell or organism possess three copies of one **chromosome**, for example **Down's syndrome** (trisomy 21). Each cell

usually has 46 (i.e. two copies of each) chromosomes, but in trisomy there are 47.

Trophoblast

The outer layer of cells of the mammalian blastocyst that gives rise to the placenta. The trophoblast develops into two layers. The inner is called the **cytotrophoblast**.

Turner syndrome

A condition in human females caused by lack of a second sex chromosome: 45,X or XO. Such individuals are phenotypically female, short and usually sterile through underdeveloped ovaries.

X inactivation

In mammalian females, the random cessation of transcriptional activity of one X **chromosome**.

X-linked recessive disorders

Disorders due to a mutation on the X **chromosome**, usually only affecting males, but can be transmitted through healthy female carriers (e.g. **haemophilia**, **X-SCID** and **muscular dystrophy**).

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