CLINICAL CANCER GENETICS: POLYPOSIS AND FAMILIAL COLORECTAL CANCER *c*.1975–*c*.2010

The transcript of a Witness Seminar held by the History of Modern Biomedicine Research Group, Queen Mary, University of London, on 25 September 2012

Edited by E M Jones and E M Tansey

Volume 46 2013

First published by Queen Mary, University of London, 2013

The History of Modern Biomedicine Research Group is funded by the Wellcome Trust, which is a registered charity, no. 210183.

ISBN 978 0 902238 85 5

All volumes are freely available online at www.history.qmul.ac.uk/research/modbiomed/wellcome_witnesses/

Please cite as: Jones E M, Tansey E M. (eds) (2013) *Clinical Cancer Genetics: Polyposis and familial colorectal cancer c.1975–c.2010*. Wellcome Witnesses to Contemporary Medicine, vol. 46. London: Queen Mary, University of London.

CONTENTS

WHAT IS A WITNESS SEMINAR?

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

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

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

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

[1] See pages 143–6 for a full list of Witness Seminars held, details of the published volumes and other related publications.

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

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

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

Most of our volumes to date have been published under the series title, *Wellcome Witnesses to Twentieth Century Medicine.* As a reflection of our moving timespan into the twenty-first century we have changed the series title to: *Wellcome Witnesses to Contemporary Medicine.*

---

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

ACKNOWLEDGEMENTS

This is the first Witness Seminar to be held under the auspices of our new Wellcome Trust Strategic Award 'The Makers of Modern Biomedicine'. While building on the style and success of our previous meetings and volumes (listed on pages 143–6), we are now focusing on five main themes in contemporary biomedicine; one of which is clinical genetics (further details are available on our Group's website: http://www.history.qmul.ac.uk/research/modbiomed). Professor Peter Harper is our official adviser on this segment of the project, and the theme of cancer genetics, with a focus on polyposis, developed over the course of several conversations with him. Peter also advised us on suitable participants and chaired the resultant meeting. We are most grateful for his input.

Thanks are also due to Professor Timothy Bishop for agreeing to write the introduction for this volume. For permission to reproduce illustrations in the main transcript and a range of material in the appendices, we thank: Ms Kay Neale for an invitation to St Mark's Hospital to interview her *in situ* at the Polyposis Registry and for lending precious archival material and a photograph of the Hospital; Professor Jane Green for permitting us to reproduce illustrations from her PhD thesis; Professor David Harnden for contributing an essay *in lieu* of his attendance at the seminar and Ms Linda White of Greenspond Historical Society in Newfoundland.

As with all of our meetings, we depend a great deal on Wellcome Trust staff to ensure their smooth running: the Audiovisual Department, Catering, Reception, Security and Wellcome Images. We are also grateful to Mr Akio Morishima for the design and production of this volume; the indexer Ms Liza Furnival; Mrs Sarah Beanland and Ms Fiona Plowman for proof reading; Ms Catriona Gilmour Hamilton (Oxford Brookes University) for her comments on the transcript; Mrs Deborah Gee for transcribing the seminar; Mrs Lois Reynolds, Ms Caroline Overy and Mr Alan Yabsley for assisting with running the seminar and Mr Adam Wilkinson who assisted in the organization of the meeting. Finally, we thank the Wellcome Trust for supporting this programme.

Tilli Tansey

Emma M Jones

School of History, Queen Mary, University of London

ILLUSTRATIONS AND CREDITS*

* Unless otherwise stated, all photographs were taken by David Sayer, Wellcome Trust, and reproduced courtesy of the Wellcome Library, London.

ABBREVIATIONS

5q	Chromosome 5 long arm
AFAP	Attenuated familial adenomatous polyposis
APC	Adenomatous polyposis coli gene
BRCA1	Breast cancer gene 1
BRCA2	Breast cancer gene 2
BSHG	British Society for Human Genetics
CAPP	Concerted action for polyp prevention
CHRPE	Congenital hypertrophy of the retinal pigment epithelium
COX2	Cyclooxygenase-2
DoH	Department of Health
FAP	Familial adenomatous polyposis
FIT	Faecal immunochemical test
FOBT	Faecal occult blood test
HLA	Human leukocyte antigen
HNPCC	Hereditary non-polyposis colorectal cancer
ICG-HNPCC	International collaborative group on HNPCC
ICRF	Imperial Cancer Research Fund
LOH	Loss of heterozygosity
MAP	*MUTYH*-associated polyposis
MEN1	Multiple endocrine neoplasia type 1
MEN2	Multiple endocrine neoplasia, type 2
MSH2	Gene for HNPCC, type 1
MLH1	Gene for HNPCC, type 2
MUTYH	Gene relating to MAP, also referred as *MYH*
MYH	See *MUTYH*

NHS	National Health Service
PDGFRA	Platelet-derived growth receptor gene
TS	Tuberous sclerosis
VHL	Von Hippel-Lindau disease
XP	Xeroderma pigmentosum

INTRODUCTION

This Witness Seminar records key activities in clinical cancer genetics in relation to hereditary colorectal cancer and related syndromes. From the mid-1980s, the evolution of clinical cancer genetics in the UK focused extensively around the Cancer Family Study Group. The Group, of which I was Secretary (1990–2002), brought together clinicians and researchers to discuss their shared interest around families with many diagnoses of cancer. However, it was in the early 1990s that the Group's prominence and activity increased, partly as clinical cancer genetics emerged as a discipline and partly as a recognition of the potential outcomes of the increasing efforts to document and dissect the human genome.

While case reports of families with large numbers of cancer cases have been documented for several hundred years, the 1970s and 1980s saw the systematic characterization of these syndromes. Henry Lynch in Nebraska, David Anderson in Texas, Madge Macklin in Canada and Eldon Gardner in Utah all recorded extensive sets of pedigrees with extreme over-representation of the most common cancers. Particularly notable was the early age of onset, the high risk of cancer and the potential for multiple cancer diagnoses in the same person (and not always at the same anatomical site). Some families exhibited an excess of breast cancer, others of bowel cancer – although in some of the breast cancer families, multiple women were diagnosed with ovarian cancer.

Within the bowel cancer families, a broader spectrum could be observed as some of the families also involved endometrial and other cancers. In epidemiological terms, these families, some of which had 20 or more diagnoses of the same cancer could not be explained by extreme ascertainment and/or chance. Furthermore, the most distantly related persons in the families often lived in geographically remote parts and did not know each other, making common lifestyle or other environmental factors unacceptable as an explanation. Finally, in some pedigrees with multiple cases of colorectal cancer, the physical characteristics of the bowel were notably different –in that some persons had many hundreds, or thousands, of bowel polyps, unlike the general population, in which older-aged persons might have one or two. Overall, the broad characteristics of these tumours (besides the ages of onset) were consistent with the more common form of that cancer in the general population. Further, this characterisation indicated that a number of these syndromes were likely to be due to dominantly inherited

mutations segregating in the autosomal genome; based on the observed patterns of disease. It became, therefore, only a matter of time until successful efforts would be made to identify the mechanism of susceptibility in these families.

Researchers took advantage of the new recombinant DNA technology, which allowed routine analysis of a person's genetic profile at pre-determined locations in the human genome. These locations were selected to form landmarks, roughly evenly spaced along each of the chromosomes (the 'Human Gene Map'). This gene map provided the opportunity to identify the genes underlying syndromes associated with a number of clinical syndromes including those involving cancer. By collecting germline DNA samples from affected and unaffected members of such pedigrees and assaying systematically these locations for each person, an indication as to the chromosomal location of the critical gene could be made by identifying which of the known landmarks ('genetic markers') was observed to pass through the pedigree in a similar pattern to the postulated gene. This process, termed 'linkage analysis' provided an evaluation of the statistical evidence in favour of the gene being in that location as opposed to elsewhere in the genome. Successful identification of the location and follow-up in more families provided more detailed evidence for the location of the gene with the ultimate goal of identifying the responsible gene.

This Witness Seminar brings together researchers who were interested in trying to understand the basis for familial susceptibility to colorectal cancer. Their rationale for this focus varied. For those with an interest in clinical cancer genetics, these families represented major clinical challenges in working out how to manage such patients (assessments, screening, intervention etc.); the notably high risk of disease for those carrying a mutation, together with the lack of adequate screening tools indicated that careful thought and improved observation were required to develop protocols for clinical management. For biologists, study of these families offered the potential to identify the critical gene using techniques which were being refined and technically enhanced by the developing Human Gene Map at the beginning of the 1990s. Identifying and understanding the genes would be of direct relevance to the particular families in which the mutations segregated, with the potential that identifying the underlying biological mechanism would impact on our understanding of the more common forms of the cancer. The clinical geneticists also recognised that the number of families in their geographical region was limited and so efforts to compile empirical observations would require collaboration across many centres to provide any kind of numerical justification for proposed clinical protocols. The late 1980s and early 1990s reflected, therefore, a time of great

shared interest among researchers and clinicians; all with a wish to understand susceptibility in these families. The Cancer Family Study Group formed the bridge between research and clinical practice, by providing opportunities to discuss implementation of research ideas, interpretation of results and translation of the findings into clinical benefit.

While the Cancer Family Study Group had been started a number of years earlier, around 1990 was the time when broader interest in the topic grew and our activities expanded. The enthusiasm and focus of all parties was evidenced by the regular attendance of a hundred or so people at each of the six monthly meetings. In the early days, the encouragement for the Cancer Family Study group came from Professor David Harnden, Professor Sir Walter Bodmer and Professor David Steel; bringing together the major cancer charities and the MRC. Following the successful linkage mapping of genes associated with colorectal cancer, for which the UK groups made significant contributions, the activities focused further on collaborative studies facilitated by a shared health service and the combined academic and clinical skills in the Group. Studies included efforts to identify optimal approaches for screening persons at the greatest risk of cancer, and to develop chemoprevention for colorectal cancer. The positive outcome to these preventative studies described in this seminar highlights the long-term impact of these efforts.

The combination of the intellectual excitement involving the acquisition of the tools and basic knowledge to interrogate the genome, the joint efforts of clinicians and scientists to characterise the causes of inherited susceptibility, the early insights into carcinogenesis and the potential to translate these findings into patient benefit in the short term make this, if not unique, certainly a particularly notable period in medical research.

Finally, this Seminar records the activities in and around colorectal cancer but the activities of the Cancer Family Study Group were broader and included discussion of other related topics with the most significant activity overall involving hereditary susceptibility to breast cancer. The major contributions made to other studies including breast cancer will be discussed elsewhere.

Professor Timothy Bishop
Leeds Institute of Cancer and Pathology, University of Leeds
St James's University Hospital

CLINICAL CANCER GENETICS: POLYPOSIS AND FAMILIAL COLORECTAL CANCER *c*.1975–*c*.2010

The transcript of a Witness Seminar held by the History of Modern Biomedicine Research Group, Queen Mary, University of London, on 25 September 2012

Edited by E M Jones and E M Tansey

CLINICAL CANCER GENETICS: POLYPOSIS AND FAMILIAL COLORECTAL CANCER *c.*1975–*c.*2010

Participants*

Professor Sir Walter Bodmer
Professor Sir John Burn
Professor Gareth Evans
Professor George Fraser
Professor Jane Green
Ms Christina Harocopos
Professor Peter Harper (Chair)
Professor Shirley Hodgson
Professor Alan Lehmann
Professor Eamonn Maher
Dr Pål Møller
Ms Kay Neale
Professor Robin Phillips
Professor Julian Sampson
Professor Ellen Solomon
Professor Tilli Tansey

Apologies include: Professor Timothy Bishop, Professor Douglas Easton, Professor Rosalind Eeles, Professor David Harnden, Dr Victoria Murday, Professor Sir Bruce Ponder, Professor Peter Rigby, Professor Mike Stratton, Professor Ian Tomlinson, Dr Geoff Watts

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

Figures 1 and 2: Professor Peter Harper and Professor Tilli Tansey.

Professor Tilli Tansey: Good afternoon ladies and gentlemen and welcome to this Witness Seminar on Clinical Cancer Genetics. I'm Tilli Tansey and I'm the head of the History of Modern Biomedicine Group which is based at Queen Mary University of London. It's the successor body to an organization that was started by the Wellcome Trust in the early 1990s to create links between scientists, clinicians and historians of medicine, and to create material resources for the study of recent medicine, which we regard as post Second World War. The initial body was set up by Sir Christopher Booth and myself. I'm sure you'll be very sorry to learn that Sir Christopher died just two months' ago, but he was active and involved in these meetings almost until the end.[1] We developed this Witness Seminar format in 1993 for a meeting on monoclonal antibodies. We get together a group of experts who are interested in a particular field or development and ask them to tell us about what really happened; the stories behind the published papers. What went on? What failed? Who was funding the research? Who were the drivers? Who were the resistors in different organisations? We have encouraged a number of 'mirror' meetings around the world so, although our meetings are predominantly British in focus, there are a number of meetings elsewhere that will also try to create a body of information about the development of particular topics and subjects across the world.

[1] Sir Christopher Booth (1924–2012) was a clinician, medical researcher, educator and medical historian. He was Professor of Medicine at the Royal Postgraduate Medical School, Hammersmith Hospital, from 1966 to 1977 and Director of the Medical Research Council's Clinical Research Centre at Northwick Park from 1978 to 1988. He was co-founder, with Professor Tilli Tansey, of the History of 20th Century Medicine Group at the Wellcome Trust in 1990, now the History of Modern Biomedicine Research Group, Queen Mary, University of London. For obituaries, see Anon. (2012), Richmond (2012) and Peters *et al.* (2012).

The meetings are recorded, transcribed and ultimately published. They are all made freely available on the web and also published in hard copy via print on demand. Nothing is published without your say so, so after this meeting you will get to know me and my team very well because we will be in touch with you throughout the editorial process. To date we've held over 50 such meetings and our efforts have been rewarded by a recent large strategic award from the Wellcome Trust called Makers of Modern Biomedicine which you can see advertised on the screen behind me.[2] This is the first such meeting under that new award that we are holding. We have five particular identified themes for that award, one of which is genetics, and we also have a dedicated adviser for genetics, Peter Harper.[3] One of the first things he's advised us to do is to hold this meeting. So, without further ado, I'll hand over to Peter.

Professor Peter Harper: Thank you, Tilli and, again, welcome to all of you. I should say that there are one or two people who, with weather mainly as a factor, can't be here. We've got John Burn, hopefully on a phone link in a later part of the meeting, so we hope that will work. Ian Tomlinson I gather can't be here and I think another weather casualty is Tim Bishop, which is a shame because it means that some of you will have to think about things like linkage and what Tim might have contributed.[4] I'm Peter Harper, a now-retired medical geneticist from Cardiff, and I should say this is not a field that I am really expert in – which is perhaps why I'm chairing it – it is one I've watched grow up and flourish from its early stages in this country.

It's perhaps worth saying a word or two just about how this Witness Seminar came about. Ten years ago we held a seminar entitled *Genetic Testing,* that concentrated really on laboratory aspects of human and medical genetics and some folk, myself included, felt there was room for another one on clinical genetics.[5] Five years ago we were lucky enough to be able to hold that further seminar.[6] I've got a copy

[2] The History of Modern Biomedicine Group's website homepage is: http://www.history.qmul.ac.uk/research/modbiomed (visited 23 January 2013).

[3] See biography on page 110–11.

[4] Professor Ian Tomlinson is Principal Investigator and Group Head of Molecular and Population Genetics at the Wellcome Trust Centre for Human Genetics, Nuffield Department of Medicine, University of Oxford; http://www.ndm.ox.ac.uk/principal-investigators/researcher/ian-tomlinson (visited 17 January 2013). For Professor Bishop, who wrote the introduction, see page 18, note 39 and biography on page 105.

[5] Christie and Tansey (eds) (2003).

[6] Harper *et al.* (2010).

Historical context Pre-1975 material on clinical cancer genetics
Clinical cancer genetics development in the UK Cancer Family Study Group
Case study Polyposis: clinical aspects and registers other forms of familial colorectal cancer
Research and clinical practice Gene mapping and isolation Practical applications
People and organizations Who does what, and where? Professional bodies and monitoring groups

Table 1: Outline of programme for Clinical Cancer Genetics: Case Study and Context, c.1975–c.2010.

here if anybody wants to see it but it's on the web.[7] Needless to say, when we had that seminar there were still lots of things that there wasn't time to cover, including cancer genetics. Rather than just have a little bit about cancer genetics in a more general seminar I felt very strongly, and Tilli agreed, that it deserved a seminar of its own. So here it is.

Now, even devoting a specific seminar to cancer genetics it pretty soon became clear that one couldn't cover all of the field. The first kind of pruning we made was to decide to concentrate on the more clinical and applied aspects because there was so much basic cancer genetics research, it would fill days and days. And then, even with that focus, it looked like being difficult to give really good time to both familial colorectal and familial breast cancer, and so, very arbitrarily, we decided to concentrate on familial colorectal cancer and polyposis and to leave breast cancer mainly to the more general aspects in the second part of the seminar.

So this was really how that came about; the outline programme you've had circulated but there's a rather more detailed outline that's been put on your chairs which hopefully gives a bit of focus to the topics we're hoping to cover during the meeting. But if something important is not listed we'll make sure it comes up.[8]

---

[7] See http://www.history.qmul.ac.uk/research/modbiomed/wellcome_witnesses/volume39/index.html (visited 18 January 2013).

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

Figure 3: Clinical Cancer Genetics Witness Seminar.

One item particularly which I think does deserve to have some discussion is the new aspects of therapeutics resulting from genetic advances. Do please remember that you'll have the opportunity to put more detail in the written volume and things like photos and whatever, so that is material which can be added; really, as Tilli said, the purpose of this afternoon is to get your own experience as witnesses to an important and rapidly developing field.

Now that, I think, is all the immediate background that's needed but perhaps it's sensible to go on straight away to a brief introduction to pre-1975 material. 1975 was only chosen very arbitrarily but we really wanted to make sure that the focus was on the actual experience of those people who are here rather than on the more distant past. But, on the other hand, I think it's right and proper that we should acknowledge that clinical cancer genetics didn't just start then, and there were important people and important work beforehand. So I would like to ask any of you who can to just bring up very briefly some of the important early workers in the field, because I don't think we should forget them. There are one or two of them that come to my mind, all in North America actually.

I'll just throw out their names: people like Alfred Knudson,[9] Henry Lynch,[10] Eldon Gardner[11] and Madge Macklin.[12] But who would like to say a word or two about any of these or others?

Professor Sir Walter Bodmer: The first proper description of polyposis as a dominant was by Lockhart-Mummery, from St Mark's Hospital, in a paper in 1925 in *The Lancet* which long predates anything that came later.[13] Of course Gardner thought he was looking at a different disease. Then there were the families that Henry Lynch later looked at, that original family described by Warthin.[14] I remember very well when Lynch was talking about these things – everybody thought they were just anecdotes that you didn't take very seriously. So there was actually very little substantial evidence, there were no proper breast cancer families as far as I'm aware until somewhat later.

Harper: I hope that the St Mark's group a little bit later on will be able to give us a history of it from their perspective, because a lot of these things did begin in London. Are there other people that need to be brought out from the past?

---

[9] Dr Alfred Knudson (b. 1922) is particularly known for his influential 'two-hit' theory of tumour formation; see note 96. See also his biography on page 112 and Knudson (2005).

[10] Dr Henry Lynch (b. 1928) is renowned internationally for his research in familial colorectal and associated extra-colonic cancer. Between 1970 and 1990, at the University of Nebraska, Lynch defined hereditary non-polyposis colorectal cancer (HNPCC), now also known as Lynch syndrome (type II). See his biography on page 113–14.

[11] The cancer geneticist Professor Eldon Gardner (1909–1986) established the existence of a hereditary form of cancer of the lower digestive tract, which became known as Gardner syndrome. See Gardner and Stephens (1950), and also Gardner's biography on page 108–9. The Eldon Gardner papers, 1936–1986, are held at the archives of the University of Utah.

[12] Dr Madge Macklin (1893–1962) was influential in the sphere of hereditary breast cancer research. See her biography on page 114.

[13] Lockhart-Mummery (1925). Mr J P Lockhart-Mummery (1875–1957) was a leading surgeon at St Mark's Hospital. His son, Sir Hugh Evelyn Lockhart-Mummery (1918–88), also became a surgeon at the hospital. See their biographies, on page 113. Founded in 1835, St Mark's Hospital, London, specializes in the treatment of intestinal and colorectal disorders, and researches the causes and treatments of these disorders both nationally and internationally; http://www.stmarkshospital.org.uk/about-st-marks (visited 7 January 2013). For a full history of this institution see Granshaw (1985). Archival records for St Mark's Hospital, 1840–1996, are available at St Bartholomew's Hospital Archives, reference 405 K, and also at London Metropolitan Archives, references A/KE/258/005 (1909–1927), A/KE/546/011 (1929–1931) and A/KE/543/010 (1938–1948).

[14] See Lynch and Krush (1971) and Warthin (1913). Dr Aldred Scott Warthin (1866–1931) was a pioneering researcher in hereditary familial cancer. See his biography on pages 116–17.

Professor Gareth Evans: About 1860 there was a Parisian doctor, Broca, who described a very strong pattern of breast cancer in his wife's family and said that this was hereditary.[15] That's often cited as one of the first examples. I know we're off the subject of bowel cancer but just for the sake of completeness.

Dr Pål Møller: *Traité Des Tumeurs* was written by Paul Broca and published in Paris in 1866.[16]

Professor Shirley Hodgson: Also, Lionel Penrose's publications about breast cancer in the 1940s.[17]

Harper: One person I'd like to mention is Madge Macklin.[18] She was Canadian, although she worked for part of her career in the northern United States. I'm sure I'm right in saying that there was a 1959 paper of hers on breast cancer where she both described large families and did an overall study showing increased risk in first degree relatives.[19] But maybe there's something more to be said about Madge Macklin?

Professor Jane Green: My comment really has to do with Henry Lynch. I am so impressed with how he persisted with teaching everyone that there was such a thing as hereditary colon cancer, even when many people thought that the evidence was against that, that it was environmental clusters and so on. He really impressed me with how, when the genes were found, he just kept on as he always had, that he had understood this for a long, long time.[20]

---

[15] Broca (1866). Pierre Paul Broca (1824–1880) was a French physiologist, today most widely recognized for his identification of 'Broca's area' – the part of the brain generally associated with speech – and his founding role in the constitution of anthropology as a scientific discipline. In addition to his cerebral and ethnographic work, he published a wide range of medicine-related studies during his lifetime, including contributions to anatomy, surgery and pathology, this latter constituting the two-volume work cited above. See also Schiller (1992).

[16] Dr Pål Møller wrote: 'The book was not available in Norway, but I persuaded the French to lend me the original for a week in the 1990s. It was considered valuable and delivered through a lot of formalities…. None of those today claiming to have discovered inherited breast-ovarian cancer has to my knowledge ever referenced that book.' Note on draft transcript, 22 October 2012.

[17] See, for example, Penrose *et al.* (1947). Professor Shirley Hodgson's father was the geneticist Lionel Sharples Penrose. For an in-depth obituary see Harris (1974).

[18] See note 12.

[19] Macklin (1959).

[20] See note 10.

Hodgson: Just very briefly, I remember him saying that he'd been told by his superiors that he should stop doing these terrible familial colon cancer clinics that were wasting everyone's time, and do some 'real medicine'.

Harper: There's one query that I might put out: there was a study by Arthur Veale when he was at the Galton Laboratory and I can't remember whether he used St Mark's material for that or what, but it was again a pretty early study.[21]

Ms Kay Neale: You've just reminded me of the name of the person who helped Dr Dukes and Dr Bussey to determine the dominant nature of polyposis.[22]

Bodmer: It was Lockhart-Mummery who pointed out it was dominant already in 1925.[23] If you read *The Lancet* paper…

Neale: Okay, I stand corrected.

Bodmer: There is a paper by Harrison Cripps in 1882, which I have often quoted in the past, who described two cases of what were clearly polyposis and noted they were rare cases, and a brother and sister who very clearly showed it was a Mendelian dominant.[24] But, of course, they got much more data later.

Neale: St Mark's Polyposis Register started in 1924 as a result of John Percy Lockhart-Mummery having an interest in family diseases and Dr Dukes having an interest in polyps turning into cancer.[25]

---

[21] Arthur Veale was New Zealand Medical Research Council Fellow and an Honorary Research Assistant at the Department of Eugenics, Biometry and Genetics – the Francis Galton Laboratory of National Eugenics – at University College London and also an Honorary Research Fellow in Genetics at St Mark's Hospital, London. He was also responsible for setting up the first medical genetics services in New Zealand. St Mark's Polyposis Register was the subject of Veale (1960). His doctoral research Veale (1961a) was later published as Veale (1965). For a significant essay of Veale's on clinical cancer genetics, see Veale (1961b). See also Palladino (2002), in particular pages 147–8.

[22] Dr Cuthbert Dukes (1890–1977) was the first pathologist at St Mark's Hospital, appointed in 1922. See his biography on page 107. For Dr H J R Bussey (1907–1991) see pages 21–3 and note 64.

[23] See note 13.

[24] Harrison Cripps (1882).

[25] Ms Kay Neale explains how the register of 1924 became the 'registry' during the 1950s; see page 20. See also Dukes (1952). Note that seminar participants used the terms 'register' and 'registry' interchangeably at times, with only Ms Kay Neale clearly explaining the distinction between the terms in relation to St Mark's Hospital. See also pages 19–25 and Appendix 2 on pages 88–96 for further details of the evolution and work of St Mark's Hospital's Polyposis Register/Registry.

Figure 4: Professor Sir Walter Bodmer.

Møller: In addition to what Shirley mentioned, I would like to say that Henry Lynch always referred to the Warthin paper from 1913 as the start of inherited colorectal cancer, and one of the points that I would like to bring up today is nomenclature.[26] We call it colorectal cancer, as did the Warthin paper, but later the *MSH2* mutation was as much associated with endometrial cancer as with colon cancer. The initial phases were built on the concept 'one gene, one disease in one organ', which is completely wrong. They are all multifactorial, multi-organ cancer-predisposing factors and Henry Lynch understood colon cancer better but he didn't talk much about the endometrial cancer.[27]

Harper: Are there any other studies from continental Europe – the early ones – that we should just mention, before we get into the detail on polyposis and colorectal cancer?

What you might call the founding event of clinical cancer genetics in the UK was the Cancer Family Study Group. Walter, I'm on the point of asking you to tell us as much as possible about it, particularly because I had hoped that somebody from the north of the UK too, such as Tim Bishop, might be able to say something. David Harnden, I also should say, quite a long time ago sent

---

[26] See note 14.

[27] Dr Pål Møller wrote: 'He [Lynch] did come to the conclusion, however, that there were two forms of inherited colorectal cancer: site specific inherited colorectal cancer and inherited colorectal cancer, including extra-colonic cancers as well. He described this in a book chapter in 1985 and suggested the names Lynch syndromes 1 and 2 respectively.' Note on draft transcript, 22 October 2012. See also Lynch and Lynch (1985).

apologies but he has sent a little summary which we hope we will be able to include in the published volume.[28] But Walter, tell us about the Cancer Family Study Group.

Bodmer: Just to give a bit of background; I came to the Imperial Cancer Research Fund (ICRF)[29] in the summer of 1979, and it was earlier that year that Ellen [Solomon] and I published the first really clear idea that you could use linked markers extensively to get a complete genetic map and identify diseases that way.[30] It was natural to me when I came to the ICRF to have an interest in setting up genetics in that sense and I mentioned that in the first report that I produced in 1979.[31] We had meetings of the then directors of the various cancer institutes, which included the Paterson, the Beatson Institute for Cancer Research and ICRF.[32] David Harnden at that time was director at the Paterson lab.[33] It was probably through meeting in that way and hearing what people had said that I gathered that he and Ray Cartwright had set up a cancer families study group, but that had more or less fizzled out and hadn't continued.[34] So David Harnden and I agreed that we would restart something that was called the Cancer Family Study Group, that would meet every six months alternately between the Paterson labs in Manchester and the ICRF labs in London.[35] The first of those meetings was on 30 January 1984 according to my diary. They

---

[28] See Appendix 4 on pages 122–5 and biography on pages 109–10.

[29] The Imperial Cancer Research Fund merged with the Cancer Research Campaign (formerly the British Empire Cancer Campaign when it was founded in the 1920s) to form Cancer Research UK in 2002; http://www.cancerresearchuk.org/about-us/who-we-are/our-story/our-history/ (visited 16 October 2012). See also Austoker (1988), which has an epilogue by Sir Walter Bodmer.

[30] Solomon and Bodmer (1979).

[31] Imperial Cancer Research Fund (1979), in particular pages 2–3.

[32] The Paterson Institute for Cancer Research is based at the University of Manchester; http://www.paterson.man.ac.uk/About/ (visited 29 October 2012). Sir George Thomas Beatson founded a research department at the Glasgow Cancer Hospital in 1912, which became the Beatson Institute for Cancer Research in 1967. The current institution conducts research into cancer cell behaviour and has close links with the University of Glasgow for the clinical application of its research findings; http://www.beatson.gla.ac.uk/About/Introduction.html/ (visited 11 January 2013). See also the same website's history page.

[33] See note 28.

[34] Professor Ray Cartwright was Director of Leeds University's Leukaemia Research Fund Centre for Clinical Epidemiology, 1987–2003.

[35] See also introduction.

continued for quite a while and are part of what's now, I've forgotten what it's called, within the British Society for Human Genetics (BSHG).[36] The idea was not that it was a talking shop and a conventional meeting; the idea was mainly that it should stimulate collaborative studies on families aimed at finding linkages. So that's the origin of the Cancer Family Study Group which more or less continued most of the time, as I recall, during which I was at the ICRF.

Harper: One of the really important things about the group was that it involved a number of other centres, including ourselves in Cardiff, who wouldn't have otherwise been involved.[37]

Bodmer: That's really a later story that we can talk about, the gradual build-up of cancer family clinics, of which St Mark's was the founder. I can mention that now, because gradually it was to some extent with support from the ICRF that there was activity in a number of different places. And that came later.

Harper: Am I right that the provision of samples was an important aspect, or one of the aims of the group?

Bodmer: The aims of the group were to collaborate with collecting materials so you could do linkage studies, which obviously meant collecting samples, but the idea was that it should be collaborative. It did stimulate some collaborative studies on that. Others may have recollections of further things that were done.

Harper: Who'd like to come in at this point about the early days of the Cancer Family Study Group?

Professor Ellen Solomon: As always with these historical things, it's hard to put yourself back in time; once you know something you know it and one can't return to quite the state of ignorance one was in at that point. It's quite fascinating to watch the way it happened and I think it was a combination of things. Linkage was the tool we had then and it was just taken as given that were we to get enough families with a dominant disorder, we would find it.

---

[36] The BSHG is a professional forum for geneticists founded in 1996; http://www.bshg.org.uk/society/about_us.htm. The Cancer Genetics Group, part of the society, is a 'national, multidisciplinary organisation' for 'those with an interest in hereditary predisposition to cancer including clinicians, counsellors and scientists'; http://www.ukcgg.org/ (both websites visited 11 January 2013). Formerly the Cancer Genetics Group was the Cancer Family Study Group. See note 39 and also Sir John Burn's comments on page 57.

[37] The Department of Medical Genetics at the University of Wales' College of Medicine of which Harper was Professor of Medical Genetics from 1971 to 2004.

Figure 5: Professor Gareth Evans.

Harper: Can I ask in terms of archiving the records of the group: have its early records and correspondence about its founding, been securely archived?

Bodmer: I should think the answer is almost certainly no. If there is anything on the records of the meetings it would be in my own papers[38]

Evans: I can only really comment on the fact that I know that when I took over as secretary of what was then the Cancer Genetics Group there were no archives that I was handed on. However, I know that Tim Bishop was secretary for many years, probably starting before 1990 when I was first attending the meetings, so it's possible that Tim does have some things squirreled away that at least go back into the late 1980s[39]

---

[38] The Walter and Julia Bodmer archives project is taking place at Oxford University's Bodleian Library, where Sir Walter has donated his archive. The cataloguing of Sir Walter and Lady Bodmer's papers has been funded by the Wellcome Trust's Research Resources in Medical History programme. Further details are available at http://blogs.bodleian.ox.ac.uk/theconveyor/2011/05/11/the-walter-and-julia-bodmer-archives-project/ (visited 24 April 2013). The catalogue is scheduled to be published and the archival material available early in 2014.

[39] Professor Timothy Bishop has provided his archival papers of the Cancer Family Study Group (CFSG) for deposit with the records of this Witness Seminar at the Wellcome Library, London, at GC/253. The collection includes administrative papers, correspondence between members, and externally with the NHS and Imperial Cancer Research Fund, among other public and professional organizations. A membership list for 1988 is included, as are the records of the Steering Group meeting in November of that year. Within the correspondence are items concerning debates about protocols for DNA samples' storage and also the transition of the CFSG to the Cancer Genetics Group from 1999 to 2000.

Bodmer: Just let me get the dates right: the Genetic Epidemiology Laboratory in Leeds under Ray Cartwright was set up in 1987 and by 1988 ICRF had appointed Tim Bishop as the director – so the 'late 1980s' means about one year.[40]

Harper: Therefore the key documents would perhaps be from quite a few years before that, about the founding of the group?

Bodmer: Yes, it had been going for about five or six years by that time.

Møller: I was asked to build a cancer genetics clinic in Norway in 1988 because I had graduated in HLA genetics and was known as the guy doing the multifactorial genetics; that was why. Looking around the world at that time, the organization I found of interest was the European Mathematical Genetics Meeting where Tim Bishop played a central role, together with Gerard te Meerman in Groningen and Francoise Clerget-Darpoux in Paris.[41] They were very much engaged in the initial descriptions of what this was about.

Harper: Perhaps this is an appropriate point just to ask: at what point did the Cancer Family Study Group turn into the Cancer Genetics Group?[42] How did this evolve?

Evans: Sir John Burn is the person who was pivotal in that change.[43] Gradually through the early 1990s the group became more and more genetics-oriented, it was always very genetics-oriented in terms of the linkage of families but there were a lot of surgeons like the esteemed Robin Phillips here, and gastroenterologists, and many other people who attended the group regularly when it was meeting in London and Manchester.[44] But then, gradually, it became much more a group for geneticists, genetic counsellors and there were some psychosocial researchers

---

[40] See note 34. Professor Timothy Bishop clarified that 'The Genetic Epidemiology Laboratory is now the Section of Epidemiology and Biostatistics, Leeds Institute of Molecular Medicine.' Note on draft transcript, 27 February 2013.

[41] Dr Pål Møller wrote: 'Clerget-Darpoux later became a central player in the erection of the International Genetic Epidemiological Society (IGES).' Note on transcript, 22 October 2012. Dr G J te Meerman has, since 1981, been the Assistant/Associate Professor in Mathematical Genetics and Bioinformatics at University Medical Center Groningen and University of Groningen; http://www.rug.nl/staff/g.j.te.meerman/cv (visited 11 April 2013).

[42] See note 39.

[43] Sir John Burn attended the second half of the meeting. See page 55.

[44] See comments from Sir John Burn on page 57.

Figure 6: Professor Jane Green.

involved. It was a stage, when Tim Bishop was secretary, and John was president, that John decided that really the group would be better affiliated to a mainstream genetics society, as a sort of subgroup to strengthen it in some way because it had really lost some of the original multidisciplinary feel. It was put to the members of the Cancer Family Study Group at the time that this would be a good idea but it would probably mean changing the name to the Cancer Genetics Group, which became affiliated to the BSHG.[45]

Green: I'd like to mention something about the beginnings of cancer genetics in Newfoundland because we began really with the presentation of large families, recognizing that there was something in these families that was different than the average. One family called it 'The Curse of the Smiths'. Each affected family felt the same way and cancer genetics really began in 1982, in order to provide for each family's needs. I worked in an ocular genetics clinic and a family with Von Hippel-Lindau (VHL) disease was referred to the clinic and within a month we had all the specialists together, to begin a multidisciplinary clinic. In each case, the beginnings of the study of a particular hereditary cancer was because of the needs within a family. Newfoundland, at that time, had very large families. In many of these families 10, 12, 15 siblings was not uncommon and, if you have family sizes like that, the hereditary cancer families were obvious. Because of the settlement patterns and distribution of the population in Newfoundland, it has a

[45] See note 36. Papers relating to this transition are available in Professor Timothy Bishop's archives of the Cancer Family Study Group, which are being deposited with the records of this seminar at the Wellcome Library GC/253. These materials confirm that the Cancer Family Study Group formally became the Cancer Genetics Group in 2000.

very interesting genetic history.[46] Newfoundland – the island part of the province – is 111,000 square kilometres: it is almost half the size of the UK and the peak population, which would have been in the late 1970s, was 575,000 people. It is about 512,000 now. Everyone lived along the coastline and the coastline is almost 18,000 kilometres – a very indented coastline with many small islands offshore. People had settled primarily in the late 1700s and early 1800s.[47] Newfoundland wasn't one isolate, Newfoundland was many isolates. Every community was almost its own genetic isolate and so if you had somebody who immigrated to Newfoundland and had one of these mutations, the children, the grandchildren, the majority of the descendants tended to be in the same area and if there was something like hereditary cancer, whether it was polyposis or hereditary non-polyposis colorectal cancer (HNPCC) or multiple endocrine neoplasia (MEN), it was obvious that there was something different about that family. So in each case, even though it was only a small branch of the family that was referred, they were huge families, and immediately clinical services developed and were provided by the specialists that were in Newfoundland. Because the families were so large and because they were so well characterized, they became very valuable in various linkage studies and studies to define the clinical characteristics and variability within the diseases. In terms of cancer genetics services for families, I didn't really realize how early in fact this was. Clearly for us the first question was: What is present in the family? How can we look for it and find it early? And how can we treat early? Then, because the families were so large, if there was a way with linkage or knowing the gene then obviously that would streamline the service and make it that much easier for these families.[48]

Bodmer: As I recall, there were certainly people, I thought, from Newfoundland and from Iceland who came regularly to the Cancer Family Study Group in the UK. That was starting early in 1984. Certainly Iceland and, I thought, some from Newfoundland.[49]

---

[46] For historical context see Heagerty (1928) and Hunter *et al.* (eds) (1986). See also the current, online version of the latter text; http://www.library.mun.ca/hsl/healthbib/index.php (visited 24 April 2013).

[47] Mannion (ed.) (1977).

[48] See Green (1995).

[49] For clinical cancer genetics in Iceland, see Tulinius (1985). The Icelandic Cancer Registry has operated since 1954; http://www.krabbameinsskra.is/indexen.jsp?id=aboutics (visited 6 February 2013). Professor Jane Green has suggested that, if there were participants from Newfoundland, of which she is uncertain, 'The people from Newfoundland would have been Dr William Marshall, Dr Bodil Larsen, and possibly Sharon Buehler, who were all in Immunology, and very interested in a large Newfoundland family with common variable immunodeficiency, Hodgkin's disease and other malignancies.' Note on draft transcript, 11 March 2013. See also Buehler *et al.* (1975).

Figure 7: Dr Pål Møller (left) and Professor Julian Sampson (right).

Harper: Were there other defined groups, can anybody tell us, at that point? I'm not aware of any in the United States that were equivalent. Well, I'm thinking more not of individual workers but of groups or informal societies.

Evans: I can address that. It's straying into the breast cancer field but probably the one international group is the Breast Cancer Linkage Consortium which was set up in 1989, prior to the identification of the *BRCA1* gene in 1994.[50] That spawned a huge amount of collaborative research across Europe, Australasia, North America and there was a European grant that was obtained in order to keep that group going and it eventually foundered about eight or nine years ago when there was no more funding, but it spawned new groups such as the Collaborative Oncological Gene-environment Study (COGS) initiative, which is looking at modifiers of breast cancer risk.[51] But I suppose that was the biggest group that I'm aware of, which was about getting together people – clinicians, molecular biologists, etc. to pull together family research to identify genes. Many, many countries were involved with that.

Bodmer: When did that start?

---

[50] Founded in 1989, in France, the Breast Cancer Linkage Consortium (BCLC) was an international network of scientists, whose membership cooperated to share information about inherited breast and ovarian cancer; http://www.humgen.nl/lab-devilee/BCLC/history.htm, (visited 30 October 2012). See also Miki *et al.* (1994).

[51] COGS commenced in May 2009, with the aim of identifying 'individuals with an increased risk of breast, ovary and prostate cancer'. The study is funded by the European Commission and the 7th Framework Programme; http://www.cogseu.org/index.php/general-information (visited 30 October 2012).

Evans: That would have been, I guess, 1991/1992.

Møller: In 1991, I joined the third meeting of this international collaborative group on hereditary non-polyposis cancer (ICG-HNPCC), today called Lynch syndrome.[52] The group issued the Amsterdam criteria to clinically define inherited colorectal cancer.[53] Hans Vasen in Leiden, the Netherlands, became the ever-lasting secretary.[54] Tim Bishop was instrumental in the early years for developing the concept of inherited colorectal cancer, because at that time it was all statistics.[55] Also, I would like to add to what Jane said, that we have had the same experience in Norway about genetic isolates, not only along the coast side, but inland as well.

Harper: I think it's time to now move on to our case study: polyposis and familial colorectal cancer. Maybe it's just worth me saying why we did decide on this rather than say, breast cancer. From my perspective there were three reasons: first, it shows very well the links and interplay between the various rare Mendelian cancer syndromes and common cancers; also it's a good example of the close collaboration of clinical workers and laboratory workers in mapping the genes; and there are very clear benefits in terms of applying the new advances. So, for all those reasons, I felt that if one was having to choose a particular area, polyposis and familial colorectal cancer was the best. But I am fully aware there are going to be other people, but of course they're likely to be some of the

---

[52] Dr Pål Møller further elaborated: 'When ICG-HNPCC merged into InSiGHT and reduced the meeting schedule to one intercontinental large meeting every second year, the European members of ICG-HNPCC continued to meet annually (in Mallorca) and took the name the Mallorca group. In addition, to coordinate European research, we undertook to issue clinical guidelines which are by and large followed in, close to, all European countries.' Note on transcript, 22 October 2012. See Vasen *et al.* (2007) and Lynch *et al.* (2003).

[53] At the first Amsterdam meeting of the ICG-HNPCC, criteria 'for a clinical diagnosis of HNPCC based on family history were established', quoted from Lynch *et al.* (2003). In subsequent meetings the original criteria were revised. Bodmer *et al.* (1994) defined the criteria thus: '…at least three relatives with colorectal cancer, one of whom should be a first relative of the other two (but the three should all be related to each other), at least two generations affected and at least one of the relatives should be below 50 years of age', quote on page 219.

[54] Hans Vasen is now Professor of Inherited Tumours at Leiden University Medical Center in the Netherlands. He is also the Administrative Director of the International Society for Gastrointestinal Hereditary Tumours (InSiGHT) and Editor-in-Chief of *Familial Cancer*; https://www.lumc.nl/con/7010/65176/91008101620439?setlanguage=English&setcountry=en, (visited 30 October 2012).

[55] See also introduction.

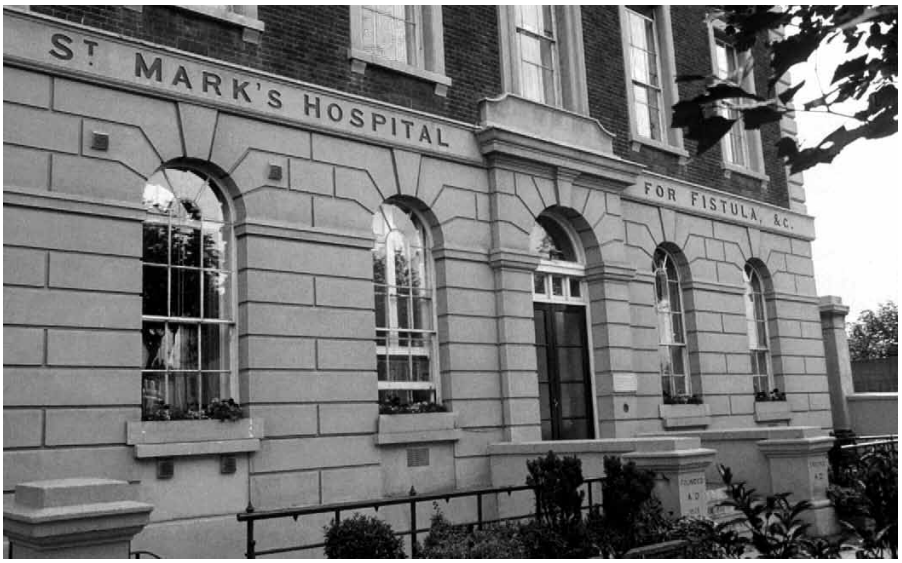


Figure 8: St Mark's Hospital, *c.*1994 under its former title and location on City Road (1854–1995). The hospital was previously located on Aldersgate Street from 1835 and is now situated in Northwick Park, as part of the North West London Hospitals NHS Trust site.

people who are not here, who disagree with that. Anyway, I think we ought to go back and give the St Mark's Hospital group a chance to tell us how their clinical studies of polyposis and the register evolved.[56]

Neale: Sir Walter has already told us that J P Lockhart-Mummery first described the dominant inheritance of polyposis at St Mark's because he did have an interest in hereditary diseases. It was Veale who later confirmed it by looking at more families.[57] That's where that link came in. In the 1920s Dr Dukes, the Consultant Pathologist, decided that because of this knowledge St Mark's should start to collect information about all families where there were patients with multiple polyps and a hereditary history of bowel cancer.[58] In 1918, J P Lockhart-Mummery did take out a colon and join the small bowel to the sigmoid colon and that was the first surgery that was done to try and prevent bowel cancer in a polyposis patient.[59] But it was really in the 1940s, post-war,

[56] See also Appendix 2 for further information about St Mark's Polyposis Register on pages 88–96.

[57] See note 21.

[58] See note 22.

[59] Lockhart-Mummery (1919).

Figure 9: Ms Kay Neale (left) and Professor Robin Phillips (right).

when we had more knowledge about anaesthetics and blood transfusions – antibiotics, of course, were also beginning to come on the scene – that it was safe for the surgeons to take out the colon and join the small bowel to the rectum. And by 1953, I think,[60] it was decided that this was a safe operation to do and at that stage the surgeons, being by this time J P Lockhart-Mummery's son Sir Hugh Lockhart-Mummery[61] and Sir Henry Thompson,[62] they decided that they should persuade the relatives of people with polyposis to come and be screened so that they could have surgery before they got cancer. So that's really how the registry started. I guess it was a register up to that point, but once they started to employ the staff to encourage people to come and be screened, it became the registry.[63]

---

[60] See note 134.

[61] See Granshaw (1985), page 285 and note 13.

[62] Mr Henry Reynolds Thompson (1908–85) was Resident Surgical Officer at St Mark's Hospital in 1939. In 1947 he was appointed surgeon to St Mark's, Woodford Jubilee and Forest Hospitals.

[63] Ms Kay Neale wrote: 'Before the early to mid-1950s, when a treatment became available, there was no active encouragement to get relatives screened. Until that point the information was collected for research, after that it was a combination of research and clinical care.' Note on draft transcript, 5 April 2013. Lindsay Granshaw notes, 'Polyposis families were followed up with particular care. Dukes and his assistant, H J R Bussey, worked out an elaborate filing system to enable new cases to be entered and their families traced'. See Granshaw (1985), page 270; for registry see also pages 345–52.

Harper: May I ask at this point: screening was colonoscopy of some sort, was it?

Neale: Screening would be by rigid sigmoidoscopy, there were no colonoscopes at that stage. The colonoscope came in the 1970s. So it was rigid sigmoidoscopy just looking at the rectum, then it was in 1960, I think, that Dick Bussey did his thesis on what we now call familial adenomatous polyposis, and his definition of polyposis was that there should be more than 100 adenomas throughout the colon and rectum.[64] Over the years there's been a lot of discussion about whether that is an accurate statement and I think Dr Bussey's purpose in saying that was that we would collect, for research purposes, information on the people that we were absolutely certain had this condition. Of course, now that the gene has been identified, we know that there are people with fewer polyps and not necessarily quite so spread who do have mutations in the adenomatous polyposis coli (*APC*) gene. But his aim was that we would have a pure group of patients on which to do the research.[65]

Harper: That's a remarkably far-sighted attitude in terms of linkage research, isn't it? Perhaps a bit less so in terms of patients, but, in terms of making sure you don't mix things up with linkage, it's very valuable. Can you tell us a little bit more about Dick Bussey because he seems to have been a very pivotal person.

Neale: Dick Bussey was a grammar school boy who came from a family that did not have the resources to put him through university. He started working with Cuthbert Dukes when he was 17 years old and Dukes soon recognized that he had someone who was both intelligent and meticulous. He encouraged Bussey to go to university to do a degree in chemistry and then later, of course, he did his PhD in polyposis, in familial adenomatous polyposis (FAP).[66] I don't know what else to say about him. He was an amazingly gentle person, I only ever

---

[64] Bussey (1970). Cuthbert Dukes employed H J R Bussey who worked in his former laboratory in 1924. In her history of St Mark's Hospital, Lindsay Granshaw writes, 'Bussey was then 17, but proved to be the longest-serving member of the staff of St Mark's. He later acquired a BSc and PhD (and was awarded an OBE) and was still at the hospital after 60 years of working for Dukes and his successor Basil Morson, and on his own research (in particular familial polyposis).' Granshaw (1985), quote on page 223. See also obituary for Dr Bussey on pages 95–6.

[65] Ms Kay Neale wrote: 'I should like to clarify that in the Registry, patient information is filed in family files. These are categorised in two groups; one in which we are confident about the diagnosis and the other in which the diagnosis is in doubt. Patients in which the diagnosis is in doubt are cared for according to their clinical need but not included in research where a genetic diagnosis is required.' Note on draft transcript, 23 October 2012.

[66] See note 64.

Figures 10 and 11: Dr Bussey's original Polyposis Register patient record cards, St Mark's Hospital, London.

heard him cross once. As much as I questioned him or didn't understand what he was saying, he would patiently go over it again and say that if someone didn't understand something it was the fault of the person not explaining it properly, not the person who was being a bit dim. [Laughs] I worked with him for many years. I became very friendly with him.

Harper: How did the register originate? Was this St Mark's patients or was it from a wider range from the beginning?

Neale: Well, it started with St Mark's patients but Dukes, of course, would lecture and publish in the journals of the day.[67] He soon acquired an international reputation and so people would send pathological slides or descriptions of cases

[67] Ms Kay Neale wrote: 'The first colectomy with ileorectal anastomosis for FAP at St Mark's Hospital was done on 8th December 1948. Dr Dukes wrote, ten years later, "It would be difficult to find a more promising field for the exercise of cancer control than a polyposis family, because both diagnosis and treatment are possible in the precancerous stage and because the results of surgical treatment are excellent."' Note on draft transcript, 23 October 2012. See Dukes (1958), quote from page 413.

of polyposis from all over the world, and Dr Bussey would record them all and catalogue them. So sometimes we had full families; sometimes we would just have the slides titled something like 'Girl from Thailand'. But of course in those early days we did not know if polyposis was an international condition. Dr Bussey had cards that he called his 'cohort cards', because of course this is before computers, and the cohort cards would list the years of birth of patients who had polyposis and the part of the country that they lived in. We weren't even sure if there were cases of polyposis throughout the UK, although now we know they are all over the world.

Harper: Did you have from the very early stage a systematic approach to contacting healthy relatives or was that something which came a bit later?

Neale: It was started in the 1950s and there's a wonderful record in St Mark's archive which describes Dr Dukes and somebody else driving down, I think, the A23 road on a Saturday morning looking for the relatives of a family – of course, we wouldn't be allowed to do this today. He came across one member of the family who wouldn't talk to him at all. The next house he went to, the lady there was surrounded by 23 children. She had something like eight of her own, and eight she'd taken in from a sister who had died from polyposis, and a few more from somewhere else.[68] I know that Henry Thompson one day went to visit someone at home who wouldn't agree to be screened, and Thompson was an Oxford blue boxer and the person that he went to visit was from an East End London boxing family.[69] And he said that he would challenge the man who wouldn't be screened to a boxing match and the purse would be the examination. [Laughter] So there were lots of stories like that from the early days when the surgeons really went out of their way to find these people.[70]

Harper: Have surgeons changed since then?

Neale: Surgeons have changed enormously since I started at St Mark's in 1974. I think the big difference that I've found since I first started working at St Mark's is that we, the research workers, as I was when I first started there, were not employed as nurses. I was employed as a research worker and we were not

---

[68] The archives that Ms Neale refers to are the family files still retained at St Mark's Hospital.

[69] See note 62.

[70] Public attitudes towards cancer diagnosis are discussed by, for example, Patterson (1987) in the context of modern America.

allowed to step over the chalk line unless we were told. The patients belonged to the surgeons. I don't know really exactly when it was, but gradually as the new generations came in they really did appreciate the help that was given to them by the research workers and gradually we became people with clinical responsibility.

Harper: Does that reflect the surgical perspective as well?

Professor Robin Phillips: Kay knows an awful lot more about it than I do but I can only say, from my perspective that the old generation of surgeons essentially did private practice where they earned their money. They came and they would do the odd operating list or odd clinic or whatever within the NHS hospital. The situation was exactly as described – the management of polyposis patients was in the different surgeons' hands and all the different surgeons would manage it differently. There was nothing that was standardized, they weren't really trying to sort that out. It was only later on that we managed to move the funding and the care of polyposis patients into the NHS, and the modern standard of care is that we have an oversight committee that agrees the management of every polyposis patient and permits them to be cared for by different consultants under the oversight of this polyposis committee. It's a multidisciplinary team which would be a standard of care. So we have very much standardized care in the last 25 years, I guess, and have lots of studies looking at clinical issues in order to find out what we should be doing for the patients.

Neale: When I started working with Dr Bussey and Dr Ritchie in 1984, the three of us were funded by money from research funds. Dr Bussey and Dr Ritchie were funded by the St Mark's Hospital Foundation.[71] Dr Ritchie actually worked voluntarily and just received her petrol costs.[72] I was funded by Cancer Research UK, not Imperial Cancer Research Fund, to work in the Polyposis Registry. The ICRF became CRUK – thank you, Sir Walter. So there were just the three of us. Now we have a team of two nurse practitioners, a nurse specialist, a nurse endoscopist, a full-time and part-time administrator, all funded by the NHS, and I'm funded by Imperial College.[73] The department

[71] The charitable body associated with the Hospital; http://www.stmarksfoundation.org/index.php?page=about (visited 23 January 2013).

[72] Dr Sheila Ritchie was Registrar for the Polyposis Registry from 1973 to 1989.

[73] Ms Kay Neale wrote: '[The registry] is now mainly funded by NHS staff fulfilling a clinical role but continuing to record patient information which is also used for research.' Note on draft transcript, 5 April 2013. The registry has been funded from various funds, including Cancer Research UK, The Newman Trust and The St Mark's Hospital Foundation; http://www.polyposisregistry.org.uk/stmarks/SMhome.htm (visited 23 January 2013).

actually has become an NHS department and I can imagine that once I retire it will continue to run – I mean, I'm hoping it will continue to run in the same way that it's always run. That will depend on the director, I guess, at the moment it's Professor Phillips. It is expected that the Assistant Director, Miss Sue Clark, will become director when Professor Phillips retires.

Phillips: There are problems because a lot of these cohort cards are on top of the shelf, there isn't the storage space supplied by the NHS to be able to look after some of it. We have the information transferred from the old cards into computerized systems but we always have to wonder what we're going to do with the old cards.

Neale: They're Dr Bussey's original cards. When we first got a computer in the polyposis registry, Dr Bussey could find information quicker in his cards than we could on the computer because the computer clicked over so slowly. But those cards now do still exist but are not used.[74] Of course, they do have all the patient information so it may be difficult. I don't know where one would archive that.

Bodmer: I remember those cards and I remember seeing Dr Bussey with the information. He was rather resistant to computerization as I recall.

Harper: Before we move over to the gene mapping and isolation side, does anybody want to say anything about any other polyposis registers that might have existed either elsewhere in UK or in continental Europe?

Evans: Well obviously St Mark's was the exemplar. And because St Mark's actually had people from all over the UK under them, I think there was not so much of an initiative originally to set up regional registers. That did happen to some extent starting around 1989/1990 and Manchester has had a familial polyposis register since 1990 and we actually published just this year a paper on the impact of that register on the survival of people similar to the St Mark's results, showing an improvement in life expectancy based on a register approach.[75] We were rather shocked when we did a survey of all the other parts of the country and found that no other polyposis register was active apart from St Mark's. Unless someone can tell me that my registrar, Susan Huson, was wrong, I know that registers were certainly set up in Newcastle and in other parts of the country. Because

---

[74] See Appendix 2 for reproductions of samples of Dr Bussey's cards and an explanation from Ms Kay Neale about their contents, recorded in a separate interview with her on 29 April 2013.

[75] Wilding *et al.* (2012).

Figure 12: Professor Shirley Hodgson.

of lack of funding, many of them have just ceased to really exist in an active sense – that is, actively following and chasing patients. Now it's just genetics departments doing it through their normal approach rather than through a specific register.

Professor Julian Sampson: Mary Littler set up some registers for a number of Mendelian cancer syndromes, including polyposis, in Wales.[76] They were initiated before I arrived in early 1989 so it must have been about 1985/86?

Harper: She published her paper in 1989 in the *British Medical Journal*.[77]

Sampson: I think pretty rapidly from 1989 to 1990, we computerized the registry in Wales for FAP, not at that time for other inherited cancers. We developed a computerized family-based register so that the working record was the pedigree rather than the individual patient. At that time Walter [Bodmer] and others had identified a number of linked markers for FAP and our register had the facility to write the linkage input files directly from the family pedigree as the base-record. This was only a temporarily necessary step, but writing those input files was quite a business if you had to do it without a programme that would set them up for you.[78]

---

[76] During this period Mary Littler was Research Officer at the Institute of Medical Genetics, University of Wales College of Medicine.

[77] Littler and Harper (1989).

[78] Professor Julian Sampson qualified that this temporary step had only been necessary 'until the gene was cloned'. Note on draft transcript, 27 February 2013.

Hodgson: I think the idea for having a centralized registry to arrange follow-up and surveillance for family members was the ideal, but it needed to be staffed by individuals who would enter the data and arrange to communicate the recommendations for screening to the relevant individuals. In the 1990s, a number of places such as St George's and Guys had *ad hoc* registers, which ran based on the local genetics register.[79] We did have many discussions in the Cancer Family Study Group and with health service providers about trying to obtain funding on a higher level, but this was never attained, largely because it wasn't clear who should be providing such funding. The other thing was, and Kay will help with this, but of course there was the Danish Polyposis Registry. Do you know when that was set up?

Neale: In the early 1970s, I think.

Hodgson: By Bülow and his other colleagues in Scandinavia.[80]

Neale: The Swedish registry was started about 1975 by Dr Thor Alm.[81]

Solomon: Someone will have help to help me with the timing of this, but there must have been something similar set up in Edinburgh?

Bodmer: I don't know about that but just going ahead a bit, when it came to doing the linkage studies and we were looking for the families, the other group we collaborated with was one in Liverpool and that was at the Broadgreen Hospital and I've got the paper here.[82]

Møller: We had a polyposis register in Norway which was always kept separate and was never to this day integrated in genetic clinics. When I started out with all the other inherited cancers, I was actually told by the union for medical genetics that I was no longer part of them because cancer genetics was too specialized.

---

[79] South West Thames Regional Genetics Service – now part of St George's Healthcare NHS Trust – was established in 1986; http://www.southwestthamesgenetics.nhs.uk/. Information about Guy's and St Thomas' NHS Foundation Trust genetics service is available at: http://www.guysandstthomas.nhs.uk/our-services/genetics/overview.aspx (both sites visited 17 January 2013).

[80] The Danish Polyposis Registry was founded in 1971. See Bülow (1986).

[81] The Swedish Polyposis Registry commenced in the late 1950s. See Björk *et al.* (1999) and also Alm (1975).

[82] Bodmer *et al.* (1987).

Phillips: You may want to discuss the separation or the integration of the Polyposis Register from HNPCC and other cancers and perhaps why it happened. Certainly, to this day, polyposis at St Mark's is kept entirely separate from the others and there are very good reasons for it. It's a clinical problem and the patients have clinical problems – they need clinicians to look after them – whereas a lot of the other conditions, including the Lynch syndromes, are management problems. They can have managers rather than clinicians looking after them. They can be looked after remotely, they don't need clinical experience about their particular case or the observation of the polyps in their stomach, or at what stage you are getting worried about it. You need to have the clinical experience to understand that, it can't be offloaded elsewhere. So we very much kept those separated.

Harper: I'd like now to perhaps open the discussion on mapping and isolation of the genes because that's a key part of this seminar.

Bodmer: Just to comment on that: the first Leeds Castle polyposis meeting was in 1985 and we established in the ICRF a St Mark's unit which was for all aspects of colorectal cancer.[83] In 1984, in the unit's first report, they talked about genetic studies on polyposis coli and other family susceptibilities, so while there was this tremendous emphasis on polyposis, it was not uniquely so.[84] As far as I recall, even in the first polyposis meeting, there would have been a discussion of other cancer families. To give at least my own perspective on how the mapping took place and what I see as the history: as I mentioned, I went to the ICRF in the summer of 1979 and I had already decided, and Ellen came at about the same time, that I should do something in the cancer field, because I wasn't until that time involved. Looking at cancer families was an obvious thing and obviously I'd heard about the polyposis unit and what was going on at St Mark's. And remember that Cuthbert Dukes, while he was supported a lot by what was the British Empire Cancer Campaign, was also a key figure for the ICRF as well.[85] There was a very close relationship between the surgeons who were on the ICRF Council and the surgeons at St Mark's that made the contact there quite easy. My records suggest that I really started having discussions about how to get

---

[83] This first international meeting of polyposis experts, at Leeds Castle in Kent, is described in more detail on pages 78–9.

[84] This unit was called St Mark's Colorectal Cancer Unit. See Imperial Cancer Research Fund (1985). See also note 31.

[85] See note 29.

things going in around about 1981. That was certainly with John Nicholls who, you will remember, was much involved then, and probably also Basil Morson.[86] Ian Todd, of course, I knew extremely well and so he was always involved in the background but only became more involved when it came to setting up the unit.[87] He was extraordinarily helpful then and agreed to become the first director of the unit, which was very important because it provided a back-up for the registry that eventually became integrated into the unit. But in fact the first work on collecting blood samples was done by my late wife, Julia.[88] She was involved, and Kay has reminded me, she would have been working with Sheila Ritchie at that time.[89] Julia started collecting blood samples from FAP patients early in 1982 with a view to doing linkage studies. The first paper was actually in the *British Journal of Surgery* in 1985 because there had been suggestions that there would be a linkage with HLA.[90] It was the thing we could look at quite easily and by that time we had only relatively few markers. The collection of this material at that early time made it much easier to do the mapping quite quickly in 1986 and early 1987. The trigger was when Vicky Murday came to St Mark's as an early clinical geneticist. By that time, the Royal College of Physicians had hardly got the idea of how to train clinical geneticists who were dealing with adult diseases. Shirley can comment more on that. Vicky Murday was actually formally an appointment in the colorectal unit but working in my lab towards the end of 1985, early 1986.[91] It was Vicky who pointed out the paper that had appeared in 1986 by Herrera *et al.* that had described a single case of an individual with mental retardation who also had FAP and had a chromosome 5 deletion.[92] That immediately suggested that that was the place to look for linkage and we were lucky in that it was. With Peter Scambler and others we were able to get one

---

[86] Professor John Nicholls was Consultant Surgeon to St Mark's from 1978 to 1999, then Senior Surgeon from 1999 to 2006; http://www.aininfo.co.uk/LGIA/JN.htm (visited 11 April 2013). In 1956 Basil Morson succeeded Cuthbert Dukes as Director of the Research Department at St Mark's Hospital.

[87] Sir Ian Todd was Senior Surgeon at St Mark's Hospital in 1983. See Neale and Bülow (2003), page 1.

[88] Sir Walter Bodmer wrote: '…it was this work that largely enabled the rapid linkage studies because so many of the DNA samples needed had already been collected.' Letter to Ms Caroline Overy, 6 October 2012. See Lady Bodmer's biography on page 105.

[89] See note 72.

[90] Bodmer *et al.* (1985).

[91] Dr Victoria Murday had been appointed as a Research Fellow in St Mark's Hospital Colorectal Unit by spring 1985. See Imperial Cancer Research Fund (1985), page 239.

[92] Herrera *et al.* (1986).

probe that was actually key to the linkage. It actually very quickly showed a close linkage in the family material that we had. That was published in August 1987 alongside the work that Ellen was doing on allele loss.[93] So that mapping actually happened pretty rapidly because of the fact that the samples had already been collected, which was absolutely key. The existence of the register, the existence of the family data, the fact that one could go there with the collaboration, get the blood samples and the DNA was absolutely key to be able to do the mapping.

Harper: Walter, may I just ask at this point: was there any hint of evidence from linkage studies with protein markers apart from the HLA?

Bodmer: No.

Harper: Or was it really straight from DNA?

Bodmer: There was nothing of any use and the HLA stuff was really only to get things going. It was exceedingly unlikely that that would have been anything to do with it. There was even a suggestion of an association with a particular haplotype and so it was really as an exercise to get the other linkage studies going. That's the essential story. Ellen maybe can talk more about how we then further pursued the question of trying to find the gene, which was a collaborative study and which was helped actually by finding a patient who Gareth can talk about that turned out to be a very mild case of polyposis with a rather long deletion in the region that overlapped where we knew the polyposis gene was. Arguably, that patient was probably the first case of polyposis that was actually diagnosed by the molecular technique before the gene itself was found.[94] The gene was actually found by two American groups independently and they just had the luck of the draw that they had a smaller deletion than we did. As soon as the gene was found it was possible very quickly with the resources we had at hand to find mutations in it. I hope Robin Phillips won't mind my saying that I think the surgeons at first were extremely unwilling to accept that a mere laboratory scientist might be able to detect FAP more easily and more securely than they could. I once remember being asked, 'Don't you have to be careful in case the genotypes change with time?' [Laughter]. Anyway, maybe I should pass it on to Ellen Solomon.

---

[93] Solomon *et al.* (1987).

[94] Sir Walter Bodmer wrote: '... there really is no reference for this as I am not sure that case was ever published at all … the outcome of our later molecular mapping work [was] described in Varesco *et al.* (1989)'. Note on draft transcript, 9 March 2013.

Figure 13: Professor Ellen Solomon.

Solomon: I'm going to pedal backwards just a little bit to the early 1970s and the patient with the 5q deletion and how extraordinary that was. In parallel, Knudson, of course, had published his work on loss of heterozygosity (LOH) in familial tumours and producing retinoblastoma, and Ray White then published an extremely seminal paper showing that you got LOH in retinoblastoma.[95] So it became very clear that with something like FAP – a clearly dominant disorder – one could ask the same thing: as to whether the tumours in non-familial cases sustained loss of heterozygosity. So at the same time that the linkage was being done at the ICRF, we looked for LOH in FAP tumours and indeed there was linkage, as we now know, on chromosome 5. So it was a double-pronged approach to confirming that locus and, I think, one that has stood the test of time very well for many of the tumours.

Bodmer: Of course, that fed into the Knudson hypothesis.[96] You mentioned Al Knudson earlier, he really established the idea that the genetic mutations that gave inherited susceptibility in the germline would also be found somatically.

---

[95] See Knudson (1971).

[96] Dr Alfred Knudson summarized the principle of his 'two-hit' theory of cancer tumour formation as follows, in 2005: 'Dominantly heritable cancers of several types were known and seemed to promise real "cancer genes". It was clear that inheriting one of these genes was not sufficient for tumor formation. There was a problem with the mechanism of penetrance,' and he explained the limits of his theory, 'Two genetic "hits" could not explain the most important category of cancer, the carcinomas. However, in some instances they could explain the origin of benign precursors to these carcinomas, which may yet be shown to play a role in all carcinomas.' Knudson (2005), quotes from pages 7–8. See also, for example, Devilee *et al.* (2001). See also note 9.

That was a very important conceptual step forward to see that this hypothesis was true also for common cancer like colorectal cancer. And just a very brief comment, if I may, I used to show a picture we had of a young girl's chromosomes, which had the deletion in, in all my popular lectures on genetics and how we mapped polyposis and so on. I was giving a lecture – I think it was possibly in Chester, it was certainly in Wales – and I showed this picture and a lady came up to me afterwards and she said, 'That's my daughter's chromosomes you've just shown.' She was a teacher. It was as a result of that, because I think the girl hadn't been explored further, I urged her to get in contact to make sure that she was followed up. And she was.

Harper: I should say, Walter, that Chester is actually on the English side of the border. [Laughter]

Evans: In fact, if you're Welsh like me it's still legal to shoot me with a bow and arrow after midnight if I'm within the walls of Chester. [Laughter]

Bodmer: I'm well aware where Wales is, but if you go and talk in Chester you're quite likely to get a lot of people from Wales.

Harper: Very true.

Evans: So, yes, that girl is a fascinating case, especially in terms of genotype/phenotype correlations. She obviously has a total deletion of her *APC* gene but she had very mild disease. On her first screen, no one could find any polyps. She has gradually developed polyps and I would say is in the bottom 10 per cent of affectation with polyps. So also, anecdotally, she was in the CAPP1 study and her mother was convinced that the aspirin had worked and in fact she did have a few polyps and they disappeared.[97] We didn't see any at the next screen. So she's certainly been a case in point in terms of FAP and the study of FAP. She'll be in her late thirties now.

---

[97] CAPP (Colorectal Adenoma/carcinoma Prevention Programme) 'is a programme of genetically targeted trials', formerly known as Concerted Action for Polyp Prevention. CAPP1 started in 1993 with the participation of carriers of FAP in 34 European centres trialling the effect of 600 mg aspirin and/or 30 g resistant starch. Aspirin was shown successfully to reduce polyp size and therefore reduce the risk of cancer development. CAPP2 similarly trialled aspirin and starch preventative measures for carriers of HNPCC and ran from 1998 to 2007, with follow-up continuing until at least 2017; http://www.capp2.com/ (visited 28 August 2013). See comments from Sir John Burn on page 81.

Figure 14: Greenspond (near Wesleyville), Newfoundland, 2005.

Bodmer: Could I just add briefly to that because I think it's interesting taking us further ahead. Subsequently, a number of other gene deletions were studied, I think largely in a study that Oliver Sieber did with Ian Tomlinson in which we were involved and generally showed that when you had the gene deleted you had mild disease.[98] And that was a very interesting observation because it showed that the mutations which are either missense and truncating had effectively had a dominant effect in the heterozygote. If you just knock the gene out, you don't get sufficient effect from haplo-insufficiency. So it shows an interesting interaction between the clinical observations on sometimes only one patient and some of the genetic correlates.

Harper: I'd like now to move across to Lynch syndrome, or HNPCC, it's gone through a variety of names. Perhaps it would be good to ask Jane Green to tell us about her early experience that developed from the perspective of Newfoundland.

Green: I think it really started from the polyposis family, which has what is called the attenuated phenotype of polyposis (AFAP). This very large polyposis family, which has a founder effect with seven families, 200 affected people, that

[98] Sieber *et al.* (2002).

we have completely joined, is important in that regard.[99] I was studying the first of these AFAP families from the north-east coast and travelling to review records in the old Twillingate Hospital first, and then there was a branch of the family that was further west – not far by sea but by road some distance – and I went to see the records of that family in a hospital called Botwood. There was a young family doctor there whom I had known because she had just graduated from medical school and she was very interested in the follow-up of the AFAP family. This was 1989 or 1990, and shortly thereafter she sent a referral letter to me which said 'Please see another family with AFAP' and this turned out to be one half of the family, later called Family C, which was the family that mapped *hMSH2*.[100]

As with the polyposis family, the critical thing was to determine who actually was affected when they were talking about ancestors, because somebody may have had abdominal surgery for some other reason. Was it the same cancer that was in the family or was it something completely different? So that was why all the records were looked at very closely. I started out from the information about a young woman who had had colon cancer. Her father had died of stomach cancer and his four brothers had all died of stomach or colon cancer. Her father had been 54, the others had been between 29 and 39 and so it was quite devastating to that family. I took the history from her and she'd had two colon cancers but she also had endometrial cancer. As I looked at the other records, the majority of the women had had endometrial or ovarian cancer first and no one had large numbers of polyps in the first records that I reviewed. So very clearly, this was not the same condition that I had become used to, the AFAP. Almost at the same time, a surgeon had spoken to me in St John's and said, 'There's a gentleman upstairs who says "there's too much colon cancer in my family." Could I go and see him?' He had his second colon cancer at 63 –his first colon cancer had been at 38. He also had prostate cancer and he died within a year, but he first gave me all the information that he had collected on his family and put me in touch with his daughter, whom I contacted subsequently, and his wife, so I had access to others in the family. I spent many hours on roads in Newfoundland going to different small communities and talking to people

[99] See Green (1995), in particular chapter four; Clinical and genetic screening in a family with atypical familial adenomatous polyposis, pages 194–233. See also Spirio *et al.* (1999).

[100] See page 39. See also Appendix 3, on page 97 for a reproduction of the 'Family C' pedigree from Green (1995).

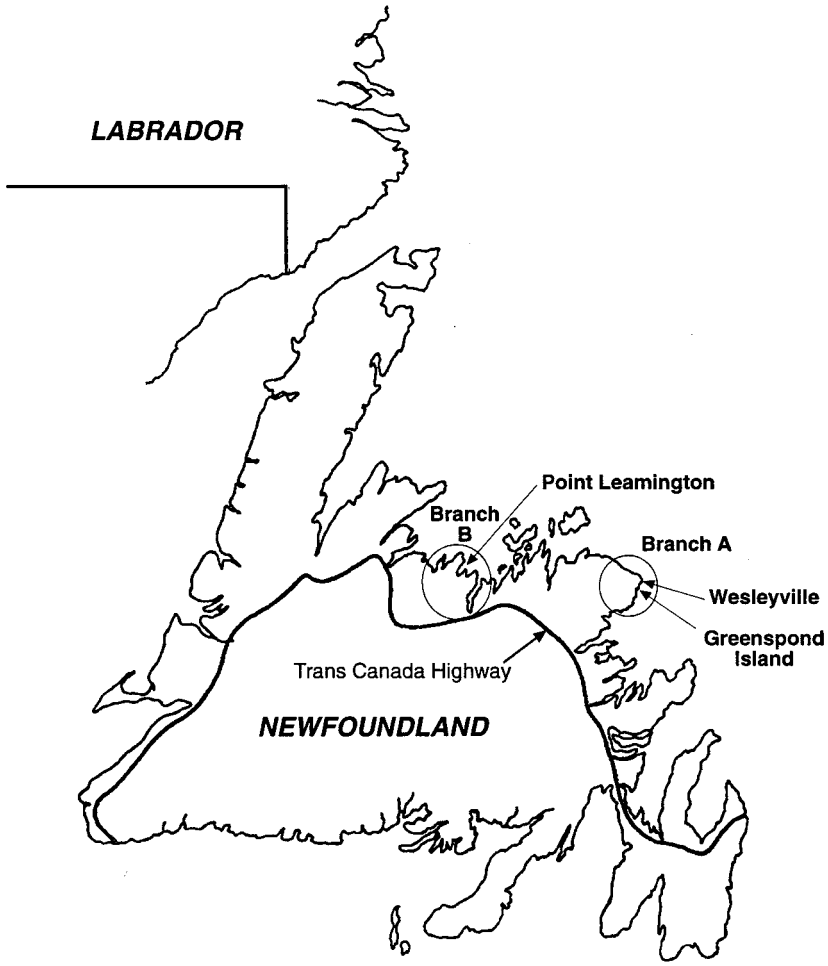


Figure 15: Geographic location of two branches of a Newfoundland HNPCC family. The present-day Trans Canada Highway shown in this illustration was completed in 1965.

in their homes.[101] Every time somebody said, 'I'll speak to my grandmother because she knows more of the history,' or 'You need to know about that other part of the family' and they would contact them. Even before the days of ethics

[101] See Green (1995), in particular chapter five; Development of a screening program for hereditary non-polyposis colon cancer, pages 234–85. A popular account of Jane Green's research and its impact in the international cancer genetics research community is given by Waldholz (1997), in chapter ten; Ishmael's tale, pages 148–64.

concerns, people wanted us to get the full picture. They knew there were other people that could help with the family history. The gentleman, who was from Wesleyville, told me that one sister had two colon cancers and had died in her early 50s; the other sister had had endometrial cancer.

As I put the pedigrees together they were very, very interesting because, as Pål said, there was very little about endometrial cancer in terms of Lynch syndrome at the time. This wasn't polyposis – it fitted best with Lynch syndrome but the endometrial and ovarian cancers were striking in these two families. Now it turned out they were the first two HNPCC families I had seen but they also both came from the north-east coast, one from a more easterly area that had been settled first in the late 1600s where there were ship builders, and master mariners, who did go westwards along the coast. The second community was westward along the coast and I had suspected from quite an early time, even though there were no names in common at that point, that they might be related. It was two years before I went to the community of Moore's Cove near Fortune Harbour, about 150 miles west of Wesleyville, and happened to see the proof in 1992.

After talking to a woman in Moore's Cove whose father had died at the age of 29 of colon cancer, and he was part of the family of the first proband, her husband finally came inside. The fishermen tended not to come in and talk to those like myself who were not originally from Newfoundland – and he said, 'Now she must have a cup of tea before she drives home.' Not knowing quite what to say to me he brought the Bible for me to look at. The Bible had nothing written inside the front cover; but it did have a sheet of paper inside the back cover, which was the marriage certificate of his wife's great-grandmother and it said, 'Julia Ann T… of Wesleyville, married to John W… of Point Leamington.'[102] The gentleman seen in hospital in St John's was a T…. of Wesleyville – I could then go to the archives in St John's and find the exact connection four generations back. So this was one very large family.[103] At that point, the family, then called Family C, was large enough to do the mapping. So it was the clinical picture and the knowledge of the migration patterns within Newfoundland, the settlement and migration over the centuries that gave the clues. The year before, in 1991, I was at the Bar Harbor course,

[102] The surnames of the individuals are anonymous for their privacy.

[103] Professor Jane Green further explained: '… this family with the two probands being third cousins once-removed, both descended from a couple who settled near Wesleyville in 1791.' Comment on draft transcript, 2 April 2013.

in Maine.[104] That was the year that the *APC* gene had just been identified, by Ray White's group in Utah, and so several of the lecturers in that two-week course were talking about colon cancer.[105] Representatives of Bert Vogelstein's lab were there as well as those from the University of Utah's Department of Human Genetics.[106] They, the Utah group, were saying that they were very pleased to have found the *APC* gene and the importance of it. Some people there still said, 'There is no such thing as a HNPCC gene' but others said, 'We just need a big enough family.' Most families were identified as a large family on paper with many people deceased, so I drew on a napkin what I knew of the Newfoundland family with the two parts that I thought were connected and within six months I was able to confirm that they were. It was at that point that I was asked by Bert Vogelstein and Albert de la Chapelle if I was interested in collaborating and sending DNA samples to their laboratories to attempt to map and clone the genes.[107] Most of the samples we already had collected but we did collect some further samples in the December of that year, when a young man, aged 27, had a new diagnosis of colon cancer. The family called me, and Vogelstein's lab thought that that sample would be very important, so the family

[104] Bar Harbor refers to the campus of the Jackson Laboratory, a not-for-profit, independent genetics research centre which holds a variety of courses and conferences aimed at the international biomedical research community.

[105] Groden *et al.* (1991). Jane Green wrote in her PhD thesis: 'A fortuitous discussion at the short course in Medical Genetics at the Jackson Laboratory, Bar Harbor, Maine in July 1991 with members of Bert Vogelstein's group initiated a collaboration between the laboratories at Johns Hopkins University and the University of Helsinki (with expertise and manpower for mapping and cloning genes, but lacking informative families), and myself (with two well-documented HNPCC families … but without the resources locally to carry out intensive linkage studies).' See Green (1995), pages 477–8.

[106] Dr Bert Vogelstein is Clayton Professor of Oncology and Pathology at the Howard Hughes Medical Institute and Director of the Ludwig Center for Cancer Genetics and Therapeutics at the Sidney Kimmel Comprehensive Cancer Center of the Johns Hopkins University School of Medicine, Maryland, USA. See http://www.hopkinsmedicine.org/kimmel_cancer_center/experts/Laboratory_Scientists/detail/6424146D144F331F200D784A751851DB/Bert_Vogelstein. His laboratory is credited with discovering that the *TP53* gene on chromosome 17 was a key to the characteristics of colon cancer cells. With his collaborators, Vogelstein has also demonstrated the role of *APC* mutations in colorectal cancer and, more specifically, FAP. For fuller details, please see http://www.hhmi.org/research/investigators/vogelstein_bio.html (both websites visited 17 January 2013).

[107] Albert de la Chapelle was the first Professor and Chair of the Department of Medical Genetics, University of Helsinki, Finland, 1974–1997. He is now Professor of Molecular Virology, Immunology and Medical Genetics at the Arthur G. James Cancer Hospital and Richard J. Solove Research Institute at Ohio State University, USA; http://www.cancergenetics.med.ohio-state.edu/2729.cfm (visited 16 January 2013). See also Rowley (2003).

travelled through a snowstorm to provide the blood samples.[108] From that point on, it was a question of working through the linkage and, since it was the 345th marker that demonstrated linkage, it took some time. Most of the linkage studies were actually done in Albert de la Chapelle's lab in Helsinki. That was all very successful but it showed that there were labs who could do the work, but the labs had to have connections to families with available DNA samples and, as Dr Bodmer mentioned, with the clinical information that absolutely confirmed who was affected and who wasn't. So I think that's where the Newfoundland family turned out to be extremely helpful.

Harper: Thanks very much indeed.

Møller: I want to add a little to Jane's story because some of us were very offended that the lab parties examining the family material took too much credit without recognizing the clinical research they benefited from. You [Jane] gave them the whole Family C. Then the ICG-HNPCC group had a meeting in Houston organised by Patrick Lynch, the son of Henry.[109] At that time you had the gene by linkage, but you didn't have the gene itself. So we actually felt it was a historic moment. We rose to our feet to celebrate this moment and we officially named the gene Colon Cancer 1 (*COCA1*). And we thought that was a very funny name to have invented in America. However, others had previously identified the *MSH2* gene taking part in mismatch repair in other species like yeast and, following that path, came to independently identify *MSH2* mutations in humans to cause colorectal cancer.[110]

Harper: Perhaps it's a good point to focus on the interplay between the linkage studies and the candidate genes?

Bodmer: Just to comment on that, Modrich had shown that you got this mismatch repair phenomenon in cancers from colorectal patients and that immediately suggested that the mismatch repair genes were involved.[111] In fact, we were working at the same time, 1993, with Peter Karran at the Clare Hall Laboratories and he had just shown that one of the cell lines that we worked

---

[108] See Waldholz (1997), pages 162–4.

[109] Patrick Lynch is Professor at the Department of Gastroenterology, Hepatology and Nutrition, Division of Internal Medicine, University of Texas; http://faculty.mdanderson.org/Patrick_Lynch/ (visited 17 January 2013).

[110] Reenan and Kolodner (1992).

[111] Parsons *et al.* (1993).

with was deficient in that gene.[112] We were about to make the point that maybe that was the gene for the families when, of course, what was published initially was the linkage to chromosomes 2 and 3.[113] It was the candidate guess that those would be mismatch repair genes because of Modrich's work that led to the identification of *MSH2* and *MLH1* specifically based on that homology with the yeast-paired genes in which Kolodner was one of the key people.[114] I forget which way round it was that the two were discovered. Kolodner was the key person because he knew all about mismatch repair, and Fishel also – they were both on it about the same time.[115] That was a very different story in its way from the FAP where there was no clue to the function, and the function of it actually uncovered the whole role of the WNT pathway in human cancers.[116]

Green: The first paper, in terms of mapping the locus for a colorectal cancer gene, was May 1993.[117] In terms of identifying the gene, the first paper was 3rd December and the second the 17th December, which was extremely rapid.[118] It was exactly because, through looking for the LOH and because by that time the markers being used were CA repeats,[119] what was seen was the result of the

---

[112] For a review of developments in colorectal cancer research during 1993 see Bodmer *et al.* (1994). See also Bicknell *et al.* (1994). The Clare Hall Laboratories are part of Cancer Research UK's London Research Institute, Hertfordshire, north of central London; http://www.london-research-institute.org.uk/research/groups/clare-hall (visited 17 January 2013).

[113] Fishel *et al.* (1993).

[114] Richard Kolodner is Professor of Medicine, Executive Director for Laboratory Science and Technology, New York Office – Ludwig Institute for Cancer Research, and Head of the Laboratory of Cancer Genetics, San Diego Branch – Ludwig Institute for Cancer Research, at the University of California's Institute for Genomic Medicine, San Diego. His laboratory uses 'the yeast *Saccharomyces cerevisiae* to study the genetics of DNA mismatch repair and to identify the genes and pathways that prevent genomic instability.' See http://igm.ucsd.edu/faculty/profiles/kolodner.shtml (visited 17 January 2013). See also Prolla *et al.* (1994) and comments by Sir John Burn on page 57.

[115] Sir Walter wrote: 'The history is complicated as there was a whole series of papers in 1993 first mapping the genes to chromosomes 2 and 3 and then identifying *MSH2* and *MLH1* as the relevant genes and at the same time the Parsons *et al.* (Modrich) paper showing micro-satellite instability in colorectal cancers.' Note on draft transcript, 24 March 2013. See Parsons *et al.* (1993).

[116] See, for example, Logan and Nusse (2004).

[117] Peltomäki *et al.* (1993).

[118] Fishel *et al.* (1993) was published on 3 December and, on 17 December, Leach *et al.* (1993).

[119] Cytosine/arginine repeats.

slippage and, because there were people who remembered yeast genetics, they were able to recognize what the gene could be and, sure enough, the *MSH2* gene was in the midst of the region of linkage.

Bodmer: But it was showing that you had what at first looked like LOH in the cancers from the patients, and Modrich's work, as I recall, that really established that there was the mismatch repair deficiency in cancers from the patients that actually led to the candidate genes being found.[120]

Green: Right, but it was looking for LOH with those markers that allowed them to see that.

Bodmer: Sure. We were doing LOH studies on cell lines at the same time and we had thought we'd found some funny LOH on chromosome 1. Actually, it turned out to be in that cell line because of the lack of MSH2 protein. I even remember the cell line: it was LoVo.[121]

Green: Lauri Aaltonen in de la Chapelle's lab had recognized the same mismatch repair deficiency type of picture, so that contributed as well.[122]

Bodmer: My understanding was that if you looked at the Warthin family,[123] instead of finding colon cancer you tended to find gastric cancers and nobody's mentioned that, maybe Jane knows more about that? The impression was that, actually, the spectrum of cancers that you found changed over the years because of the way they could be treated.

Green: I would agree with that because I could go back probably three generations and find records showing that there was certainly more gastric cancer earlier. There still are a few gastric cancers in that same family but that one sibship in particular with five affected brothers, three of them developed

---

[120] See note 113.

[121] 'This cell line, designated LoVo, represents an *in vitro* model for human colon carcinoma.' Quoted from Drewinko *et al.* (1976), page 467.

[122] Lauri Aaltonen is the Academy Professor for the Tumor Genomics Group within the Genome Scale Biology Research Program and Department of Medical Genetics, University of Helsinki, Finland, and Director of the Centre for Excellence in Cancer Genetics Research at the same institution; http://www.helsinki.fi/biocentrum/groups.htm#aaltonen and http://www.helsinki.fi/coe/cancergenetics/index.html (both sites visited 17 January 2013). See Aaltonen *et al.* (1994).

[123] See note 14.

gastric cancer and two of them had colon cancer, but the daughter had gastric cancer later on as well. So the frequency of gastric cancer has decreased, it was much higher earlier.

Bodmer: The Warthin family was actually not specifically colon cancer, it was said to be a dominant cancer family with a variety of cancers.

Green: Well, if you saw the Family C, the women have about a 69 per cent chance of endometrial cancer, a slightly lower chance of colon cancer and about a 25 to 30 per cent chance of ovarian cancer [Appendix 3]. There are duodenal cancers, there are rare transitional cell cancers but in another founder *MSH2* family there's very, very frequent transitional cell cancers of the renal pelvis, ureter and bladder. Because of these large families, we do tailor the screening according to what is seen in all the records. Whether we call it a registry or not, there are records of every patient that has ever been seen in these families and so if there's a new referral of a family we can go back to the old, old records and tie it together. That helps with both the mutation detection and the clinical features in the families. With *MSH2*, there are also the sebaceous cancers and keratoacanthomas. It's extremely varied presentation.

Bodmer: I thought that Jane mentioned that very interesting question of heterogeneity and it actually interacts with Chris Harocopos, who was involved in the colon cancer group. We actually happened to study a very large family in South Africa that all had the same mutation: *hMLH1*.[124] There were well over 30 cases in that family and the study that was done with quite variable expression – which is now quite a popular thing to do – was to see if you could find modifiers to explain the severity by looking at other polymorphisms. There was some suggestion of that. So I think it's just an interesting thing that when you've got those very large families and there is that variation in severity and type of the disease, there are alternative ways of trying to look. That, of course, is something that's being done in the *BRCA1* and *BRCA2* families.[125]

Harper: I'd like just to discuss one or two of the related syndromes and one in particular which certainly astonished me. If anybody had said there was a recessive form of polyposis or colorectal cancer a few years back, I would have totally refused to believe it. But that is the case and I'd like to ask Julian Sampson here to say a bit about recessively inherited colorectal cancer with polyps.

---

[124] Felix *et al.* (2006).

[125] See, for example, Couch *et al.* (2013).

Figure 16: Professor Julian Sampson (left) and Professor Alan Lehmann (right).

Sampson: The condition *MUTYH* polyposis (MAP) fits, I guess, phenotypically between the Lynch syndrome and FAP that we've been discussing. Our research group in Cardiff hadn't really had a molecular genetic research programme in colorectal cancer but we started to become interested in the possibility of alternative mechanisms underlying polyposis in addition to FAP.[126] I was predisposed to think in terms of different genes causing similar phenotypes because we worked on tuberous sclerosis, which had been considered to be one disease, but we rapidly established that there were two different genes that cause tuberous sclerosis, albeit both associated with dominant traits.[127] I see all the polyposis families referred to clinical genetics in South and West Wales, and one family came along to the clinic in Aberystwyth to see me, referred by a surgeon who thought they had polyposis but wasn't sure. In fact, he was aware that his patient had a number of adenomas – I think he'd only taken out about 12 adenomas over a number of years but more were still present. This person's brother had died of colon cancer in his 40s and he wanted to know was this polyposis or not? It was interesting, there was no dominant family history of polyposis, the family came from a very small village in the Ceredigion region, but in fact their parents had moved there some time previously from, I think, the Manchester area, so I don't recall that we were suspicious that there was any consanguinity associated with this family coming from a very small village. I've brought a copy along of the letter that I wrote after the clinic and obviously it struck me as very odd and I noted that the parents had died of heart attacks

[126] Professor Julian Sampson wrote: 'We had been using molecular genetics for diagnosis of FAP from about 1990 but did not start looking for new genes until about 1999.' Note on draft transcript, 27 February 2013.

[127] See, for example, Povey *et al.* (1991).

in old age and hadn't had any bowel problems and what I wrote was: 'It was almost certain that there is a predisposing gene accounting for the findings in this family. The findings could be consistent with an attenuated form of FAP due to an unusual mutation or with mutation at a different locus altogether.' We were thinking along these lines but, in our investigations, we were then actually rapidly waylaid by the identification of a missense variant in the *APC* gene in the family. About this time I was collaborating with Ian Tomlinson[128] and we were looking at this question of whether non-truncating mutations in *APC* might predispose to colorectal adenoma and cancer.[129] The Ceredigion family had a particular *APC* variant that was causing a lot of difficulty – E1317Q – that Walter will probably remember. So we did wonder whether this family actually had a variant form of FAP initially. But on further investigation we found that a further sibling also had multiple colorectal adenomas and that the E1317Q variant didn't segregate with the colorectal phenotype. What we were then able to do, because I'd seen the affected individuals preoperatively, was to obtain polyps at colectomy. Initially what we thought we'd do was look at the pattern of somatic *APC* mutation in these polyps and see if there was something odd about it and there was because they were G to C transversion mutations. That was something I discussed with Ian Tomlinson and he looked at this data with Jerry Cheadle and I, because we were working on families with unusual *APC* variants.[130] Ian helped to flag it up in our discussions but he didn't seem to think it was quite as interesting as it really was. So Jerry and I pursued this and, similarly to the story that we've heard about in relation to mismatch repair deficiency in Lynch syndrome, we thought that this unusual pattern must really reflect some underlying DNA repair defect. By taking a lead from *E. coli* repair deficiency states we deduced that, in the case of this family, one of the base excision repair genes was likely to be mutated, and we screened those genes and found that this was indeed the case. This family had a defect in a base excision repair gene, *MUTYH*, that was manifesting as a polyposis phenotype that looked really similar to AFAP, and the segregation in the family was consistent with recessive inheritance. Initially we had difficulty finding any other similar families and we just published our findings about this single family, which I think took

[128] See note 4.

[129] Lamlum *et al.* (2000).

[130] Professor Jeremy Cheadle is the Principal Investigator at the Institute of Cancer and Genetics, Cardiff University School of Medicine, where his research focus 'is to identify novel genes that predispose to colorectal adenomas and colorectal cancer'. See http://medicine.cf.ac.uk/person/prof-jeremy-peter-cheadle/research (visited 17 January 2013).

rather a long time to get published.[131] People were disinclined to believe it initially but this was followed up with further studies from Ian Tomlinson and from our own group, collaborating with other clinical genetics centres in the UK and elsewhere, to pick out these families from polyposis registers.[132] I think that many of these families had been wrongly thought to reflect gonadal mosaicism for *APC* in parents, producing a recessive-like or pseudo-recessive pedigree, but it rapidly became clear that this was a significant recessive form of polyposis.

Solomon: Did they have the same mutation?

Sampson: In that particular family actually, the affected people were compound heterozygotes but we know there are both homozygous and compound heterozygous families for a wide variety of mutations now.

Green: Actually, several of our families that we now know have *MUTYH* mutations were what I guess you would call pseudo-dominant in that a parent did have colon cancer but because there weren't pathological records available, we didn't know if there were polyps or not. This was presumably a sporadic colon cancer coincidentally in a family with several children having multiple polyps. So we had expected that they really were FAP until there was the possibility to check for *MUTYH* mutations.

Harper: Julian, can you give an estimate of how common this is in relation to classical polyposis because if it's even the slightest bit common, we've been misleading an awful lot of people with our genetic counselling when seeing isolated cases.

Sampson: I think a lot of these MAP families haven't actually found their way into genetics clinics because of the rather attenuated phenotype and small family size. Within the Wales polyposis register, MAP accounts for about 15 to 20 per cent of the families but the trait is recessive. On the whole these families are small, so they form a much smaller proportion of the affected patients. Many other registers actually have an even smaller proportion than that. The question is really, 'Where are these patients?' One of the things that's become apparent with population studies, where you can very easily investigate the two commonest north European MAP-causing alleles in case control settings, is that really a lot of these patients don't present with polyposis but can present just with colorectal cancer, or a very small number of polyps. The overlap with

[131] Cheadle and Sampson (2003).

[132] See, for example, Enholm *et al.* (2003).

Lynch syndrome is rather more than we initially realized. We've also looked at non-colorectal and non-GI cancers in these MAP families and certainly they have an overrepresentation of other tumour types, including some of the very rare skin tumours also associated with Lynch syndrome.[133] It's not uncommon, probably it's as common a cause of colorectal cancer as FAP used to be before it was so successfully treated surgically but it's underascertained genetically.[134]

Harper: Has it been found in many countries around the world?

Sampson: In most places. I don't think there's a lot in the eastern part of Asia, so the Japanese don't seem to be able to find very much, and the Koreans I don't think can find very much either.

Green: I'm just curious as to what you've seen as far as other cancers because we have a number of MAP families in Newfoundland. We happened to do a population-based study in between 2000 and 2005, when these *MUTYH* mutations were identified, so we looked for that in everybody that we didn't have another genetic cause. There were some suggestions in the literature of possible renal cancer as one of the cancers and I've never seen anything else since. So are there other cancers we should be looking for in those families?

Sampson: I don't think so really. We know there is a risk of duodenal cancer, but the risks of other cancers really seem to be small, although statistically a few are elevated it is really very marginally and wouldn't warrant any special screening. It really is a GI disease.

Harper: Alan Lehmann's working from the DNA repair end and meeting up with all these clinical syndromes. How do you view it from your perspective?

Professor Alan Lehmann: I should say that I'm neither a clinician nor a cancer geneticist; I'm a molecular and cell biologist. I've been working on DNA repair disorders for many years and will give a view from out of the circle for a little while. One of the first genetic cancer-prone disorders for which a molecular basis was identified was xeroderma pigmentosum (XP), and that was way back

---

[133] Vogt *et al.* (2009).

[134] Professor Robin Phillips wrote: 'In 1918, J P Lockhart-Mummery performed a prophylactic colectomy on a female patient, and an ileosigmoid anastomosis, and she lived 20 years before dying of cancer in the remaining sigmoid colon. The era of prophylactic surgery for FAP really started post war with the first colectomy and ileorectal anastomosis (a prophylactic operation to prevent colon cancer) taking place on December 8th 1948.' Note on draft transcript, 5 April 2013. See also Granshaw (1985), pages 347–52, Ms Kay Neale's comments on page 20, and in note 63; and Dukes (1952), in particular pages 302–3.

in 1968 by James Cleaver who is actually British although he did the work in the USA.[135] He showed that XP was caused by defective DNA repair. Shortly afterwards, with regard to ataxia-telangiectasia, which is one of the chromosome breakage disorders, Malcolm Taylor came from David Harnden's group in 1973 down to our lab in Sussex to look at a number of disorders.[136] Together with my colleague Colin Arlett, he showed that ataxia-telangiectasia cells were sensitive to ionizing radiation, again pointing to a defect in DNA repair associated with a cancer-prone genetic disorder.[137] Ataxia-telangiectasia together with Fanconi anaemia and Bloom syndrome form the so-called chromosome breakage disorders.[138] For all of those, there were indications way back in the 1960s and 1970s that there was an association of defective DNA repair with chromosome breakage and with cancer, indicating linkages between chromosomes and cancer. Of course now there are many other DNA repair disorders, many, but not all, of which are associated with cancer proneness. DNA mismatch repair disorders are some very important examples, which really, I think, moved DNA repair from somewhere on the periphery right to the centre of carcinogenesis. I just want to ask a point, it may not be directly relevant to this discussion, but is there any explanation why with mismatch repair deficiencies – both the *MSH2*, *MLH1* and the *MYH* types – is there this predominance of colorectal cancers when, if you were just going from the basic biology, you would predict cancers would be found in every organ of the body?

Evans: Is it possibly because those cells are turning over very much more quickly in the colon and rectum and in the endometrium, you're getting much more rapid turnover of those cells than in many of the other organs that are at risk?

---

[135] Cleaver (1968). In 1968 James Cleaver was Assistant Research Biophysicist, then Assistant Professor of Radiology at the University of California, USA; http://cancer.ucsf.edu/people/profiles/cleaver_james.3557 (visited 18 January 2013).

[136] For definitions of ataxia-telangiectasia and xeroderma pigmentosum, see Glossary pages 103 and 104. In 1973, Malcolm Taylor worked at the Department of Cancer Studies, University of Birmingham; note on draft transcript, Professor Alan Lehmann, 26 February 2013.

[137] Taylor *et al.* (1975). Professor Alan Lehmann wrote: '[Dr Colin Arlett] was group leader in cell biology and I in molecular biology. We worked together very closely for 25 years' [at the School of Life Sciences in the University of Sussex]. Note on draft transcript, 27 February 2013.

[138] Professor Alan Lehmann wrote: 'Cytogenetic studies revealed increased chromosome aberrations (e.g. breaks, exchanges, translocations) in cells from three highly cancer-prone genetic disorders: ataxia-telangiectasia, Fanconi anaemia and Bloom syndrome. These are referred to as the chromosome breakage disorders. The chromosome abnormalities are now known to result from mutations in various genes involved in the cellular responses to DNA damage.' Note on draft transcript, 26 February 2013.

Lehmann: And skin, skin cells are turning over, perhaps not quite as rapidly, but very rapidly.

Sampson: One strong possibility, I guess, has got to be that the mutational load in the colon is likely to be significant, and significantly different to other organs because of the microflora in the large bowel. I wanted to mention one other thing that I haven't mentioned in relation to the *MUTYH* research which might be interesting from a historical point of view. This is just the nature of the collaboration for the functional work. In genetics, very often when you identify a gene by positional or candidate means, it lands you in an area of biology that you know nothing about and of course we, i.e. our group, knew nothing about DNA repair. Actually, the human *MYH* homologue wasn't really being functionally studied at that time at all. I think it's a difficult protein and we tried to express it ourselves and failed. So I contacted a collaborator, but did this by internet, which was the first time I had established a collaboration not by face-to-face contact but by simply surfing on Google and looking to see who knew about *E. coli* base excision repair, and Sheila David, who was in the Department of Chemistry in Utah, came up as one of the hits.[139] So I was able to go and look at her lab, and nowadays all the labs have the photos, and you can actually see their social outings together. And she looked very nice; you know, she had sort of a woolly jumper on and obviously was very relaxed. And I thought, 'This looks like the sort of person you can phone up and talk to.' So I did. I just phoned her up and said, 'I see you work on this gene.' And she said, 'Oh yes.' I said, 'We've got a disease for it, a human colon cancer syndrome.' She was very, very excited because NIH [US National Institute of Health] was about to remove her funding [laughter] because they'd been on at her for years that she had to be more disease-focused and link her work into health in some way. As a result, she was really delighted and it boosted her career. I see she's subsequently moved to a Chair in California, which I'm sure was very nice. [Laughter] Although we had a very productive collaboration, we've never met.[140] It really was an internet-age collaboration.

Bodmer: Just two differently related comments on this last point. It's very important to distinguish the dominant from the recessive things. The *MYH* mutations are effectively recessive even though you get compound heterozygotes.

---

[139] Sheila David was Professor of Chemistry at the University of Utah until 2006; http://www.chem.utah.edu/faculty/david/david.html, before her appointment at the University of California, Davis, also as Professor of Chemistry; http://www.chem.ucdavis.edu/faculty/cf-info.php?id=81 (both web pages visited 18 January 2013).

[140] Al-Tassan *et al.* (2002).

The mismatch repair gene mutations are clearly dominant and they are very different. I don't think one can say one understands why, first of all, you don't get the Lynch syndrome mainly in the colon, you get it in many other things too. I mean, you could ask the question, 'Why don't you get that breadth of things in the *MYH* situation?' But I think it's fairly different when you have a recessive and intrinsically increased mutation rate. In every cell is a totally different situation, which is what you have with all the well-known recessive defects. Alan Lehmann was talking about the situation when you have something dominant. Now my own view is that actually in the HNPCC, the mismatch repair is nothing to do with the increased mutation rate in the cells; it's probably something to do with the effect already in the heterozygote, possibly then in the homozygote on apoptosis. That's a point of some discussion because it's quite unusual to find the repair genes mutated somatically. But the question I would have on the *MYH*, which has always puzzled me, is how either of those particular variants in recessive or compound heterozygotes give you the *MYH* syndrome? It struck me that there was a discrepancy between what you'd expect from the frequencies in the population, just from population studies, and what you actually find. That suggests that maybe you're not actually picking up most of the cases because they're below the radar screen in terms of severity, and I wonder whether you have any comments on that?

Sampson: I think it's absolutely true and the only way that you do pick these cases up is by genotyping colorectal cancer populations. That's been done and it probably accounts for 0.5 to 1 per cent of all colorectal cancers – it's not a large percentage. But many of those cases don't have the sort of phenotype that would flag them up to a genetics department.

Bodmer: Are they milder cases of colorectal cancer? Are they essentially mainly found as Dukes' A or possibly Dukes' B?[141] When they get cancers, are they less severe cancers?

Sampson: I think that's an interesting question. I don't think that's been fully resolved but certainly the prognosis seems to be slightly better for *MUTYH* bowel cancers than sporadic colorectal cancers. I think there's only one good published study, which was in *JNCI* about a year ago.[142]

---

[141] Dr Cuthbert Dukes' method of classifying rectal cancer related to how much the disease had spread: A (limited to the wall of the rectum), B (spread to extrarectal tissues) and C (present in regional lymph nodes), officially called Dukes' A, Dukes' B and Dukes' C. See Dukes (1932). See also note 22.

[142] Lynch and Lanspa (2010).

Bodmer: There's another feature of the HNPCCs because of all the mutations you do get – that's a suggestion that we made many years ago but probably still holds up – they actually have a slightly better prognosis because of the immune response.

Sampson: And the tumours from MAP patients have a lymphocyte infiltrate very similar in appearance to that seen in HNPCC.

Bodmer: Which could account for better prognosis.

Møller: I will add to the arguments here that the only way to find MAP is to test the incidental cancers, because you avoid the definition of a dominantly inherited syndrome and you escape the definition of polyposis. Also, people are using the concept of population prevalence, as Jane mentioned, and we have large areas of very ancient inbred populations in Norway, Julian has in Wales, Gareth has in Manchester and John Burn would have said he had in Northumbria. So the concept of population prevalence is, to me, fading in the shade. We have to consider mean figures for population prevalences of genetic markers with caution. The other question was: Why just colon cancer? Why didn't we ask why *BRCA* mutation carriers only get breast cancer? To me, this is about tissue differentiation. Some tissues have inactivated their safety systems if the major system fails. What we are seeing is that some organs are dependent on one system only and, if that fails, they don't have a reserve system to be activated. That is so obvious an explanation to me and, until it has been proven false, then there's no proof for any other explanation. I'll stick to that.

Evans: Very briefly, because it's very relevant, I think that one of the things that we've forgotten is that Lynch syndrome can be recessive and that Turcot originally described a family which was almost certainly a mismatch repair homozygote family, and in particular *PMS2* which is the least penetrant of all the genes, is highly penetrant when it's in the recessive form.[143] You see these families with devastating early-onset bowel cancers, brain malignancies and leukaemias, so you see the whole range of malignancy in early childhood and early adulthood, along with some other things like café-au-lait patches which means that families have sometimes been misdiagnosed with NF1, neurofibromatosis type 1, so it does show that recessive spreads a bit further than *MYH.*

[143] Turcot *et al.* (1959). *PMS2* is a mismatch repair gene.

Harper: I'm reliably informed that shortly we will have John Burn at the end of a phone.[144] The next section of this seminar is devoted to more applied aspects of clinical cancer genetics. Shirley Hodgson and then Gareth Evans will lead us into the evolution of cancer genetics services from perhaps a rather wider perspective than just the colorectal side, but thinking of clinical cancer genetics services as a whole. After that, it will be good to have some discussion on the different roles of various professionals in this.

Hodgson: I was thinking about how to encapsulate what clinical cancer genetics is. It's the sort of thing that people at cocktail parties come up and say, 'What do you do?' You wonder how to explain. I then thought, you can divide it up into a number of different aspects. First, there was a traditional aspect that I'll just briefly allude to, which is ascertaining people who have a family history of, say, bowel cancer, and trying to work out from that what their cancer risk is, and then trying to work out whether or not screening or other prophylactic measures might be appropriate. That is what Joan Slack set out to do in the Family Cancer Clinic in London in the 1980s with Vicky Murday, based on a polygenic theory of colorectal cancer susceptibility.[145] That's certainly the bread and butter of what we do in the clinics now. Then there's the conventional genetic counselling for Mendelian genetic conditions, including genetic testing for confirmation of the diagnosis, predictive testing for relatives of somebody with a known mutation, and identifying other cancer-predisposing conditions, such as people with Cowden syndrome. Then there's the question as to whether you should be actively ascertaining the relatives of those affected people who may be cousins and distant cousins of the proband, and all the issues that we know about, including confidentiality, and who you disclose results to, and how

---

[144] Professor Sir John Burn was unable to travel to London because of adverse weather conditions in Newcastle and had to participate in the meeting remotely by telephone.

[145] Dr Joan Slack was a Consultant in Clinical Genetics and Senior Lecturer at the Royal Free Hospital and School of Medicine's Department of Clinical Genetics. Ms Christina Harocopos wrote: 'The clinics were initially set up at the Royal Free Hospital until appropriate clinic space could be found at St Mark's Hospital.' Note on draft transcript, 17 March 2013. See also Houlston *et al.* (1990): 'In 1986 a Family Cancer Clinic was opened at St Mark's Hospital as part of the North East Thames Regional Genetics Service for relatives of patients with colorectal cancer. The clinic was supported by the Imperial Cancer Research Fund and publicized in the national press. Clear guidance was given that screening was available for first degree relatives of patients who had developed colorectal cancer before the age of 45 and members of families in which multiple cancers had occurred.' Quote from page 366. The Family Cancer Clinic is still screening, treating and counselling people at St Mark's Hospital; http://www.stmarkshospital.org.uk/family-cancer-clinic (visited 18 January 2013).

you should ascertain the at-risk relatives. That, of course, leads into questions we discussed a little earlier, which are the ideas of establishing a registry which would then be able to organize the ascertainment of people at risk, recalling people for screening, and so on. Setting up such registries is something which isn't really the remit of a genetics department, but it is no-one else's remit either, and obviously our work would lead into the need for a registry. Then there are the aspects of multidisciplinary clinics which I'm sure Eamonn will talk about, for multisystem diseases like VHL disease and so on, where you need a number of different professionals to look after and arrange surveillance for the affected people, as in the wider world; on the whole, medical clinics only deal with one system at a time. So it's very helpful if individuals with these genetic conditions can be seen by a number of different clinicians at the same time. Then there's the problem of how to try and ascertain families who are not aware of the genetic implications of a family history of cancer, and who are often not ascertained for genetic counselling, or for cancer susceptibility. There are a number of studies about this which have been done in ethnic minorities funded by Macmillan, in which I was involved – a study of whether you should try and be more proactive in ascertaining people from ethnic minorities with a family history of cancer where they're not used to seeing geneticists, and also addressing other aspects of how to deliver this kind of service.[146] There is the question as to whether much genetic counselling in family history clinics could be done by clinical geneticists or whether it could be done by counsellors or nurses. Or should it be done in other ways? Would telephone counselling be a good way of doing this? So there are a lot of questions in terms of service delivery.[147] There are also the broader aspects: the most cost-effective strategy for ascertaining people at increased cancer risk; and deciding at what level of risk you should offer screening, which requires a dialogue with healthcare providers in the National Health Service. I'm sure Gareth will talk about that, because if you ascertain families whose risk of cancer is above a certain level, there needs to be a decision regarding who should be screened, how much that would cost and what the cost-benefits are. Clearly, there is a broad range of things that we find ourselves dealing with as clinical cancer geneticists and, as geneticists, we may not perhaps be appropriately trained to some extent to deal with all

---

[146] See, for example, Gulzar *et al.* (2007).

[147] Professor Shirley Hodgson wrote: 'A study I did assessing clinical cancer genetics services in different European countries in the 1990s indicated that such services were much more developed in countries where counsellors and nurses were allowed to participate in such service delivery.' Note on draft transcript, 10 October 2012. See Hodgson *et al.* (1999).

those different aspects. Of course, in the future we are going to be walking into another minefield in terms of other genes of very low penetrance, which people are going to find out about in genome-wide association studies, and testing for genetic variants, which is now becoming available commercially, so that in the future such tests are going to give us information about small alterations in risks.[148] So that's the background thinking and I just wanted to say a small amount about the way that colon cancer susceptibility counselling started in the UK. I know that Chris [Harocopos] can say more about this. Vicky Murday was very much involved with the first clinics that were set up with Joan Slack in 1986.[149] This arose out of the work that Eileen Lovett had done many years ago when she looked at the families of patients at St Mark's Hospital with colon cancer and found that their relatives had a higher incidence of colon cancer than the general population.[150] The degree of increased relative risk was further analyzed by Joan Slack with Vicky Murday and Richard Houlston,[151] and Chris Harocopos was also involved, in trying to quantify the increased risk of colon cancer in relatives of affected patients with different degrees of family history. From that grew the idea of having a clinic which would take people who had a family history of colon cancer and assess their risk on the basis of a polygenic model, if they didn't have an autosomal dominant family history, of course. The Family Cancer Clinic offered colonoscopies to people who had more than a one-in-ten risk of dying of colon cancer, and faecal occult blood testing for the less strongly predisposed individuals. They then went on to audit the management of those families and found really that their findings confirmed that their first premise was correct. These people were at increased risk and they were indeed finding more cancers and polyps in this group than you would expect in a general population. So it seemed that they were barking up the right tree. That led to a flourishing clinic at St Mark's Family Cancer Clinic with a lot of

---

[148] Professor Peter Harper wrote: 'Regarding genome-wide association studies, the early ones, from around 2003 up to around 2008 – widely used in both the US and UK – were rather disappointing, largely because the markers were often too far from the relevant genes, but also because the statistical tests used allowed many false positives. Recent ones have shown many more robust disease associations, though in many cases the associations are quite weak.' Email to Ms Emma Jones, 16 April 2013. See, for an example of an early genome-wide association study, Klein *et al.* (2005). For analysis of genome-wide association studies and discussion of their future relevance to clinical practice, see Hirschorn and Gajdos (2011).

[149] See note 145.

[150] Eileen Lovett, surgeon, was a Research Fellow at St Mark's Hospital in 1975. See Lovett (1976).

[151] See note 145.

support from Walter Bodmer and the ICRF.[152] Then I came in when Vicky left and started to run the clinic from there.[153] Of course, we got a lot of experience from it too in terms of finding families and being able to ascertain new families with different conditions who came through the doors. We could also audit the pick-up of polyps and cancers from people at different degrees of risk. In about the early 1990s I know that Bruce Ponder started a clinic in London, which was mainly, I think, more concerned with familial melanomas.[154] Then it really evolved very rapidly and has become what it is today.[155] But when it first started, there were very few referrals to genetics clinics for a family history of cancer and now it's certainly nearly 50 per cent of all referrals, which of course has turned genetics services upside down.

Evans: To continue the story and I'm perhaps one of the first bespoke cancer geneticists, although it sounds like Vicky and Shirley were fairly bespoke as well. I was brought in, at the beginning of 1990 in Manchester, to set up cancer genetics services because there was really nothing there.[156] There was the odd patient being referred, so I went round the country and saw what was available: Joan Slack set her clinic up in 1986; Bruce Ponder's clinic was actually at the Royal Marsden, and he'd set this up in 1987, and Tony Howell set up a breast cancer family history clinic in Manchester in 1987.[157] These were largely clinics

---

[152] See page 28.

[153] See page 29.

[154] Sir Bruce Ponder was CRC Fellow and Senior Lecturer in Medicine, Royal Marsden Hospital (1980–1987), then Reader in Human Cancer Genetics and Head of the Section of Cancer Genetics (1987–1989), University of Cambridge. He has been the Director of Cancer Research UK's Cambridge Research Institute since 1989 and is also the Li Ka Shing Professor of Oncology, University of Cambridge. He was invited to this seminar but was unable to attend. See *Who's Who 2012*; http://ukwhoswho.com/view/article/oupww/whoswho/U31108 and Ponder, Sir Bruce (Anthony John); http://www.cambridgecancer.org.uk/about-us/directors-foreword/ (visited 16 October 2012).

[155] The Royal Marsden's Cancer Genetics Unit 'offers services to individuals and families concerned about a risk of inherited cancer'; http://www.royalmarsden.nhs.uk/consultants-teams-wards/clinical-units/pages/cancer-genetics-unit.aspx (visited 25 January 2013).

[156] At the time, the organisation was the Central Manchester Healthcare NHS Trust; http://www.cmft.nhs.uk/your-trust/our-history.aspx (visited 13 March 2013).

[157] Professor Gareth Evans wrote that Bruce Ponder's clinic was based at the Royal Marsden in London and that it was 'mainly for breast and ovarian cancer predisposition'. Note on draft transcript, 21 February 2013. Anthony Howell is currently Professor of Medical Oncology at the Manchester Breast Centre, University of Manchester, and works closely with Professor Gareth Evans; http://www.breastcentre.manchester.ac.uk/Tony_Howell/Professional_biography (visited 20 February 2013).

that were set up for research, to get the families, and to research the families. Very quickly after 1990, which I think was a fairly pivotal year with discovery of genes, there started to be publicity around inherited cancer, and the public became more aware of it and we started to see referrals coming in.[158] To some extent the amount of referrals was based on whether there was a service, so if you didn't have a service you didn't get referrals. So we, in Manchester, saw an exponential rise in referrals for breast cancer between 1990 and about 1995, and it's pretty much plateaued since then.[159] We followed the same exponential referral pattern for bowel cancer, which started in about 1994/95 and peaked in about 2000. I think virtually all parts of the country have seen the same exponential referral patterns with it plateauing off, except for parts of the country that set things up a bit later. It's important to talk about the role of all the people in the service. Most centres will have a pretty much full-time cancer geneticist who does very little else, although there are examples of centres such as Birmingham, I think, who have a more regional aspect to their referral and working methods so they're not necessarily as specific.[160] There are centres that will have two, or two-and-a-half, cancer geneticists. But the role of the genetic nurse specialist, the genetic counsellor, which was developed through the courses in Manchester and Cardiff,[161] deals with an enormous amount of the work that goes on: the initial contact with families, constructing the pedigrees, etc. Most centres have counsellors that are pretty much specifically cancer genetics although again there are those that mix and match and do a bit of other genetic diseases. Gradually the services have been set up around the country, so every genetics department has a service. I remember Cardiff really setting up your [Harper's] service from scratch through a very successful research project. Was it Wellcome-funded? I can't remember which. Or it was MRC-funded, one of those.[162] You set the All Wales Cancer Genetics Service up on the back of, basically, a randomized

[158] For newspaper publicity, see, for example, Mihill (1991) and Angler (1991).

[159] See also the work of Professor Gareth Evans' research group at the University of Manchester in breast cancer prevention in connection with the charitable organzation Genesis Cancer Prevention Centre; http://www.genesisuk.org/ (visited 9 April 2013).

[160] West Midlands Regional Genetics Service, Birmingham Women's NHS Foundation Trust; http://www.bwhct.nhs.uk/wmrgs (visited 5 March 2013).

[161] MSc degrees in genetic counselling are taught at the universities of Cardiff and Manchester, for example.

[162] Professor Peter Harper confirmed that his service was locally funded. Note on draft transcript, 9 May 2013.

control trial.[163] It took until about 2000 before the whole country had some sort of cancer genetics service embedded within NHS departments. We don't really yet have a clinical guideline for bowel cancer, although I think it probably will happen. My involvement with breast cancer has been through NICE [National Institute for Health and Clinical Excellence] having a Guideline Development Group for familial breast cancer.[164] Since 2002 I was chairman of this Guideline Development Group and I'm now clinical lead. That group really decides pretty much what should happen around the country in terms of management, in terms of who gets surveillance, who gets MRI screening surveillance, who has access to risk-reducing mastectomy, who should always have access to genetic testing. Now it's only guidance, so it can be ignored, but the idea is to get rid of the postcode lottery of Josephine in Cornwall getting her genetic test while her sister in some other part of the UK doesn't get one.

Harper: John, would you like to comment in terms of, not just the North East, but how you have seen the overall development of cancer genetics services over the past 20 years?

Professor Sir John Burn: I think it's already been picked up that cancer was very much not on our genetics agenda when we were coming into the subject in the 1970s and 1980s. When I set up my consultant service in Newcastle in 1984, I don't think I saw any patients at all. I became involved through Alistair Gunn, who was a very active, well respected colorectal surgeon, who had worked at St Mark's and wanted to get a sense of the FAP world.[165] We got a bit of money from the region to employ Pam Chapman and we also got some money via Walter Bodmer's efforts through ICRF to pay for her, and we started working on FAP. I was actually very rapidly enthused by the topic because I realized we could make such a huge difference. Despite the fact that St Mark's had a national register, as I expected, we found about 70 families, of which only three were on their register because we were obviously so remote. Also, it was apparent to me that in the FAP

---

[163] This unit is part of the All Wales Medical Genetics Service, which provides specialist genetic services to individuals and families with, or concerned about, rare genetic conditions; see http://www.wales.nhs.uk/sites3/home.cfm?orgid=525 (visited 11 February 2013).

[164] In July 2010, the Department of Health requested that NICE prepare a clinical guideline for diagnosing and managing female patients with inherited breast cancer. The draft guideline was issued in June 2013; see http://www.nice.org.uk/cg164 (visited 15 August 2013).

[165] Dr Alistair Gunn died on 24 December 2010. His forthcoming obituary in Plarr's *Lives of Fellows* had not been published at the time of writing; http://livesonline.rcseng.ac.uk/biogs/E001820b.htm (11 February 2013).

Figure 17: Professor Sir John Burn.

world there wasn't a genetic perspective; it was being approached from a surgical perspective, and I was very keen to bring in the DNA markers and get into that side, which you've already, I think, talked about. We set up a very comprehensive service through Pam and through Alistair Gunn; so we actually set up a system of telling people, based on our probability calculation, who should or should not be offered endoscopy and how frequently. I very studiously avoided getting drawn into the other areas of cancer. Obviously, like Gareth and others, I was involved in things like NF [neurofibromatosis] but breast cancer really was fairly minimal, although I did get a bit involved in p53.[166] But it wasn't really until I set up the CAPP studies with Tim Bishop and John Mathers, to start looking at chemoprevention in FAP, that I became much more closely involved with Tim, who I believe couldn't make it to this meeting either, but he's obviously been a leading player in the field for all that time as a genetic epidemiologist for ICRF and CRUK.[167] We had some families in the North East and one in particular called the Durham family, which a GP called Ted Knaggs had described in a paper in the *Journal of Medical Genetics* in 1972,[168] and this was just after Henry Lynch had described 55 cases of colorectal cancer in one family.[169] Essentially we all sort of nodded towards papers like that and said, 'Yes, but we don't really believe it's

[166] p53 is a tumour protein gene, known officially as *TP53,* mutations of which are associated with the development of several cancers. This gene has been mapped to chromosome 17.

[167] See note 4.

[168] Dunstone and Knaggs (1972).

[169] See Lynch and Krush (1971).

genetic'. And it very obviously was a dominant pedigree. We started mapping that with Tim's group in Leeds and we also started working on another family which we found in the Northumberland area. Meanwhile, the international collaborative group on HNPCC led by Hans Vasen was obviously getting going, but I tried to keep out of that because I was trying not to get too dispersed. But then we got sucked into it big time, partly because of these big families that we were mapping and also through Bruce Ponder putting us in touch with Richard Kolodner, who was looking for some samples from an HNPCC family to try out his theory on mismatch repair.[170] So we sent some DNA from two of the families we were working on with Leeds, one of them being our Northumberland family, and that was the *MSH2* family that appeared in Kolodner's *Cell* paper, or one of them.[171]

Harper: John, maybe I could just stop you there because we've had a good discussion earlier this afternoon on the research side and we've moved on now more to the applications.

Burn: Well, it was relevant in a sense to our service because the minute we got that marker, we then kicked into predictive testing in our dominant families generally and meanwhile we'd appointed Fiona Douglas as a consultant and specialist, round about the mid-1990s.[172] We started systematically developing cancer genetics in our clinics like everyone else. I guess my other generic observation was that I, by then, had become very involved with the Cancer Family Study Group of which Tim was the secretary.[173] In 1996 I became the chair of that group and, having just finished the construction of the BSHG along with Peter Farndon and yourself [Harper] and others, it seemed to me that we needed to bring that group closer to the BSHG.[174] So, as chairman in the period from 1996 to 2002, I was mainly involved from an administrative point of view in a sense, or a political view, of getting that group to become the Cancer Genetics Group of the BSHG, in 2000, which of course Gareth and others now run extremely well and it continues to prosper.[175]

---

[170] See note 154 for Ponder and note 114 for Kolodner.

[171] See discussion on pages 39–40 and Kolodner et al. (1994).

[172] Dr Fiona Douglas is now a Consultant in Clinical Genetics at the Institute of Genetic Medicine, International Centre for Life, Newcastle upon Tyne; http://www.newcastle-hospitals.org.uk/staff-profiles/12872.aspx (visited 26 February 2013).

[173] See pages 10–15, and introduction.

[174] Dr Peter Farndon was based at the Clinical Genetics Unit of Birmingham Maternity Hospital.

[175] See Professor Gareth Evans' comments on pages 15–16.

Bodmer: I'd just like to say a little bit from the organizational viewpoint of the role that I was able to play from the ICRF because we'd mentioned the Cancer Family Study Group and that made me aware at least of the amount that could be done – having genetics clinics looking at cancer as an adult thing was not the traditional goal of genetics clinics. So, having seen also what could be done at St Mark's, in the ICRF we thought there was a case for trying to create places where cancer family studies and genetics would be done in association with oncology units. Outside St Mark's, I think the first group that we set up formally was the one that I've already mentioned with the genetic epidemiology unit in Leeds, originally under Ray Cartwright, starting in 1987 and then taken over a couple of years later in 1989 by Tim Bishop when he came from the States. That then grew further. Though the ICRF didn't actually formally provide grants, we felt there was a case for providing some support in a number of places where there was an opportunity to develop cancer family clinics in the way that we've heard. As John's mentioned, one of the people we supported was Pam Chapman in Newcastle, we also provided some support in Cardiff. These grants were generally to fund someone like a nurse, who could be involved in helping with the aspects of the cancer family clinic that went alongside what the genetic consultant would do. In the end, because we'd set up an oncology unit in Oxford, it seemed to make sense to set up something there. That's when George Fraser started a cancer family clinic quite specifically in Oxford, in 1990.[176] There was also some support of Kay McDermot, I think in the Royal Free, and Vicky Murday had moved up to Leeds to be the consultant there.[177] So what we felt we were doing was helping, of course, to set up cancer family clinics in different centres where there was strong oncology. That contributed significantly to the development of this idea. Nick Wright, who became the Director of Clinical Research at the ICRF, was very helpful in discussing these developments, and in the annual reports of around 1991/92, Nick made very specific mention of the role the ICRF was playing in supporting cancer family clinic activities and quite specifically he mentioned in the 1991/92 report that this was a responsibility for the care of patients in that setting, that should be

[176] See note 179.

[177] Dr Kay McDermot succeeded Dr Joan Slack as Consultant/Senior Lecturer for the Royal Free Hospital's Department of Clinical Genetics; see note 145. Dr McDermot wrote: 'Subsequently I moved to Imperial (regional genetic unit at Northwick Park Hospital) as Consultant/Senior Lecturer and have since retired.' Email to Ms Emma Jones, 17 April 2013.

Figure 18: Professor George Fraser.

taken over by the NHS.[178] We'd had a lot of discussion about that and how that could be achieved. As I recall, and I thought you [Harper] might have been involved in this, or John Burn might remember better, there was a group of people who actually gathered together to make the case to the NHS that this should be a provision that was arranged to be throughout the country in an appropriate setting where you can have the family clinic alongside the oncology provisions that were needed to deal with the cancer cases. I'm not sure what happened to that, and then that led to the sort of network that John has mentioned and he can probably comment more because by the time that was going, I was leaving the ICRF.

Professor George Fraser: I have a paper with me which describes the main features of the Oxford Imperial Cancer Research Fund Genetic Clinic in its first seven years, between 1990 and 1996, and the marked increase in patient referrals which occurred during those years.[179] Comments about such large increases have been made in the cases of other clinics mentioned at this seminar. I was told two years ago by a colleague in the Department of Clinical Genetics

[178] Imperial Cancer Research Fund (1992). See, in particular, Wright N A 'clinical research', pages xvii–viii.

[179] Fraser (1999). Professor George Fraser wrote: '36 patients [were] referred in 1990 and 2165 patients [were] referred in 1996.' Letter to Ms Caroline Overy, 12 November 2012.

in Oxford that in 2010 – thirteen years after I had retired in September 1997 – referrals with respect to cancer made up as many as 50 per cent of all referrals to the department for counselling. I started the clinic on 1 January 1990 in collaboration with Dick Lindenbaum, a consultant in the department. I have always been extremely grateful to him for having made it possible for me to join the department in 1985 as an honorary consultant in connection with my employment by the ICRF. Susan Huson, a recently arrived consultant to the Department of Clinical Genetics, was a third member of the clinic at its outset.[180] Sadly, Dick died in April 1992.[181] I then directed the Oxford Imperial Cancer Research Fund Genetic Clinic in collaboration with Susan until my retirement in 1997.

Møller: I would like to mention two very brief examples to bridge a gap between research and today's clinical practice. One is that, once upon a time, I was looking for something and found something else: *MSH6*.[182] The problem with *MSH6* is not that it has high penetrance for endometrial cancer; it's less penetrant for endometrial cancer than *MSH2*. The problem is the lack of colon cancer – if that's a problem – making *MSH6*-associated disease a sex-limited trait, not having complete penetrance and escaping all the clinical definitions of Lynch syndrome because of the skipped male generations.[183] As Patrick Watson – the statistical guy in Henry Lynch's group – always remarked: The Amsterdam

---

[180] Professor George Fraser wrote: 'Dr Susan Huson was a Consultant in Clinical Genetics throughout her time in Oxford [1989–2004].' Email to Ms Emma Jones, 4 March 2013. See also http://www.mangen.co.uk/PersonnelDetail/185.aspx. Dr Huson is a now Consultant in Clinical Genetics to the Central Manchester University Hospitals NHS Foundation Trust; http://www.cmft.nhs.uk/saint-marys/our-services/clinical-genetics.aspx (both websites visited 20 February 2013).

[181] For his obituary, see Sacks (1992).

[182] Dr Pål Møller wrote: 'In the Dutch–Norwegian collaboration we had published that the key clinical information to identify a mutation-carrying family with *MLH1* or *MSH2* mutations, was endometrial cancer. This observation was but reflecting the obvious interpretation of the Warthin family G from 1913, and was among the arguments for ICG-HNPCC to revise the Amsterdam Criteria to include endometrial cancer as affected phenotype (to be known as AMSII criteria). We then set out to look for modifiers of penetrance/expression of *MSH2* putatively determining who might contract endometrial cancer. Because of the biological relation between *MSH2* and *MSH6*, the latter was an obvious place to start looking. We did find no modifying effect of *MSH6*, what we found was that *MSH6* was a major factor causing Lynch syndrome by itself when mutated, but predominantly endometrial cancer.' Note on draft transcript, 22 October 2012. See Wijnen *et al.* (1998; 1999).

[183] See Sjursen *et al.* (2010).

criteria were never meant for clinical practice.[184] We have for years been part of the collaborative networks to find the prostate cancer genes, which were never found because we have looked for them with the concept of one, or a few, highly penetrant dominant gene, or genes, which was a wrong concept. Then we looked into our Lynch families and found that mismatch repair mutation carriers have as much prostate cancer as *BRCA2* mutation carriers.[185] So what do we have to do now? We can't run clinical practice based on the old research terms, we had to go into these families by extended segregation analysis and prospective studies to redefine the penetrance and expression of the mutated genes because the current clinical criteria are based upon outdated research concepts. You cannot determine in advance what to find and look for finding that only. We have to get out of the logical flaw of describing our selection criteria as research findings.

Green: As far as the prostate cancer in *MSH2,* I totally agree. One reason I think this was missed earlier was because so much early death from colon cancer meant that men didn't survive long enough to then have prostate cancer, but we definitely see this now. All our cancer genetics was clinical right from 1982 when the VHL family was referred to the ocular genetics clinic. There was a need there; it was clear. There were six sisters, three of whom were noted to be affected at that time. There was obviously more family history; there was more than just the eye examinations they needed. Therefore it was necessary to get everyone, all the specialists, together to deal with it. Because Newfoundland is also extremely rural, there are very long distances and very small communities so that you can't have your cancer genetics service in each community. It's organized from St John's, the capital, where the main tertiary care hospital is located. But for VHL, then MEN2, MEN1, FAP and HNPCC potential carriers, it was necessary to get their family history, review the records to see who actually was affected, and to find the full details of the cancers seen.[186] This was how the screening was organized. From the first day people were met in their homes to get family history, they were immediately given a letter, a follow-up letter and the screening recommendations. If there was new knowledge then there was

[184] See note 53 for the Amsterdam criteria. Dr Pål Møller wrote: 'They were a research tool to identify a few families to find the genes. Their positive and negative predictive values in clinical settings were never documented; their purpose was to find some mutation-carrying families to study (high specificity), not to find them all (low sensitivity).' Note on draft transcript, 22 October 2012.

[185] See Grindedal *et al.* (2009).

[186] See Green (1995).

another letter. Every time going out to the communities, we went to the rural hospitals or the family doctors in the area to let them know what family history was there. Because if we knew that there was a big MEN1 family and we had four branches, there could be a fifth branch or a sixth branch and we had to make sure that the family doctors in these areas knew about MEN1 if they were in that area. With the atypical MEN1, every Newfoundland family has its own characteristics and if you're in the North East then it's the AFAP and somewhere else the HNPCC. So our aim was to educate local healthcare providers so that they could help in identifying new cases and help in the screening that could be organized. In doing this, the AFAP family was initially recognized as typical FAP because of individuals with hundreds or thousands of polyps. Reviewing the family history and records, there were 93 members affected at that time. A third had only right-sided polyps; a third had less than 100 polyps but it wasn't necessarily the same third; some had as few as 10 at the time of cancer. There were individuals who were screened and had no polyps until they were 46 but now our youngest three, with colectomies because of the number of polyps, have been 10 and 11 years of age. It concerns me when I see literature that talks about attenuated FAP as 'late onset', 'mild', 'lower risk of cancer'. In our family and in the large Utah family that Randy Burt has published about, there is as high a risk of cancer but there is variability in number, age at onset of polyps and their location.[187] As I see it, this variability is the key to AFAP. If you have a small family, you may not see that and you may start screening and think that you should start screening members in their twenties but somebody will have cancer before that. So I think that these large families can be very instructive beyond the location that they occur. What we did was to go out and make sure that the family doctors, the rural doctors, knew what was there and knew how to recognize these families. We also now have what's called the Community Cancer Genetics Clinics so that every person with colon cancer has an option of referral for review of their pedigree so they can be counselled about whether they belong to the group that should have the faecal occult blood test (FOBT) or the faecal immunochemical test (FIT) for family members, or an intermediate screening or the high-risk screening. The same people who were one day dealing with the colon cancer families, HNPCC or FAP, might the next day be dealing with VHL or MEN1, or breast cancer. We don't have enough

[187] Professor Randall Burt is the Senior Director of Prevention and Outreach at the Huntsman Cancer Institute, and Director of the Familial Colon Cancer Clinic, University of Utah. Further biographical details are available at http://www.huntsmancancer.org/research/cancer-investigators/burt-randall (visited 15 January 2013). See also, for example, Kerber *et al.* (2005).

Figure 19: Professor Eamonn Maher.

staff to have separate clinics for all of these cancers. This is a service that needs to provide for those families that have these higher risks – then you can think breast cancer one day and FAP another day.

Harper: We've talked so far mainly about colorectal cancer and a little bit about breast cancer services, but you've brought up some of these rarer, more specific syndromes, including VHL. I'd like to ask Eamonn Maher to say a bit about how the services evolved for that particular condition, at least in the West Midlands.

Professor Eamonn Maher: Probably I should start off by describing the developments in East Anglia. I started in genetics in Cambridge in 1988 and John Yates handed me a paper to say that the VHL gene had just been mapped to chromosome 3 and why don't we study this?[188] Prior to this there had been a very nice paper from Cardiff, with Susan Huson as the first author describing VHL families studied in Cardiff.[189] Like so much of what we've heard today, the initial driver to setting up new clinical services for VHL patients in Cambridge was the fact that we were starting a research study. We were collecting families for linkage studies and we needed to evaluate affected and apparently unaffected members of the family to see whether they were sub-clinically affected. This involved putting the at-risk relatives of the patients through the clinical genetics

[188] In 1988 Professor John Yates had an academic post at the University of Cambridge, subsequently becoming Reader (2001) and then Professor of Medical Genetics (2003). He contributed to the History of Modern Biomedicine Group's Witness Seminar on *Clinical Molecular Genetics in the UK* c.*1975*–c.*2000,* in February 2013, which is scheduled to be published in 2014. See also Seizinger *et al.* (1988).

[189] See note 180. Huson *et al.* (1986).

eye clinic that was run with Tony Moore, then in Cambridge and now based at Moorfields Eye Hospital.[190] We also screened them for kidney tumours and in the first few patients we studied, we detected sub-clinical retinal angiomas and renal tumours and so our radiological colleagues were happy for us to implement a screening protocol similar to that which Susan Huson and others had suggested previously. As we went round the country collecting VHL families, we found that most were not under surveillance and they needed local follow-up and screening and, more often than not, that was done through a local geneticist. So that was my experience of how VHL clinics developed. One other thing I would like to mention, that perhaps hasn't come out yet, was just how exciting at the time everything seemed because there were amazing scientific discoveries being made and at the same time we were inventing new clinical services to try and match up with the scientific developments. Then, the number of people in clinical cancer genetics was quite small, probably just one or two people from each genetics centre, so you'd be able to ring up the person in Manchester, such as Gareth, and swap anecdotes and ask for patients, etc. Talking about FAP, and John Burn will confirm this, for a while ophthalmologists were really critical in the stratification of FAP patients because we were all looking for congenital hypertrophy of retinal pigment epithelium, or 'chirpies' [CHRPEs] as John helpfully put it. That involved setting up special clinics for these patients, or at least putting them through the eye genetics clinics that we had.[191]

Harper: John, do you want to say a quick word about the CHRPEs while Eamonn's brought them up?

Burn: I should insert by the way that Grace Aherne, working with Derek Roberts, used to work with the ophthalmologists.[192] She had a really good handle on all the retinoblastomas so there was some genetic cancer work going on. But yes, when I got into FAP, I was looking for something to work on and

---

[190] See, for example, Maher *et al.* (1990). The clinic in Cambridge was based at Addenbrooke's Hospital. Ms Samantha Lawrence, Moorfields Eye Hospital, wrote: 'Anthony Moore is a Professor of Ophthalmology at the UCL Institute of Ophthalmology. He is an honorary consultant ophthalmologist at the Hospital for Children, Great Ormond Street, London and Moorfields Eye Hospital, London.' Email to Ms Emma Jones, 1 February 2013.

[191] See Hodgson *et al.* (1994).

[192] Dr Grace Aherne was a clinical assistant in the Department of Human Genetics, Newcastle University. Derek Roberts (b.1925) was a Professor of Human Genetics at the University of Newcastle upon Tyne until his retirement in 1990; see Harper *et al.* (eds) (2010), pages 46–7.

we landed on this not very well-realized observation that there was this extra colonic feature of, as I jokingly said to the surgeons, 'little black dots on the back of your eye'. We got lots of people and tested them and demonstrated you could very reliably identify the gene carriers on the basis of that feature in a very substantial proportion of families. In parentheses, my wife never forgave me: I used her as a control in the study and a not very sensitive ophthalmologist told her that if she didn't stop using contact lenses she'd go blind. She blamed me for that for some reason. So we did start to diversify into a broader perspective rather than just looking at colorectal surgical intervention. If I could just say generally on that point: Eamonn picked up a very key point there that we went through phases. In our previous Witness Seminar we talked about how dysmorphology flowered in the 1970s and 1980s, and really overgrew, if you like, as a specialty.[193] Then, at the end of the 1980s and early 1990s, when the capacity to do monogenic diagnosis really started to kick in, that started to change the temperature again. In particular, Gareth and others started to bring in systematic approaches to the big ticket cancers, breast and colon. We saw another change again because the counsellors really started to come into their own. It wasn't necessary to understand all the Mendelian syndromes, you could actually start working on a more standardized care package and screening programme. For the first time it really started making a big difference to patient survival and long-term prognosis. I think that changed the nature again of our specialty in the late 1990s; around about the time the Cancer Family Study Group was transforming itself into more of a service type organization – and that was a big change.

Harper: I think the point you've made John, and the point Eamonn made about this extraordinary time of excitement, partly just because it was so exciting that all the genes were coming out, but also because the clinical studies were such an integral part of that, you really felt that you'd contributed something, it wasn't just a question of handing over a few samples. The labs were dependent totally on getting the phenotype right and then at the same time there was this remarkably short interval between some apparently esoteric study or finding, and then being able to apply it, as with the DNA repair genes. Things sort of leapt from yeast to applications for human patients and that's something we'll come back to in a minute when we're dealing with how perhaps the classical, surgical approaches had to cope with all these geneticists coming in.

---

[193] See Harper *et al.* (eds) (2010), pages 63–8.

Maher: I want to mention two quick things, one of which was the, let's say, inventing of new services, or at least that is how it felt at the time, and how it seemed that we were doing it without a manual. Then Shirley Hodgson suggested that we write a book on cancer genetics which I think was certainly helpful at least for my education![194] In addition, when I moved from Cambridge to Birmingham in 1996 there was a slight change of climate there in terms of service provision so I went from a centre where Bruce Ponder was, and where there was a big interest in cancer genetics and we were almost encouraging referrals, to a centre where there had been this huge increase in referrals and they were thinking, 'How on earth are we going to deal with this?' At least in the West Midlands and probably beyond, Trevor Cole was very influential in the concept of triaging into those that really didn't need to see a geneticist, those who just needed to be offered screening but didn't require formal genetic assessment, and the high-risk ones who did need to see a geneticist.[195]

Harper: I think Trevor Cole had picked this up quite a bit from Jonathan Gray's studies in Cardiff.[196] I want to move across for a moment to another slightly parallel and similar condition, which is tuberous sclerosis. Julian, can you just tell us how the isolation of the genes helped in the way of developing our genetic and other services for that disorder?

Sampson: The situation in disorders like tuberous sclerosis is very different because of the associated impact on cognition and behaviour, and reproductive fitness is very low. In a large proportion of cases, two-thirds are sporadic and the actual malignancy risk is very low, although tumours of the brain and kidney can be quite serious and require major interventions. So that is very different to the sort of situation that we've been talking about with dominant disorders that are associated with large families. That was the exception in tuberous sclerosis; the impacts have been very different. They've really been in relation to the availability through genetic testing of prenatal and preimplantation diagnosis. Clarification of genetic status in family members where that is uncertain, is

---

[194] Hodgson and Maher (1993).

[195] Trevor Cole was Consultant in Clinical and Cancer Genetics from 1992 to 2002 at the Birmingham Women's NHS Foundation Trust, where he is now Consultant and Honorary Reader in Clinical and Cancer Genetics; http://www.bwhct.nhs.uk/research-and-development/key-researchers/trevor-cole (visited 20 February 2013).

[196] Professor Jonathan Gray was Clinical Director of the All Wales Medical Genetics Service. See note 163.

much less of a problem than it is in the disorders with very much more age-related penetrance that we've been talking about today. So I think the situation with tuberous sclerosis is quite different and really the impact is now turning into an impact on therapy based on an understanding of gene function. So yes, very different altogether to what we've been talking about so far.

What I did want to mention was to pick up on some points from what Eamonn said in relation to the evolution of cancer genetics services. These were coupled early on to linkage studies where clinical phenotyping was very important. I think the development of these services during a phase of genetic linkage research studies helped to propel a very proactive philosophy of wanting to see all the family members and even wanting to see those clinically unaffected family members, perhaps whether they wanted to be seen or not. Very often, once they understood the situation, they did want to be involved but not always initially. That was rather different from the more reactive development of services for things like Huntington's disease or even dysmorphology where really we were there to answer the patient's immediate questions.[197] In comparison, the focus in cancer families was often about future generations, which is something we tended to hear much more about. That pushed a proactive approach to cancer genetics which is beginning, certainly in some services – I think in ours – to disappear again because of concerns about confidentiality and data protection, partly because of the sheer volume of work. You can't be absolutely proactive in working so rigorously through extended families. The things we heard about from Jane, this incredible genealogy that you were able to undertake in Newfoundland to work through these big families, and, similarly, the proactive approach that was taken for FAP and in VHL disease, is not entirely applicable now that we're moving into situations where we're dealing with genes of lower penetrance and less certain natural history and less efficacy of interventions for family members that are affected. There are much more difficult and personal decisions for people to take, such as having a prophylactic mastectomy as opposed to prophylactic colectomy that we've been talking about with FAP.[198] So I think things have changed in terms of the drivers, the philosophical drivers of the service delivery.

---

[197] See Harper *et al.* (eds) (2010), pages 63–8; 76.

[198] See, for example, Ghosh and Hartmann (2002).

Evans: Coming back to the triage issue, in the breast cancer area it certainly became the way things were done, with local family history clinics in secondary care and then referring them up to tertiary care. That model is not complete around the country but it certainly is in some parts of the country, very much the model of secondary care family history and a tertiary care genetics clinic. That was encapsulated in part in the Harper report,[199] and in fact in the Calman report,[200] says someone smiling down on me from up there,[201] and also the NHS Cancer Plan have formed really a lot of the thinking in the NICE Guideline Development Group for Breast Cancer.[202] But in terms of bowel cancer, that really hasn't happened in the same way. Yes, the screening occurs in secondary care but the development of secondary care bowel cancer family history clinics has not been so well done throughout the country. We do have a few around us in the North West of England but it has been much less the case.

Lehmann: Somebody, I think it may have been Shirley, mentioned multidisciplinary teams and so I thought it might be of interest to recount our experience with xeroderma pigmentosum (XP). I've been doing lab diagnosis of XP for about 30 years and until 10 years ago I'd never seen a patient. I first saw them when the XP support group started having annual meetings. About three years ago a dermatologist from St Thomas' put in an application to the NHS National Commissioning Group to set up a multidisciplinary clinic for XP and there's something like 100 patients in the country.[203] It's a little bit like Jane was describing in Newfoundland – each patient is in a different part of the country so you can't have a specialist who knows a lot about XP everywhere. So this clinic was set up and started about two and a half years ago. We have a dermatologist, ophthalmologist, neurologist, geneticist, psychologist and, very importantly, specialist nurses with myself as a consultant scientist and we're closely tied in

---

[199] Department of Health (1996). This publication is more commonly known as the 'Harper report', as is usual after the Chairman.

[200] Department of Health and the Welsh Office (1995).

[201] Professor Gareth Evans was referring to Sir Kenneth Calman's appearance on the homepage of the website for the History of Modern Biomedicine Research Group, projected on a screen behind the Chairman during the meeting; http://www.history.qmul.ac.uk/research/modbiomed/index.html (visited 25 January 2013).

[202] See note 164.

[203] Guy's and St Thomas' Hospital's XP Clinic, to quote from its website, is the 'only designated national service for xeroderma pigmentosum'; http://www.guysandstthomas.nhs.uk/our-services/dermatology/specialties/xeroderma-pigmentosum/overview.aspx (visited 15 January 2013).

with the support group.[204] We see a few patients every couple of weeks and these patients really are seen by people who know a lot about the disorder, and the patients, I think, now are getting a much more satisfactory service. From my point of view, before we started I thought I knew everything there was to know about XP and, having started to see patients, I quickly realized that I knew very little about XP because every patient is different and none of them looks like the textbook. So that's the way we're going. We're trying to now extend this model to other DNA repair disorders.

Tansey: Can I just ask you to develop that a little bit because you mentioned multidisciplinary teams and I'd like to follow up on something that Shirley said; a number of you have raised the subject of funding, and only Walter has addressed it specifically. Getting multidisciplinary teams funded is often very difficult, so could you say something about how that happened and who negotiated it?

Lehmann: The lead on this was Dr Bob Sarkany. He was the dermatologist from St Thomas' and he put in an application to the NHS National Commissioning Group, which has funds for these purposes. But obviously if everybody put in an application for all 5,000 genetic disorders the funding wouldn't go round, so it sounds quite expensive, and it is, but once you've got approval then, as far as I understand it – I haven't been directly involved – as long as the service is providing what it set out to do and you can show that the outcomes that you proposed have been fulfilled, then you get continued funding.

Phillips: I did want to comment on multidisciplinary funding and some of the other bits. I think it's probably the relevant time. We were hearing how the field was changing and becoming more exciting. I can tell you, from my point of view, it was changing and it was frustrating because we had enormous difficulties with funding. We had absolutely no NHS funding for being able to do these things and also the NHS was changing, you went through different processes. You could go forward and sometimes you could price things and make a charging band out of it to try and get the money. For example, how much were you going to charge for DNA analysis and how much were you going to charge for checking for a known mutation? The laboratories that had done the work were research laboratories and they couldn't be trusted in terms of the sequence, whether it was the blood result of that named individual. The quality that you got was much better in an NHS service laboratory, with the checking of the patient identity as samples

[204] For the XP Support Group, see http://xpsupportgroup.org.uk/ (visited 16 April 2013).

went through: the fact is that you could actually get samples muddled in research laboratories.[205] We were having to deal with this and trying to come up with policies in a research laboratory: when we got a result we had to repeat it. It was only when we got two matching results from a research laboratory that we would accept it. We had difficulties because the surgical staff didn't really understand a lot of what was going on as far as we were concerned: germline was something to do with a species of bacteria. [Laughter][206] Our level of knowledge of these things was very different. Then we were confronted by the fact that the geneticists knew absolutely nothing about the subject – they didn't know anything about polyposis. They needed to be educated in polyposis, but they didn't know that they knew nothing about polyposis. So we had those frustrations. Then we had the issue that we had our own patients that came to St Mark's but we were aware that, in the Thames regions, there were a load of patients that weren't coming to us and a woman called Joy Newman gave a sum of money and funded a thing called the Thames Region Polyposis Registry.[207] But we had difficulties here because there were no controlling clinicians. Within St Mark's Hospital each surgeon had a different antibiotic prophylaxis, a different bowel preparation, whether or not they used antithrombotic medication. To some extent we could manage patients within St Mark's but you go out to the Thames regions, how are you going to deal with this because these patients weren't 'owned' by us. If we started tracking or doing things about these patients, it was almost impossible to know how to influence practice, so this was a very, very hard time.

Harper: Perhaps I ought to say something about the report which my name seems to have got attached to.[208] I think the things that Robin has been mentioning led to the need to try and get some not just widespread, but coordinated initiative

---

[205] A similar discussion occurred in a previous Witness Seminar; see Overy *et al.* (eds) (2012), pages 60–1 (Dr Linda Tyfield) and page 63 (Dr Richard Jones).

[206] In genetics, the term 'germ' refers to the reproductive cell line, from which gametes originate, while surgical staff interpreted 'germ' in the bacteriological sense.

[207] Professor Robin Phillips wrote: 'It was funded with money from one Dr Joy Newman, a medical practitioner with an interest in FAP, who made a substantial donation to St Mark's Hospital. She was aware at the time of her donation of very uneven ascertainment of FAP cases in London, and little genetic interest, and wished through this Registry to help trace patients and put them in contact with their local (as opposed to St Mark's) service.' Note on draft transcript, 5 April 2013. Dr Joy Newman is listed as a Patron of the St Mark's Hospital Foundation in its 2006 Annual Report; http://www.stmarksfoundation.org/uploads/media/Annual_report_2006.pdf, see page 4 (visited 15 January 2013).

[208] See note 199.

of how cancer genetics services might and should evolve. I can't even remember why I was asked to chair it – I think because I didn't know terribly much about it. But my experience was a very positive one. We managed to get together a lot of the stakeholders, as they're called now: surgeons, oncologists, geneticists, genetic counsellors, nurses and various others. The thing that impressed me was that people were remarkably willing to be cooperative and there was a distinct lack of territoriality, which actually did surprise me. Thinking about why this might be so, one of the things was that there was a huge amount of work to do, plenty to go round everybody, that it seemed to make sense to focus mainly on what people were good at and trained for. Clearly, in the case of affected individuals, it was the relevant clinical specialist, surgeon, oncologist, or whatever. But one thing that also impressed me fairly early on was that, actually, most surgeons or other clinical specialists don't want to spend the majority of their time with completely healthy people, they'd prefer to be dealing with people that actually have the problem, whereas geneticists are quite used to dealing with ramifying families of whom perhaps the greater part are completely healthy and might not even carry the relevant gene. So things came together, in terms of that report at any rate, far more easily than I'd imagined. Then it disappeared into the bowels – a rather appropriate word perhaps – of the Department of Health (DoH) and it stayed there a long time and for some reason emerged in the form of a letter to the Chief Medical Officer because I was told at that time there was some political constraint against the department getting advice from anybody, or something like that.[209] But I think that report did have some effect in getting things going and I know that people would take along a copy to their various authorities and say, 'Look, it says in this DoH document that we ought to have this or that.' The powers that be are always more impressed if you can wave a document at them than if you just talk to them, and I think this is what happened. One thing that did come up was this triage concept, again bringing in genetic counsellors and other groups for the large number of low-risk people, and that was particularly the case perhaps in breast cancer more than in colorectal cancer. Can I come back to you, Robin, perhaps and ask what do you think was the psychological aspect in terms of you being a surgeon? You've got a series of well-established tests for people at risk: at what point did you actually come to believe that this DNA worked?

---

[209] Professor Peter Harper wrote: 'The 'letter' to the CMO for England was not really a letter at all but was the report itself. For some obscure reason it could only be classified as a letter.' Note on draft transcript, 7 March 2013.

Phillips: I'm still learning. We set up a DNA testing service on our own through the Kennedy-Galton laboratories at Northwick Park and that was a big uphill struggle.[210] I think the problem was the provenance of the blood and the results; we couldn't trust it. Until you could go through an NHS screening laboratory with its set-up, you always had a little degree of uncertainty of what you were getting.[211] If you got a negative result on a known mutation, had they mixed the blood sample? You had these sorts of issues. Now we're perfectly in tune, if we know the mutation and are told there isn't one, or the lab says there isn't a mutation, we discharge the patient. We have little difficulty with that. If you say you can't find the mutation, that's another matter. It may be a different condition.

Neale: I'd really like to say I think he's being a bit unfair. [Laughter] Robin put an awful lot of effort into arranging for the funding of the NHS testing service to be started at St Mark's and it was at the time when the Conservative government had the money following the patient.[212] We in the registry had to do an enormous amount of work, making sure that the contracts went out and the contracts came back before we were allowed to test the patients. We had the most horrendous filing system that followed all these bits of paper round so that we didn't do the test before we had the money, and Robin's idea was that we would be the national testing centre, but of course other regional genetics centres soon set up their own and the system changed anyway so it didn't matter. But when we first set it up, he's right that we weren't 100 per cent certain that we could trust the laboratory so we chose some family members that had got the condition, who had different names, and we sent them up to make sure we got the same result back on all of them.[213] Of course, after one or two we really did trust them and it was an enormous amount of work at first because we had

---

[210] North West Thames Regional Genetics Service (Kennedy-Galton Centre), Middlesex, offers genetic counselling and diagnostic services in the catchment area of the North West London Hospitals NHS Trust, http://www.nwlh.nhs.uk/_microsites/nwthamesgenetics/ (visited 15 January 2013). The Service is one of the UK Genetic Testing Network (UKGTN) centres. The UKGTN 'is a collaborative group of genetic testing laboratories, clinicians and commissioners of NHS genetic services and involves patient support groups'. Further details are available at http://www.ukgtn.nhs.uk/gtn/Home (visited 15 January 2013).

[211] See Bodmer's and Harper's comments on page 76.

[212] Lord Privy Seal (1972). This government publication is otherwise known as the 'Rothschild report'. See also Reynolds and Tansey (eds) (2000), in particular pages 59–60.

[213] A similar story is recounted by Dr Felix Konotey-Ahulu in a Witness Seminar about developments in renal dialysis; Crowther *et al.* (eds) (2009), see pages 41–2.

a lot of patients that we had been screening for years that we could now offer a test and discharge. So it was wonderful for us in the Registry to give people that kind of reassurance. There were one or two patients, one gentleman in particular that I remember who had not had children because he was worried that one day he might be affected and could have the risk of passing polyposis on, and he was negative and went ahead and had a child. So it was a great time for us, but Robin did fight for that to be set up for us.

Burn: I would just like to add another dimension to what Robin and Kay have been saying because they played an absolutely pivotal role in getting this whole service going and we became very closely involved with them. There was an obvious, understandable tension which I think was widespread. On the one hand surgeons were used to seeing polyps; much more physical, identifiable, proof of disease status. And here were these new guys coming along saying, 'I've done this test and the patient doesn't need checking.' There was this awful urge to have another quick look just to be on the safe side. We, on the other hand, were perhaps a little bit too cavalier, as Robin said, about saying our research laboratories were reliable at the very beginning. I think there was an inevitable tension between the 'novelty seeking behaviour people' rushing on ahead and the 'people who are used to another way of doing it' hanging back a bit. We were in tension for a while as we gradually got the service going but that was a healthy tension. The one thing I would say is that throughout this whole period, colorectal cancer was being marked by an incredibly close working relationship between the colorectal surgeons and the geneticists for the reasons Peter said, because the surgeons are more than happy to hand over the healthy people for us to do the talking to. I think there's a distinction there in other specialties where physicians see themselves perfectly capable of talking to the healthy people as well. The other thing I wanted to say on the Harper report, which was undoubtedly very influential – there was a time, you might remember, Peter, near the time it was published, when we ended up in a huddle, I think you, me and James MacKay tried to thrash out some of the difficult points.[214] The point which I lost on – and I'm not sure still whether history will record it as right or wrong – but James was very keen that we actually move towards having cancer geneticists who had an oncology and genetics background, trying to create in essence a new subspecialty. I was keener on the generic geneticist retraining away from what we did before to what we would do in the future. I think we

[214] Dr James MacKay was a member of the Working Group for the Harper report, as Consultant Oncologist, Addenbrooke's Hospital, Cambridge. See note 199.

ended up somewhere in between, where all geneticists now do a bit of cancer work, but there are some who are much more, like Gareth [Evans] and others, who are much more in the oncological field. I think that's as it should be. We'll probably end up with a mixed model. Your report was a different approach to the one we'd done with St Mark's, and so many other rare disease areas, where enthusiasts build it up in the hope that the money will come. But the NHS is incredibly slow at adopting those services and we often really fly on a wing and a prayer for far too long as a result of that.

Møller: I would like to follow up on this and also on Julian's comment. Bodmer and I both came from HLA genetics – we know the genes, we know the environmental triggers, but there is no prevention, no cure for diabetes, nor for rheumatoid arthritis, nor for ankylosing spondylitis. What I think happened, and still is happening, was that anticipated results are oversold on false premises, especially by the labs. Understanding the genetics of cancer does not imply that we can crack the code for cancer, that we can prevent it or cure it in a short time. People have, by now, understood that cancer genetics wasn't a quick and easy way to understand and cure cancer. I think we must go back and redefine that we are dealing with, a relatively small subsample in the population with an extremely high risk for something we can do something about. We have to sell this concept of cancer genetics. I learned this at the time I was a delegate from the EC Biomed2 Demonstration Project on Familial Breast Cancer, in 1999, at a 'farm' in the countryside in the UK, where I was trained on how to communicate with journalists.[215] The 'farm' turned out to be the HUGO Centre, Hinxton Hall, and the teachers turned out to be the BBC television programme *Horizon* team, and then I was taught how to stand in front of a

[215] The project's full title was EC BIOMED 2: DEMONSTRATION PROJECT, Familial Breast Cancer: Audit of a New Development in Medical Practice in European Centres. Dr Pål Møller elaborated: 'The Demonstration Project on Familial Breast Cancer ended up with a European conference in 1999 in Heidelberg, attended by delegates from 34 European countries where we formatted European guidelines for the use of *BRCA* testing and carrier management. We at the time found ourselves in the debate on patenting genes. We had visited Myriad Genetics in Salt Lake City. We told them we did not like patenting genes, and Myriad Genetics said they would take legal actions against us for violating their patent rights. Despite Myriad Genetics having obtained the rights from the European Patent Office, however, we through a number of affiliations and actions made it so they were never able to invoke their patent rights in Europe. One of the directors of Myriad Genetics later visited me to learn how we did it, and I told him that I, having learned how to twist the population's opinion at Hinxton Hall when, a short time thereafter, I was invited to a TV discussion on something else, and made a representation for the largest political party to take the position against patenting genes in 90 seconds. It was an interesting time.' Note on draft transcript, 22 March 2013.

camera and sell a story.[216] At the end, my capacity as a salesman was judged by the head of Smith Kline Beecham in the UK. For the purpose, I invented a story that I had a pill which could prevent all inherited breast cancer and he asked, 'How many carriers are there in Europe?' I said, 'About two million.' And he said, 'Are you crazy? Do you know what it costs to develop a medicine? We will never go into it.' That attitude was the reason why the European Commission developed Orphanet and Orphan Drugs as a concept.[217] They wouldn't accept the commercial companies ignoring minority groups because they don't make money. I think we should go back now and say, 'We are not solving the riddle of cancer. We are doing genetics, but genetics is only a tool.' We have to sell that story.

Sampson: Pål's moving into the future of history! I wanted to just go back to that time when FAP molecular diagnosis was first introduced. Certainly we, and I know a lot of other people as well, actually introduced molecular diagnosis at a time before the gene was identified by using linked markers. I think it's very understandable that some clinicians outside of clinical genetics were reluctant to incorporate this approach because we talked about risks rather than certainties, we had recombination risks with these markers. That period lasted actually for a couple of years until 1991 or so and during that time we never gave any definitive answers. Even once we did, people were initially reluctant to use this DNA diagnostically in a clinical setting. We were also very cautious even within genetic services. I can remember when we started doing these tests, even using direct mutation analysis for predictive tests, we did this on duplicate samples. We did all the tests twice and we used to suggest that polyposis patients with a negative gene test had a colonoscopy at 21 years of age. These things were only dropped slowly even within genetic services, so actually there was a very cautious approach that was played out over a number of years.

---

[216] The Human Genome Centre is part of the Wellcome Trust Genome Campus, incorporating the Sanger Institute, which is located in the grounds of the Hinxton Hall Estate, http://www.wellcome.ac.uk/Funding/Biomedical-science/Funded-projects/Major-initiatives/Wellcome-Trust-Sanger-Institute/Wellcome-Trust-Genome-Campus/index.htm (visited 15 January 2013). Hinxton Hall is a Wellcome Trust Conference Centre (visited 23 October 2012).

[217] 'Orphanet is the reference portal for information on rare diseases and orphan drugs, for all audiences. Orphanet's aim is to help improve the diagnosis, care and treatment of patients with rare diseases.' It is an alliance of circa 40 countries, with funding from the European Commission and the French government, and from individual countries for their nationally based initiatives; http://www.orpha.net/consor/cgi-bin/Education_AboutOrphanet.php?lng=EN (viewed 20 February 2013). Quote from website.

Bodmer: A general point listening to this. As you know, I've been involved in the HLA field for many, many years and we were often called on, say, to do B27 typing, whether it was useful or not for ankylosing spondylitis. I was always, and I remain, against a research lab doing a service. They're not set up to do it, they don't have the rigour of following the paperwork and other things. I think that's a very important point to take into account. It's not that they're incompetent, it's that they're not set up to do these things in the way they have to be done in order to absolutely minimize the risk of making any mistakes.[218]

Harper: I think it's a very important point, Walter. And as a corollary to that, which worries me greatly, in America it is now mandatory for research labs to have to transmit the results to the patient or family, which I think is fraught with trouble simply because of the potential for errors.[219] Whereas here, on the whole, I think the policy has been across the board, certainly in genetic testing, for as soon as something is validated, the results have to be transferred to a service lab, with all the different attitudes and particularities that they may have.

Evans: I absolutely do not regret that period of time when we weren't absolutely certain, when we went from linkage to mutation and analysis, although obviously when you look at it in the cold light of day, we were saying, 'Well, actually this person's bowel cancer risk goes up from four to five per cent because of the one per cent chance you might be wrong.' Whereas, in reality, we wouldn't be screening anyone in the general population for a risk that goes up from four to five per cent. I think one of the main areas damage was done, because of that transition period, was actually in MEN2 where there are a number of documented cases of people who had low-risk results who continued to get screened and ended up having thyroidectomies and then were later found out not to be gene carriers, which is perhaps a little worse than having a few more colonoscopies. My big anecdote, from a long time ago, is actually about someone who ended up with a colectomy and had been rigorously screened in their rectum for the past 30 years with annual sigmoidoscopies. It struck me why they hadn't found a single polyp and so I went back, we did the genetic test and they didn't have the mutation, so we then had to rebleed them because we didn't believe the result.

---

[218] See also comments from Neale and Phillips, page 72 and Burn, page 73.

[219] Professor Peter Harper wrote: 'My statement about release of research results being mandatory in US is probably a bit strong … I don't think there has ever been a specific ruling. It is more that there is a presumption in favour of release of information, even when this is not specifically indicated in the protocol.' Email to Ms Emma Jones, 16 April 2013.

Of course, they still didn't have the mutation and we found out that the surgeon had actually not done a rigid siggie [sigmoidoscopy] but had done a laparotomy and had a feel of the bowel on the outside, didn't like the feel of it, so he'd taken the colon out. I actually got the original lab report and there were no polyps in the colon and he'd been having rigid siggies for 30 years.

Harper: I'm sure none of the surgeons here would approve of that.

Burn: I've actually seen a similar case where a barium enema was misread and 'miraculously' the pathology report, which definitely proved that the patient did not in fact have the disease, disappeared from the records. So I'm sure it's not an entirely isolated case.

Harper: One area I'm very glad we've got John Burn to connect us up on, but there are several people to contribute to, is the various groups – national and international – and how they have evolved. We've heard a bit about the Cancer Family Study Group, but more specifically to polyposis and colorectal cancer there's the Leeds Castle group and now InSiGHT [International Society for Gastrointestinal Hereditary Tumours].[220] John, from a distance, perhaps you can lead us into this and describe how they've evolved from what they started with into the present situation.

Burn: Well, you have an equally expert person with Robin Phillips there who's been executive officer of InSiGHT, but, very briefly, the Leeds Castle group was very much around FAP. Hans Vasen and Henry Lynch set up the ICG-HNPCC which I mentioned earlier. Many of us stood back but then got drawn in. Then through the 1990s, because of my involvement with the cancer genetics groups and through the CAPP studies, I became very involved with both groups and a number of us started to see the logic of us bringing them together into a single organization. Eventually, we started running them in parallel. We had a couple of meetings sailing side by side, and then we had a meeting in Buffalo where we officially created the society and I can lay claim to the acronym. But it was actually trying to hang onto Hans Vasen's 'hereditary tumours' title at his institute, so I suggested International Society for Gastrointestinal Hereditary Tumours, which is a bit clumsy, but InSiGHT is a very memorable term. That was in 2003 and we had our first official InSiGHT meeting where that was the

[220] InSiGHT is one of the contemporary incarnations of this group. The present society is an international, multidisciplinary scientific body dedicated to the improvement of care of patients with hereditary gastrointestinal tumours and their families; http://www.insight-group.org/ (visited 21 December 2012). See also note 52.

name on the door in Newcastle in 2005 and it's carried on every two years ever since and continues to grow from strength to strength and has about 400 to 500 people – the next one's in Australia – but the Leeds Castle stuff was first one out of the door and Robin is the expert on that.

Phillips: I think Kay Neale will be able to say more accurately but one of the main points about it was that it was a multidisciplinary senior discussion group – that was the major thing that it was supposed to be.

Neale: Yes, it started in 1985 when Sir Ian Todd had a patient with a huge desmoid tumour which he didn't know how to treat.[221] In 1985 St Mark's had its 150th anniversary meeting so, tagged onto the end of that, Sir Walter helped to fund a meeting at Leeds Castle in Kent through the ICRF where the people around the world known to have expertise in polyposis were invited.[222] I think there were 32 people, something like that. At that meeting it was agreed that it would be beneficial to have an international group so that these very rare incidences of extra-colonic manifestations of polyposis could be researched by joining together internationally. In 1987 Dr Jerry DeCosse completely funded the second meeting in Washington for about 50 people.[223] Then, in 1989, we had another meeting in England, in Wiltshire, where we began to realize that people were getting to know about the group and didn't like the idea that it was only specialists. We began to realize that we should be spreading the word to new registries, we shouldn't only have experts and we should also be teaching. At that meeting we elected our first official Chairman who was David Jagelman

---

[221] Ms Kay Neale wrote: 'Sir Ian Todd wished to seek information from clinicians around the world regarding the treatment of desmoid disease; his young patient had an abdominal desmoid tumour so large that she looked to be nine months pregnant. As a result of the meeting of 32 experts at Leeds Castle in 1985 he learned that no-one had the answer.' Note on draft transcript, 5 April 2013.

[222] See Neale and Bülow (2003).

[223] Dr Jerome DeCosse (d. 2001) was the Professor and Vice Chairman of the Department of Surgery at Weill Medical College, Cornell University and New York Presbyterian Hospital from 1978, where he specialised in the diagnosis, treatment and prevention of colorectal cancer; http://www.nytimes.com/2001/04/26/classified/paid-notice-deaths-decosse-jerome-j-md-phd.html (visited 16 January 2013). In 1988 the Leeds Castle Polyposis Group's membership comprised of the Cleveland Clinic Foundation, Johns Hopkins Hospital and New York Hospital – Cornell Medical Center in the USA; Rigshospitalet, Denmark; Helsinki University, Finland; St Mark's Hospital, UK; Mayo Clinic, USA; Tokyo University Hospital, Japan; St Erik's Hospital, Sweden and Toronto General Hospital, Canada; information from Jagelman *et al.* (1988).

of the Cleveland Clinic,[224] Florida, and the Deputy Chair was Steffen Bülow from Denmark.[225] So the next meeting was arranged for Cleveland and then the one after that in Denmark. From there we've gone on every two years growing in size until, as John said, we became formally InSiGHT in 2005 and in 2010 we became incorporated as a company and registered charity. Now we're a registered charity, we can raise our own funds and we're heavily involved with the Human Variome Project which is mainly run by Dr Finlay Macrae from Melbourne in Australia.[226]

Møller: Just to add to that: being involved in both colorectal cancer and breast cancer, we are clinically drowning in familial and inherited breast cancer. The difference between the research organizations for inherited colorectal cancers and for inherited breast cancers was interesting. ICG-HNPCC had, from the start onwards, the interdisciplinary structure with the recognition of both lab personnel, surgeons and clinical geneticists.[227] The inherited colorectal research groups have, through this, been extremely pleasant to be part of.

Harper: Thank you. We haven't really said much about genetic counsellors. I don't know whether Chris Harocopos wants to add anything or do you think it's been covered reasonably well?

Ms Christina Harocopos: I started long before they had the genes but I certainly was a CNS [clinical nursing sister] who set up the Family Cancer Clinic at St Mark's in 1986. I was employed as a genetic research assistant and family visitor to record information, take pedigrees and contact family members. Data was

---

[224] Dr David Gordon Jagelman (1939–1993) was the Founder and Director of the Cleveland Clinic's Familial Polyposis Registry. For his full biography see http://my.clevelandclinic.org/digestive_diseases/departments-centers/colorectal-surgery/weiss-center-hereditary-colorectal-neoplasia.aspx (visited 16 January 2013).

[225] See note 80. In 1985, when the Leeds Castle meeting took place, Dr Steffen Bülow worked at the Department of Surgical Gastroenterology at the Rigshospitalet, University of Copenhagen.

[226] Founded by Professor Richard Cotton in Melbourne, in June 2006, the Human Variome Project aims to 'capture and archive all human gene variation associated with human disease…[and] provide a standardized system of gene variation nomenclature', among other objectives. Quote from Cotton *et al.* (2007), page 434. See also http://www.humanvariomeproject.org/index.php/about (visited 21 December 2012).

[227] Dr Pål Møller wrote: 'The Biomed2 demonstration programme on familial breast cancer was organised by Professor Michael Steel as a clinical counterpart to the Breast Cancer Linkage Consortium because they did not include the clinical parties.' Note on draft transcript, 22 March 2013.

Figure 20: Ms Christina Harocopos.

then recorded on cards.[228] Dr Slack found opposition among the senior medical staff at St Mark's and did not find it easy with lack of clinic rooms, etc. I used to actually go round the country looking for the relatives of our families, which was amazing. Now, of course, you can't do that. Families were very happy to cooperate, and family members across the country contacted me to offer blood samples and information which were pivotal to research. I was very conscious of it being a family affair. People were never contacted by the clinic, and relatives would speak to them first to contact us. As far as I remember, very few people refused. We became very aware of what they wanted to tell us and that's how we got an awful lot of patients coming to see us. Now, you don't get that, it's very restrained. We've got a lot of ethical restraints, which is probably quite right but there isn't the same feeling. Identifying gene mutations has removed the anxiety of many family members, but the carriers need extra support and understanding. With the NHS going through constant changes and financial restraints, there is less chance of creating a permanent support structure that these families need.

Harper: I'm going to deliberately reserve the last few minutes for talking just a little bit about the impact of genetics on new therapies because I really feel that's a rather unique series of developments. John, tell us a little bit about the trials and related things.

---

[228] Ms Christina Harocopos wrote: 'At the clinic, pedigrees were obtained from those attending, risks were estimated and explained and a screening programme was offered.' Note on draft transcript, 10 November 2012.

Burn: Tribulations? [Laughs] Well, all through this entire period, from the original idea in 1990 that we might try chemoprevention, the CAPP studies were trundling along.[229] A lot of people at this meeting played a very pivotal part in CAPP1. Robin was central. We realized when we tried to do it how hard it was to actually give long-term treatment, especially to adolescents. We did eventually get that published, although that wasn't the greatest of papers.[230] However, it did get CAPP2 off the ground, which turned out to be quite influential. The two interventions that we had come up with from the epidemiologists were resistant starch and aspirin and so we set up to study a thousand people worldwide and we managed to do that. When we broke the code, we had no obvious evidence of effect but we managed to carry on long-term follow-up as planned and in 2011 reported that there was a 63 per cent reduction in colon cancer among the Lynch syndrome patients given aspirin.[231] We're about to publish the results of the starch, which was negative, but nevertheless it did demonstrate that you could do these long-term intervention studies on people who were genetically motivated because of their own risk and the risk for their families.[232] We're now trying to roll on that programme and look at different doses of aspirin and perhaps look at other interventions. It changed the game quite a lot because we now have a real intervention to offer people.[233]

Phillips: A couple of observations: one is that in the various CAPP trials that John ran, I think the major thing was that they were wonderfully educational for a group of clinicians around the world. They brought people together and they standardized care. People started off not knowing much about either polyposis or HNPCC and they learnt a lot more. We ran seven randomized control clinical trials on our polyposis patients at St Mark's and we were involved with the development of Cox2 inhibitors against colorectal cancer.[234] We've been involved with difluoromethylornithine and its effect as an adjuvant in colorectal

---

[229] See note 97 and Burn *et al.* (1998).

[230] Burn *et al.* (2011a).

[231] Burn *et al.* (2011b).

[232] Mathers *et al.* (2012).

[233] Sir John wrote: 'CaPP3 (Cancer Prevention Programme) will test three different doses of aspirin in 3000 carriers of Lynch syndrome, beginning in January 2014, with results expected in 2021.' Note on draft transcript, 16 June 2013. See http://www.capp3.org/ (visited 17 June 2013).

[234] For example, Steinbach *et al.* (2000).

cancer in prevention.[235] We've been involved in using fish oils and showing that they can make a difference.[236] The polyposis patients are a wonderful human laboratory for examining the next stage. They've got this controlled environment of the rectum which we can return to fairly easily. From the patient's point of view, of course, we've got other problems which I think are not so much of scientific interest but of patient interest: the upper gastrointestinal tract and the desmoid tumours.

Evans: Just to develop the targeted therapy; we know about targeted therapy with Herceptin for breast cancer was one of the first.[237] Then you had drugs like Glivec, which are now fantastic treatments for GI stromal tumours and there are individuals with inherited c-Kit mutations and *PDGFRA* mutations for whom, potentially, those are going to be incredibly important drugs.[238] Also in breast cancer, you've got the synthetic lethal approach, and PolyADP-ribose polymerase (PARP) inhibitors have been used in advanced breast cancer with *BRCA1* and *BRCA2* carriers and have been getting very good results in the stand-alone situation to the extent that people are widely talking about these drugs being the pill that Pål discussed: the pill that will prevent breast and ovarian cancer. Now we don't know if that will be the case, but we are moving into that era of targeted therapies, targeted at the genetic abnormality.

Lehmann: I just want to emphasize the PARP inhibitor story, which was based on knowing that the breast cancer cells had a *BRCA1* or *BRCA2* deficiency and knowing that they were involved in DNA repair. It was absolutely a rational development of a therapy directed against cells with the defective gene.

Harper: Julian, I was going to ask you to say a word about tuberous sclerosis.

---

[235] The clinical trial entitled 'A Two-Arm Phase II Chemoprevention Trial in Adenomatous Polyposis Coli Patients', started in December 2001 and its estimated completion date is October 2014. Apart from St Mark's, the other participating medical institutions are in the USA: the Cleveland Clinic Taussig Cancer Center, Ohio, and the M D Anderson Cancer Center, University of Texas in Houston, Texas. Details of the trial are available at: http://clinicaltrials.gov/ct2/show/NCT00033371?term=difluoromethylornithine+st+mark%27s&rank=1 (visited 16 January 2013).

[236] This clinical trial, 'A Two-Arm Chemoprevention Trial in Familial Adenomatous Polyposis Coli Patients Using the Purified Free Fatty Acid, Eicosapentaenoic Acid', commenced in November 2006 and was completed in April 2008. Further details are available at http://clinicaltrials.gov/ct2/show/NCT00510692?term=omega-3+colorectal+cancer+mark%27s&rank=2 (visited 16 January 2013).

[237] See, for example, Slamon *et al.* (2001).

[238] c-Kit: A receptor tyrosine kinase. *PDGFRA*: Platelet-derived growth factor receptor, alpha.

Sampson: The main impact for tuberous sclerosis has been in identifying a therapeutic target as a result of post-genomic work. As with many of these familial tumour syndromes, prior to the identification of the TS genes, the molecular pathology was not understood at all. After the genes were cloned and their functions established, this knowledge really gave the clue as to what targeted therapy ought to be effective for tuberous sclerosis. This has gone relatively quickly because it was a drug repositioning strategy rather than a drug development strategy that was followed, which was, of course, much cheaper as well. That's resulted now in a licensed application of these treatments for the tumour-related phenotypes in tuberous sclerosis. So there's a licence in the US and Europe for the treatment of tuberous sclerosis-associated brain tumours, there's a licence now in the US for renal tumours in tuberous sclerosis, and I think within a few weeks there'll be a decision about a licence in Europe.[239] I think it's one of the early examples of going from the positional cloning of genes, encoding previously unknown proteins to establishing those protein functions, identifying the target for therapy and getting a licensed drug.

Maher: VHL disease would be a second example in terms of knowing the biology, and tyrosine kinase inhibitors are now widely used for sporadic kidney cancer. This also illustrates the challenges of the disorders we're talking about because in VHL you've got a very long-term disease and effective treatment in terms of surgery and so patients will opt for surgical removal of their tumours at an early stage rather than the drugs that are available.

Bodmer: Following up the point that Eamonn's made: the biggest impact is on the mutations that occur in sporadic cancers, many of which, of course, have been suggested through the Knudson hypothesis from the family studies.[240] Ultimately, even if you take the PARP inhibitors, it may be that triple-negative breast cancers which can be treated by PARP inhibitors will be a much larger group than the actual familial cases. So it's actually the contribution through the germline studies to the somatic changes that in the end will have the greatest impact, I think.

---

[239] Novartis was awarded a licence for the drug Afinitor, with the active ingredient everolimus, by the US Food and Drug Administration in 2009. See http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails. In the European Union, the licensed drug is Votubia, approved in November 2012. See http://www.ukmi.nhs.uk/applications/ndo/record_view_open.asp?newDrugID=5344 (both sites visited 26 April 2013).

[240] See note 96.

Figure 21: Mrs Lois Reynolds.

Harper: I have found this a very stimulating meeting and so I'd like to thank you all and pass you back to Tilli to close the seminar.

Tansey: Thank you very much for coming to this meeting and sharing your reminiscences. I'd particularly like to thank those of you who have come from some distance, from Norway and from Canada, and even by phone from Newcastle. I'd like to say a couple of other thank yous, particularly to Lois Reynolds who is standing at the back. She is retiring on Friday and she has worked with me on practically every Witness Seminar we have held, over 50 meetings to date. [Applause] I'd also like to thank Peter Harper for his excellent chairing and, of course, for his very good time-keeping. I believe that Jane Green wants to add something.

Green: Sir John Burn was visiting Newfoundland to give a seminar to us in June and he mentioned this Witness Seminar and happened to have a look at my PhD thesis at the time.[241] I worked on it through the 1980s, it was regarding screening programmes for VHL, MEN1, MEN2, FAP and was capped off with the HNPCC story. John suggested that I might bring a copy of my thesis as one historically valuable document to remember this session by. So I'd like to give this copy of my thesis to Peter Harper.

---

[241] See Green (1995).

Harper: It'll be greatly appreciated. Some of you may know that we have what we call the Human Genetics Historical Library, which is a unique collection of over 3,000 volumes of books involved in one way or another with genetics – this will find a very deserved place in that and be available for everyone to use.[242] So thank you, Jane, very much indeed.

[242] See http://www.genmedhist.info/HumanHistLib/ (visited 25 January 2013).

Appendix 1

Timeline for UK Clinical Cancer Genetics Groups

1924	St Mark's Hospital Polyposis Register commences
Mid-1950s	St Mark's Hospital Polyposis Register advances to a Registry, proactively recruiting families to be screened[243]
1984	Cancer Family Study Group established ICRF-funded Colorectal Cancer Unit set up at St Mark's Hospital
1985	Leeds Castle Polyposis Group founded
1986	Family Cancer Clinic starts at St Mark's Hospital[244]
1987	Genetic Epidemiology Laboratory opens in Leeds
1989	ICG-HNPCC 'conceived' in Jerusalem[245]
1990	ICG-HNPCC first formal meeting, Amsterdam Oxford Imperial Cancer Research Fund Genetic Clinic starts
2000	Cancer Family Study Group becomes Cancer Genetics Group
2005	First InSiGHT meeting in Newcastle

[243] See page 20.

[244] See page 28.

[245] See Lynch *et al.* (2003).

Appendix 2

Archival material from St Mark's Hospital Polyposis Registry[246]

a) Register cards, interpreted by Ms Kay Neale

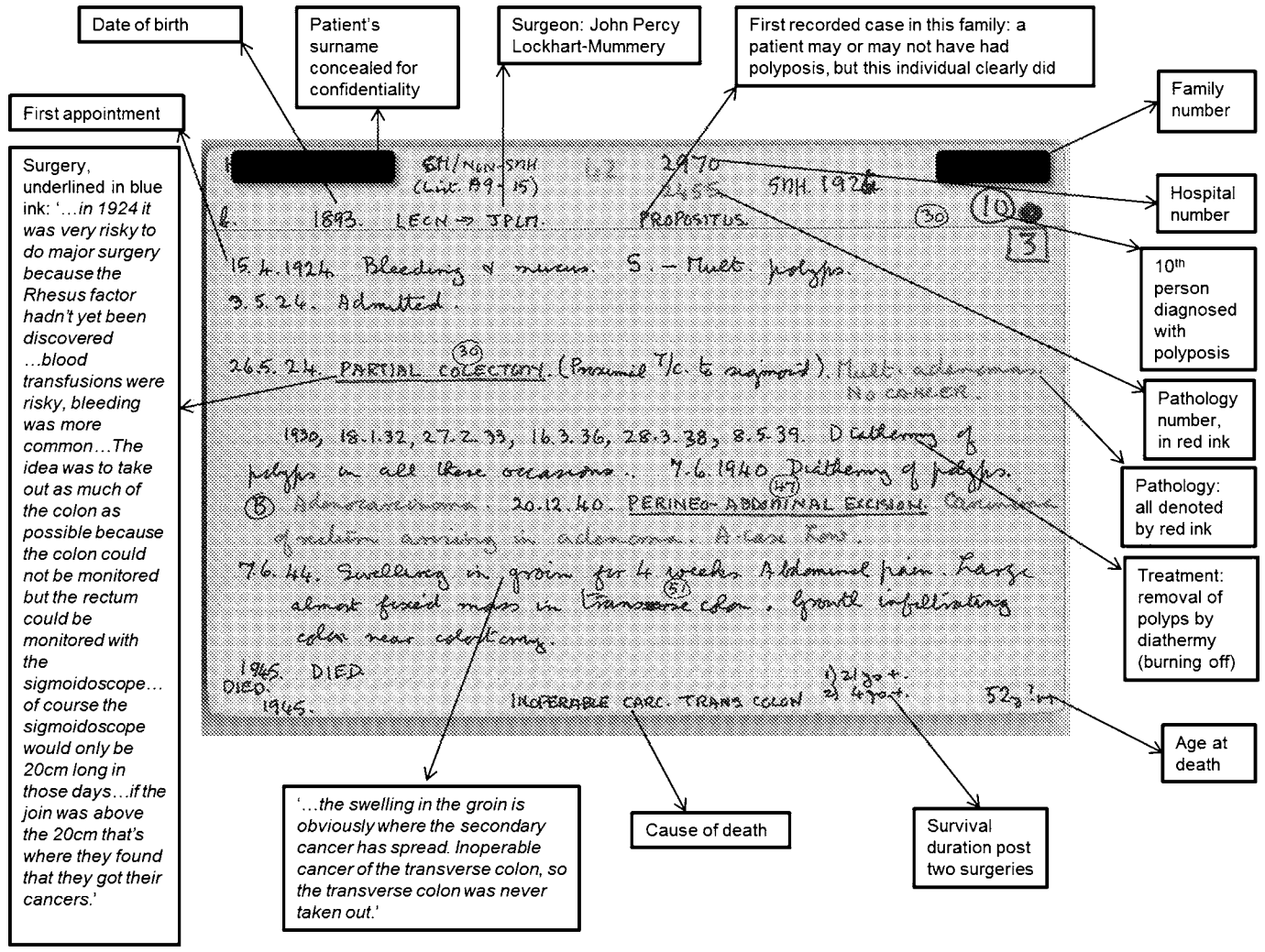
The visual materials reproduced here are examples of Dr Bussey's cards from the Polyposis Register (also available in colour on the History of Modern Biomedicine Research Group's website). In the annotated cards, the text in italics is directly quoted from Ms Kay Neale.[247] Below is some further elucidation from her on the foundation and development of the Polyposis Register and her close collaboration with Dr Bussey, compiled from notes she provided on the transcript and a subsequent interview.

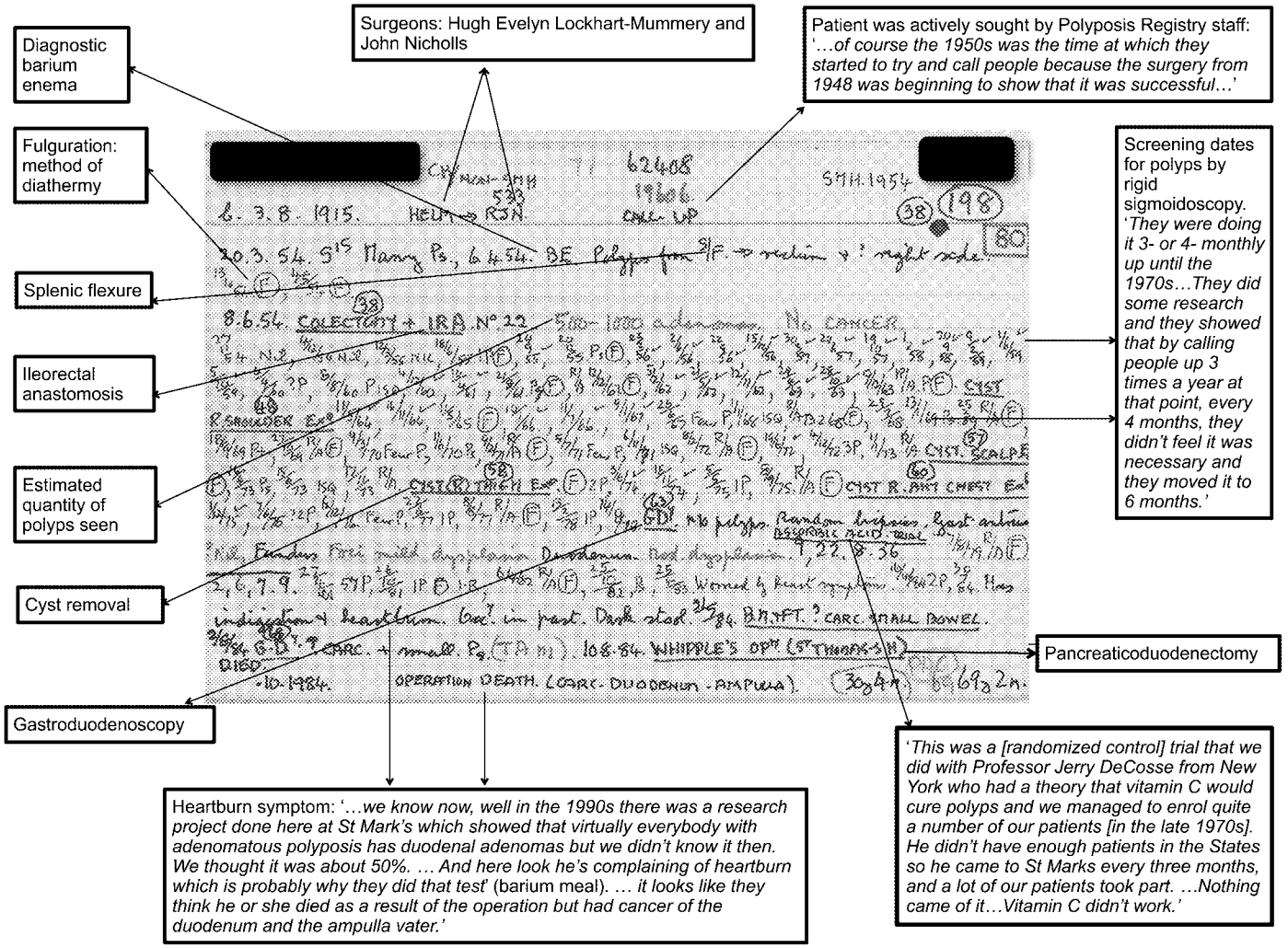
'I worked with Dr H J R Bussey for about twenty years, during which time I learned a lot about the history of the Polyposis Registry. According to him, Dr Dukes spoke to Mr J P Lockhart-Mummery about obtaining polyps for his adenoma/carcinoma research and during this conversation they decided that all information about patients with multiple polyps should be collected. J P Lockhart-Mummery was known to have an interest in inherited conditions and had noted that patients who presented with multiple polyps also had a family history of bowel cancer. 'Bussey' as he was then known, had just been appointed [in 1924] and was given the task of documenting/filing the information. I usually refer to the information collected at that time as the Polyposis 'Register' with the 'Registry' coming later when it was a Department rather than a collection of information.' Reflecting on the growth of the register by 1948 to include histories of twenty families, Ms Neale further commented, 'Dr Bussey told me many times that Dr Dukes would say that "it takes twenty years to prove that published information is wrong." I imagine that at that time they would have been building the register with a view to establishing the facts. They were cautious. As you see, it took over twenty years to collect just twenty families,

---

[246] These additional materials have been provided by St Mark's Hospital.

[247] Interview conducted with Ms Kay Neale at the Polyposis Registry, St Mark's Hospital on 29 April 2013 by Ms Emma Jones. A copy of the transcript for this interview will be deposited with the records of this meeting at the Wellcome Library, London, under archival reference GC/253.


Date of birth
Patient's surname concealed for confidentiality
Surgeon: John Percy Lockhart-Mummery
First recorded case in this family: a patient may or may not have had polyposis, but this individual clearly did
First appointment
Family number
Hospital number
10th person diagnosed with polyposis
Pathology number, in red ink
Pathology: all denoted by red ink
Treatment: removal of polyps by diathermy (burning off)
Age at death
Surgery, underlined in blue ink: '…in 1924 it was very risky to do major surgery because the Rhesus factor hadn't yet been discovered …blood transfusions were risky, bleeding was more common…The idea was to take out as much of the colon as possible because the colon could not be monitored but the rectum could be monitored with the sigmoidoscope… of course the sigmoidoscope would only be 20cm long in those days…if the join was above the 20cm that's where they found that they got their cancers.'
'…the swelling in the groin is obviously where the secondary cancer has spread. Inoperable cancer of the transverse colon, so the transverse colon was never taken out.'
Cause of death
Survival duration post two surgeries
1693. LEEDS ⇒ JPLM. PROPOSITUS.
15.4.1924 Bleeding & mucus. S. – Mult. polyps.
3.5.24. Admitted.
26.5.24. PARTIAL COLECTOMY. (Proximal T/C. & sigmoid). Mult. adenomata. No cancer.
1930, 18.1.32, 27.2.33, 16.3.36, 28.3.38, 8.5.39. Diathermy of polyps on all these occasions.
7.6.1940 Diathermy of polyps.
20.12.40. PERINEO-ABDOMINAL EXCISION
7.6.44. Swelling in groin for 4 weeks. Abdominal pain. Large almost fixed mass in transverse colon. Growth infiltrating colon near colo-ileal conn.
1945. DIED.
DIED. 1945.
INOPERABLE CARC. TRANS COLON
1) 21yrs.
2) 4yrs.
52yrs


Diagnostic barium enema
Fulguration: method of diathermy
Splenic flexure
Ileorectal anastomosis
Estimated quantity of polyps seen
Cyst removal
Gastroduodenoscopy
Surgeons: Hugh Evelyn Lockhart-Mummery and John Nicholls
Patient was actively sought by Polyposis Registry staff: '…of course the 1950s was the time at which they started to try and call people because the surgery from 1948 was beginning to show that it was successful…'
Screening dates for polyps by rigid sigmoidoscopy. 'They were doing it 3- or 4- monthly up until the 1970s…They did some research and they showed that by calling people up 3 times a year at that point, every 4 months, they didn't feel it was necessary and they moved it to 6 months.'
Pancreaticoduodenectomy
'This was a [randomized control] trial that we did with Professor Jerry DeCosse from New York who had a theory that vitamin C would cure polyps and we managed to enrol quite a number of our patients [in the late 1970s]. He didn't have enough patients in the States so he came to St Marks every three months, and a lot of our patients took part. …Nothing came of it…Vitamin C didn't work.'
Heartburn symptom: '…we know now, well in the 1990s there was a research project done here at St Mark's which showed that virtually everybody with adenomatous polyposis has duodenal adenomas but we didn't know it then. We thought it was about 50%. … And here look he's complaining of heartburn which is probably why they did that test' (barium meal). … it looks like they think he or she died as a result of the operation but had cancer of the duodenum and the ampulla vater.'

some of which would have only had one or two affected members; I doubt they saw it as a register at that time. They collected lots of information: some became important and some proved pointless.'

Speaking about those early days, Ms Kay Neale said, '…the register started in 1924 when Dr Cuthbert Dukes was studying adenomas to see if he could prove that there was [an] adenoma carcinoma sequence. And he approached J P Lockhart-Mummery to ask for some polyps for his research and J P Lockhart-Mummery explained that he had some patients who had a lot of polyps, which continued to grow over the years, and they also had a family history of relatives dying from bowel cancer. At that point the two men decided that they should start to record the details of these patients and their families. The index cards wouldn't have been written at that time. I don't know how the information was collected at that time, probably on foolscap paper… It wasn't until much later that they started their research projects, which led to H J R Bussey doing work for which he was awarded a PhD (see Bussey, 1970). And it would have been somewhere between the 1920s and when he started this work that he would have revised his filing system to start collecting data in a very organized fashion to see…because he did collect every single bit of information that he could find out about people some of which became very useful in later years and which he didn't know would be interesting at the time he was recording it.'

b) Letter from Dr C Dukes to Dr J C Burne

Below is an example of a letter from Cuthbert Dukes in the 1950s, during the proactive campaign to recruit people for polyposis screening. Please note that patients' names have been removed to preserve their anonymity.

9th May 1958.

Dear Burne,

I am most grateful to you for writing to me about Iris [redacted] I was quite right in what I said to you at Hastings: she is a member of Family 4.

I think I explained to you that I now have approximately 60 families in our records, and Family 4 dates back to the very early days when we had in here a patient named Mrs [redacted] who was admitted in 1933 and died subsequent to her operation. We got no further information about this family until one of our residents here, Mr. T[redacted], linked it up with the A[redacted] family, which we began to investigate round about 1950.

The family pedigree has been published more than once, and it was included in my article in the Annals of Eugenics in 1952, a reprint of which I am sending you herewith. On page 15 you will see that the pedigree of Family 4 is recorded, and at that time we were only aware of the existence of two children of Mary [redacted], but we now know that there were four. In the key to this family on page 19 Iris [redacted] is recorded as untraced, but this was in 1952 and since then I have of course got further information about the family, and our last records said that she had been sigmoidoscoped at Dartford and one polyp had been found.

Your kindness in informing me about this patient will enable me to bring the family records up to date, and I am going to write at once to Mrs [redacted] asking

when I can come and see her. I find that a personal visit is almost always the best way in a situation of this sort. When I have had a talk with her I have no doubt I shall get information about other members of the family and this will pedigree/ enable me to bring the family/up to date, and when I have done this I will send you a copy.

I should be most grateful if you would let me know if you come across any other members of this family. We have always had difficulty in keeping in contact with the children of Mrs [redacted], but have very accurate records of the [redacted] branch of the family. When I come down to Dartford I will drop in to see you to thank you personally for the help you have given.

With many thanks,

Yours sincerely,

Cuthbert E. Dukes, M.D.

Dr. J.C. Burne,
Pathological Laboratory,
River Hospitals,
Joyce Green,
Dartford,
Kent.

c) Untitled adaptation of Lewis Carroll's poem *You Are Old Father William,* by Dr Cuthbert Dukes, suggested by Ms Kay Neale as an example of his 'foresight and humour':[248]

"You are old, Father William," the young surgeon said,
"And your colon from polyps is free.
Yet most of your siblings are known to be dead –
A really bad family tree."
"In my youth," Father William replied with a grin,
"I was told that a gene had mutated,
That all who carried this dominant gene
To polyps and cancer were fated.
"I sought for advice from a surgical friend,
Who sighed and said – 'Without doubt
Your only escape from an untimely end
Is to have your intestine right out.'
"It seemed rather bad luck – I was then but nineteen –
So I went and consulted a quack,
Who took a firm grip on my dominant gene
And promptly mutated it back."
"This," said the surgeon, "is something quite new
And before we ascribe any merit
We must see if the claims of this fellow are true,
And observe what your children inherit!"

C E Dukes, 1952

[248] Dr Cuthbert Dukes recounted this poem in his Hunterian Lecture of 1952. See Dukes (1952), page 304.

d) Obituary for Dr H J R Bussey[249]

HENRY JOHN RICHARD BUSSEY, OBE, BSc, PHD. 1907–1991

Dr HJR Bussey

The remarkable quality of Dick Bussey's career was not just its longevity but the dedicated application of his talents to the professional practice of St Mark's Hospital. He came to St Mark's in October 1924 at the age of 17 from University College Hospital where he had started training as a laboratory technician. Dr Cuthbert Dukes required an assistant and Dick was appointed with a salary from the newly formed British Empire Cancer Campaign (later the Cancer Research Campaign – CRC). He retired from his CRC appointment in 1974 after more than 50 years service and became an officer of the Most Excellent Order of the British Empire for services to Cancer Research. But Dick continued to serve the Hospital as a Consulting Research Fellow right up to the time of his death.

From the very beginning Dick's natural talents as a collector and archivist were encouraged by his mentor, Dr Cuthbert Dukes. His neat and methodical approach is apparent in the earliest records of the Pathology Department. This was the time when Dr Dukes with his surgical colleagues Percy Lockhart-Mummery and WB Gabriel were engaged in studies on the pathology and prognosis of cancer of the rectum. Dick was the work-horse of the team and made a vital contribution to the emergence of the Dukes classification. He became responsible for all the dissections of surgical specimens, the drawings of the extent of spread and the photography. In the years after the second World War he acquired the skills of statistical analysis which bore fruit in the publication of the definitive article on the Dukes classification in the British Journal of Cancer in 1958. Although not a graduate in medicine he became an excellent pathologist by apprenticeship and was as skilled in microscopic diagnosis as in his description of the gross appearances of surgical specimens. Although rectal cancer dominated the work of the Pathology Department between the two world wars, the whole range of laboratory investigation in histopathology, haematology and blood transfusion, microbiology and chemical pathology required attention. Dick played a full part alongside his colleague George Lamb who came to the hospital in 1927 and also served for 50 years before his retirement.

Dick Bussey's work on records included the card index and numbering systems for the Pathology Department which stood the test of time until they were superseded by the computerised systems introduced in recent years. But Dick's international reputation was really based on his meticulous clinical records, filing systems and family pedigrees of polyposis families. He knew many of the patients personally and revelled in this clinical contact. He also filed all the correspondence concerning these patients. It has been said that his ability to recall data on request was faster and more reliable than the computerised system introduced in the mid 1980s!

Dick was never possessive with any of his records. Generations of surgeons, pathologists and research workers have reason to thank him for his generous and unselfish way in which he would provide information for research and teaching. This service was also freely given to many not on the staff of the Hospital who required information.

Dick Bussey had a generous and equable

[249] Morson (1990).

personality. In nearly 40 years I have never seen him lose his temper or even show any sign of irritation. He had a great sense of humour and a well developed sense of the ridiculous. As a conversationalist and raconteur he was both interesting and entertaining. He loved to pass the time of day discussing professional and any other issues with those around him. His modesty and lack of ambition were two main reasons why he failed to achieve recognition outside St Mark's until quite late in his life. It was only under pressure from Dr Dukes that he was persuaded to work at night school for his BSc (1933). Later he was pressed to work for a Doctorate of Philosophy on his polyposis studies which he was granted in 1970 (University of London, Faculty of Medicine). This was the trigger that gave him greater status and more self confidence. To all he became "Doctor" Bussey.

It might be thought that Dick was less of a "leader" in research and more an assistant who implemented the ideas of others. This is not so. His contributions to the Dukes classification, the study of the adenoma-carcinoma sequence in the large bowel and research into polyposis syndromes were all original but he largely left the publication of results to colleagues.

The social climate of the years between the two world wars, their attendant class distinctions together with the peculiarly British preoccupation with badges of status made it difficult for Dick to fit into any standard system of promotion. For most of his life there was no place for the medical scientist (which is what he was) in hospital life. He started as a "lab boy" and it is greatly to his credit that he obtained University degrees which enabled St Mark's to manufacture appropriate titles for him which reflected our respect for his work. However, until the Polyposis Registry was built with funds from the World Health Organisation in the 1970s he had to share accommodation with the Pathology Department's secretary. Before that, and for much of his career, he sat at a table in the corner of the old pathology museum (now the Histology Laboratory) sharing space with surgical research fellows and others. I doubt that all this bothered him much and it did help him to acquire over the years his remarkable store of clinical and surgical knowledge.

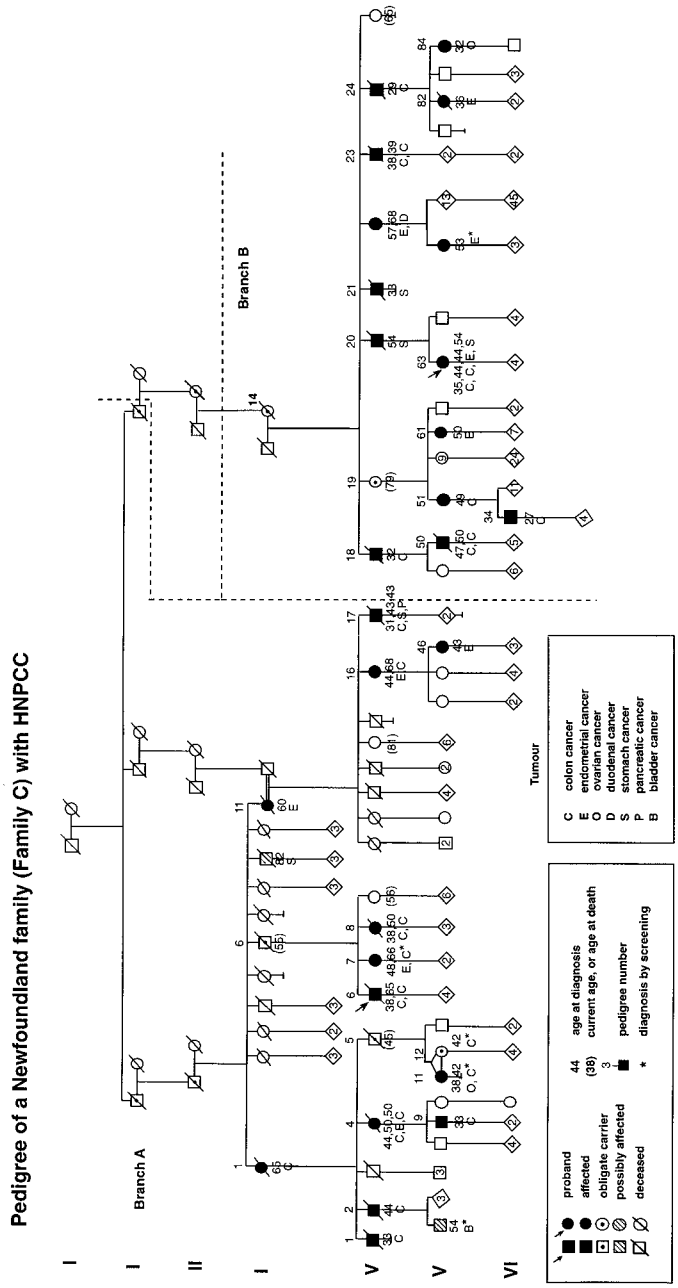
Inclined to be shy as well as lacking in self confidence, Dick's postgraduate teaching of surgeons and others was largely on an informal basis. In 1974 the St Mark's Association raised funds from its members to send Dick and his wife Daphne on a lecture tour of the United States of America and to attend a meeting of the American Society of Colon and Rectal Surgeons where he was invested with an Honorary Membership. After initial anxieties he became a successful lecturer both nationally and internationally.

Dick was devoted to St Mark's. It is no disrespect to his family and particularly his much loved wife Daphne who died in 1989 that he saw the Hospital as a place of shelter. After all, he had been doggedly travelling to and from the City Road to his home in Croydon for over 67 years without a break. But St Mark's loved Dick Bussey and admired his unselfish and highly professional dedication to his work. He was known personally to all grades of staff and his familiar and ever present figure was a source of great strength to the hospital. Dick developed painless jaundice in 1990 and had an operation for relief of symptoms. He did not allow his serious illness to affect his regular attendance at the hospital and carried on as usual with his work in the Polyposis Registry. Although increasing weakness and frailty was obvious to all he refused to give in, being concerned only that his records should be left in the good order that characterised his whole life. It is difficult to think of St Mark's without Dick. We mourn his death but will remain ever grateful for his friendship and his unique contribution to the life of the Hospital.

Basil Morson

Appendix 3

Pedigree of a Newfoundland family, 'Family C', with HNPCC[250]



[250] Reproduced from Green (1995), page 251.

Appendix 4

Cancer Genetics: a personal view, by Professor David Harnden[251]

Quite often the motivation for writing something down is that I have read an article in a newspaper that either stimulates my imagination, or recalls something from the past. In *The Times* of 1 December 2007 there were several such articles – and this is the result of one of these articles – taking me back to the time that I was newly appointed as Professor of Cancer Studies in the University of Birmingham. I will first of all quote the relevant passage from *The Times*.

> A £3 million suite of machines, to be installed at the Wellcome Trust Sanger Centre near Cambridge, will increase the capacity to decode DNA by a factor of 600. It will particularly transform cancer genetics, allowing researchers to analyse tumours for the full range of mutations that cause cells to grow out of control.[252]

It was the phrase 'transform cancer genetics' that caught my eye. When I first went to Birmingham my laboratory was funded by a local branch of what was then the British Empire Cancer Campaign (later the Cancer Research Campaign). This was quite autonomous, and separate from the National BECC organization. It was run by well-meaning volunteers who handed over the money they raised to the University which had a Cancer Research Committee. That Committee had the responsibility to give out grants to support cancer research projects in the University. In practice, the members of the Committee granted money to support research in their own departments. I could see that it would be quite a fight to get enough money to do what I wanted to do. I believed that the correct course of action would be to amalgamate the Birmingham Branch of the BECC with the National BECC organization. This would give us access to much larger sums of money, but of course we had to be able to compete for grants at national level. I was sure that we could compete, so I discussed this with several influential people and they all approved of my plan. First, I had to get the agreement of the University Senate. I had already learned from my short, but bitter, experience of university politics that it was important to

---

[251] An essay contributed by Professor David Harnden, who was unable to attend the seminar.

[252] Henderson (2007).

get the support of the Vice Chancellor before the debate in the Senate and I managed to do this. When the debate started, I outlined my plan, but then a number of the members of the University Cancer Research Committee (who had been creaming off the money for their own purposes) started to attack me as an inexperienced young upstart. The Professor of Chemistry was particularly vitriolic. The VC came to my aid, and effectively told the complainants that we, in Birmingham, had to compete at national level if our work was to be respected. I got approval to go ahead, and the Birmingham BECC was joined with the national BECC organization. Then, of course, I had to apply for grants to support our work in a nationally competitive market. I drafted my grant proposals, which were based, largely, on my ideas about cancer genetics.

At that time (1969) quite a lot was known about chromosome abnormalities in cancer cells, but they were thought to be a consequence of the disease process rather than anything to do with the causation of the cancer. Nothing was known about genes that caused cancer, and the few rare inherited cancers, like retinoblastoma, were thought to be oddities of little importance. I already had a clue that cancer genes were important from the work that we had done in Edinburgh on a specific chromosome abnormality that occurred in one type of leukaemia. I had shown, further, that male breast cancer was commoner in men with an abnormal XXY chromosome complement, suggesting that genetic make-up was important in the causation of cancer. Further, from what I had read of earlier work by scientists such as Theodore Boveri, it seemed clear that genetics would be important in cancer causation.[253] I also believed, since so many things about human beings were determined by an interaction between genetics and environment, that cancer, too, was likely to have a major genetic component. So off my grant application went to the BECC in London. The reply which came back, many weeks later, was a bit of a bombshell. Effectively, it said that the BECC Scientific Committee was surprised that I did not know that cancer was caused by environmental factors, such as smoking cigarettes, the use of tars, mineral oils and other industrial chemicals. Genetics had little or nothing to do with it. However, since I was a new professor, the Committee would give me a small grant to get me going, on the understanding that I would come back with something more sensible in a couple of years.

---

[253] Boveri (1914).

That was a bit of a setback, but we ploughed on and gradually we got a good programme of cancer genetics up and running. There was our work on ataxia-telangiectasia, which I have described in detail elsewhere.[254] Another interesting example arose when I was approached one day by an elderly GP, John Hallam, who wanted to do some research. He had become convinced that cancer in organs that were bilateral, such as kidney or breast, tended to occur at young ages, and also to run in families. We set up a search in the local cancer registry for early-onset breast cancers. As a result we discovered several families that had a significant excess of breast cancer.

Though it was others who took this idea forward, this was one of the first steps leading to the discovery of the breast cancer susceptibility genes such as *BRCA1.* I also set up a discussion group, which we called the Cancer Family Study Group, to bring together all the people (doctors, scientists, nurses, statisticians and others) who were involved in the study of families with an increased risk of cancer. This was a new concept since most meetings were restricted to medics or scientists. The group flourished, and soon Walter Bodmer, a geneticist who had recently become Director of the Imperial Cancer Research Fund, joined in. Meetings, which were held alternately at the ICRF and my Department, were often attended by more than one hundred people. The whole notion that genetics was important in the causation of cancer was beginning to be accepted. Some years later, when I was a member of the Cancer Research Campaign's Scientific Committee, it was very satisfying to find that cancer genetics was now considered its top priority for research funding!

Another interesting development occurred when I was Director of the Paterson Institute.[255] We were doing research on families with cancer susceptibility, but there was no-one with specific clinical responsibility for caring for the special needs of such families. After discussion with Rodney Harris, the Professor of Human Genetics in Manchester, it was agreed that he would try to get the Regional Heath Authority to create, and pay for, a consultant post with this responsibility. The RHA agreed, but said that it could not be done for about two years. I, therefore, approached the Wigan and District Cancer Research Fund (which had helped me before) and asked if it would be prepared to fund such a post for two years. This was a surprising, but excellent source of funds. The people there were terrific!! Luckily, the Wigan Fund was flush with money

---

[254] See, for example, Bridges and Harnden (1981).

[255] See note 32.

since one of its members had recently died and left a substantial amount of money to it. They agreed to help, and so we appointed a young clinician called Gareth Evans to look after the exceptional needs of families who had learned that they had an unusual risk of developing cancer. Gareth was a great success and became, first, a consultant and then Professor of Cancer Genetics: perhaps the first in the country with such a title.

So you see, we have come a long way from the point when, over thirty years ago, cancer genetics was not considered worthy of being supported at all by the CRC, to the position quoted from *The Times* article at the beginning of this essay, where a grant of millions of pounds can be awarded to a scheme which, it is hoped, will enable people to become aware of their inherited cancer risk, and hopefully take steps to minimize that risk.

A final word of warning: we must be careful not to go too far in this direction. Cancer genetics might be important, but we must not forget that environmental factors such as radiation, viruses and noxious chemicals *do* all play an important part in the causation of different kinds of cancer. Cancer research does have a rather unfortunate reputation of supporting, to excess, the area that is currently fashionable – for example, chemical carcinogens in the 1940s and 1950s, radiation in the 1960s, viruses in the 1970s and 1980s, and now genetics. All are important, and it is essential that the research funding bodies maintain a balanced portfolio. But we are getting there.

Glossary

The following textual and web-based sources were consulted: *Churchill's Illustrated Medical Dictionary* (1989) New York: Churchill Livingstone; *A Dictionary of Genetics* (7th edition) (2006) Oxford: Oxford University Press; Genetics Home Reference: US National Library of Medicine, http://ghr.nlm.nih.gov/; Online Mendelian Inheritance in Man (OMIM): Johns Hopkins University, http://omim.org/. Professor Peter Harper also contributed to compiling and editing this glossary.

Ascertain
The method of identifying individuals or families with hereditary traits associated with specific conditions or diseases.

Ataxia-telangiectasia
An autosomal recessive disorder characterized by cerebellar telangiectases, immune defects and a predisposition to malignancy. It may also affect the functions of the nervous system, and can manifest in early childhood with significant problems of balance, walking and facial expression.

Candidate gene
Specific gene undergoing research to determine its possible relationship to a specific genetic condition or disorder.

Colonoscope
A thin, flexible tube used to examine the lining of the bowel wall via the rectum.

Familial adenomatous polyposis (FAP)
FAP is a hereditary disorder in which polyps form early in life in the colon, becoming malignant later in life unless prophylactic surgery is performed. In attenuated FAP (AFAP), polyps develop at a later age. *APC* is the gene linked to FAP.

Gene
A gene is the fundamental unit of heredity.

Genotyping
The determination of an individual's genetic constitution.

Hereditary non-polyposis colorectal cancer (Lynch syndrome I and II)
Dominantly inherited cancer syndromes that, unlike FAP, are not associated with the manifestation of polyps in the colon. Lynch syndrome I is located solely in the colon, while Lynch syndrome II

is characterized by multiple extra-colonic cancers, including breast, endometrial, gastrointestinal, ovarian, sarcoma, brain and leukaemia, among others. The genes associated with HNPCC are primarily *MSH2* and *MLH1,* but also *MSH6* and *PMS2.* Early onset of cancer is characteristic of both HNPCC varieties, as are tumours' proximal relationship to the colon.

Human leukocyte antigen (HLA) region

An area of the human genome mapped to chromosome 6 and involved in cellular immunity. Different HLA types are associated with cancer susceptibility.

Locus

The position of a gene on a chromosome.

Loss of heterozygosity (LOH)

The structural or functional loss of one of a pair of alleles, often seen in tumours.

MEN1 / MEN2A

A gene that encodes menin, in which mutations can cause MEN1. Multiple endocrine neoplasia type 2 is a syndrome, rather than a gene, that is connected to mutations in the RET oncogene.

Mismatch Repair

Proteins that check, or 'proof read', the accuracy of DNA after synthesis.

MUTYH-associated polyposis (MAP)

A recessively inherited form of polyposis associated with mutations in the *MUTYH* gene.

Sigmoidoscopy

An endoscopic inspection of the interior of the sigmoid colon.

Tuberous sclerosis

An inherited neurodevelopmental disorder causing learning disability, epilepsy, tumours and skin pigmentation changes, among other features.

Von Hippel-Lindau disease

A dominantly inherited familial cancer syndrome characterized by abnormal tissue masses (neoplasms) in the retina, cerebellum or other parts of the central nervous system, kidney or pancreas, among other locations. Neoplasms may be a combination of benign and/or malignant.

Xeroderma pigmentosum

An autosomal recessive genetic disorder, causing hypersensitivity to sunlight and a high predisposition to developing skin cancer.

Biographical notes*

Professor Timothy Bishop

PhD FMedSci (b. 1953) was educated at the universities of Bristol and Sheffield, in mathematics and statistics, receiving his doctorate from the latter in 1978 in probability and statistics. In 1979, he moved to the University of Utah, Salt Lake City, where he commenced his post-doctoral research on investigating the links between data in the population records of Mormon families with Utah State's cancer registration records and death certificates. Remaining in Utah, he became Assistant Professor at the Department of Medical Informatics (1979–1986) and then Associate Professor (1986–1989) and Adjunct Associate Professor (1989–1997). His research in the 1980s was facilitated by the use of recombinant DNA technology to identify genetic variation and the production of genome maps to investigate the potential for identifying breast and colorectal cancer genes. Returning to the UK in 1989, he became Senior Scientist and Head of Laboratory at the ICRF in Leeds, running a research group in genetic epidemiology and familial cancer susceptibility. This group was a key research centre which contributed to international efforts to, eventually, map and identify the genes for breast and colorectal cancer. He is currently Director of the Leeds Institute of Cancer and Pathology (2011–).

Lady Julia Bodmer

Hon MRCP Hon FRCP FMedSci (1934–2001), originally studied economics, philosophy and politics at Oxford University, and later applied her training in statistics to genetics. She made important advances into HLA types and their association with juvenile rheumatoid arthritis and ankylosing spondylitis, and in the aetiology of Hodgkin's disease, Burkitt's lymphoma and testicular cancer. She was a founder of the European Federation for Immunogenetics. Her archival papers will be available along with Sir Walter's at the Bodleian Library, University of Oxford, in 2014.

Professor Sir Walter Bodmer

FMedSci FRCPath FRS FSB Kt (b. 1936) was educated at Clare College, Cambridge, UK; moving from a mathematics degree to

* Contributors are asked to supply details.

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

Professor Sir John Burn

Kt MD FRCP FRCPCH FRCOG FMedSci (b. 1952) completed an intercalated genetics degree in 1973 and qualified in medicine from Newcastle University in 1976. After further medical and paediatric training he became Clinical Scientific Officer in the MRC Clinical Genetics Unit, Great Ormond Street Hospital, London, and returned to Newcastle as their first Consultant Clinical Geneticist in 1984. He became first Clinical Director of the Northern Genetics Service (1989–2004) and Professor of Clinical Genetics, Newcastle University (1991–) and Head of the Institute of Human Genetics (2004–2010). He was President of the European Society of Human Genetics (2007), Chair of the British Society for Human

Genetics (2011–2013), Chair of the National Institute for Health Research Genetics Specialty Group, (2008–) and Director of the NIHR Collaborative Group for Genetics in Healthcare (2009–). He was Lead Clinician, NHS North East (2009–2013). Sir John was also Innovation Chair for the Human Genomics Strategy Group (2011–2013) and is a member of the NHS Genomic Strategy Board. He was knighted for his services to medicine and healthcare in 2010.

Dr Henry Bussey

OBE PhD (1907–1991) See Appendix 2, on pages 95–6, for his full obituary.

Dr Cuthbert Dukes

OBE MRCS FRCS (1890–1977) commenced his internationally renowned research into the pathology of colonic and rectal cancer in 1922, when he was appointed as the first pathologist to St Mark's Hospital. His foundation of the Hospital's Polyposis Register in 1924, with Mr J P Lockhart-Mummery, was highly significant for the development of knowledge about FAP and for its diagnosis and treatment. See Dukes (1952) and (1958).

Professor Gareth Evans

MRCP MD FRCP (b. 1959) trained at St Mary's Hospital Medical School, London, where he specialized in paediatrics before moving into genetics at St Mary's in Manchester. He undertook a Medical Cadetship in the Army and served as Medical Officer to the Royal Hussars. After obtaining Membership in Paediatrics and reaching Senior Registrar level in the Army (1989), he joined Manchester University as a Senior Research Fellow and undertook an MD (1990–1992) in cancer genetics, studying NF2. Evans was instrumental in setting up cancer genetics services for the North West of England in 1990, and he continues to work in the University of Manchester as Honorary Professor of Medical Genetics; and as Consultant in Medical Genetics and Cancer Epidemiology for the Central Manchester Hospital NHS Foundation Trust and The Christie NHS Foundation Trust. From 2002 to 2010 he was Chairman of the NICE Familial Breast Cancer Guideline Development Group, of which he has been the clinical lead since 2011. He lectures internationally on the subject of hereditary breast cancer, neurofibromatosis and other cancer syndromes. In the UK, he has developed a national medical training programme for breast cancer genetics, as well as education for professionals risk assessing and counselling those who are at risk or

are directly affected by hereditary breast cancer. Currently, he is the Chief Investigator for a National Institute of Health Research-funded project to improve techniques for breast cancer prediction (2009–). He has published more than 500 peer-reviewed research papers, reviews and book chapters, and was co-editor of *Risk Assessment and Management in Cancer Genetics* (see Lalloo *et al.* (eds) (2005)).

Professor George Fraser

MD PhD DSc FRCP FRCPC (b. 1932) qualified in medicine at Cambridge, followed by a PhD from University College London and Fellowships at the Canadian College of Medical Genetics and the American College of Medical Genetics. He was appointed Scientific Officer, MRC Population Genetics Research Unit, Oxford (1959–1961); Research Fellow, Division of Medical Genetics, University of Washington, Seattle (1961–1963); Lecturer, Department of Research in Ophthalmology, Royal College of Surgeons, London (1963–1966); Reader in Genetics, University of Adelaide (1966–1968); Associate Professor, Division of Medical Genetics, University of Washington (1968–1971); Professor of Human Genetics, University of Leiden (1971–1973); Professor of Medical Genetics, Memorial University, St John's, Newfoundland (1973–1976); Chief of Department of Congenital Anomalies and Inherited Diseases, Department of National Health and Welfare, Federal Government of Canada, Ottawa (1976–1979); Associate Professor, Centre for Human Genetics, McGill University, Montreal (1979–1980); Special Expert in Human Genetics, National Library of Medicine, National Institutes of Health, Bethesda, Maryland; attached to Moore Clinic for Medical Genetics, Johns Hopkins University, Baltimore (1980–1984); Senior Clinical Research Fellow, Imperial Cancer Research Fund; Honorary Consultant in Clinical Genetics, Cancer Genetic Clinic, Churchill Hospital, Oxford until his retirement (1984–1997). In 2007, his career was commemorated in the book, *Fifty Years of Human Genetics* (Mayo and Leach (eds) (2007)). His scientific papers have been archived at the Wellcome Library, London (reference PP/GRF). (Further biographical details for Professor Fraser are available in the records of the seminar, which will be archived in the Wellcome Library.)

Professor Eldon Gardner

PhD (1909–1986) was a zoologist and geneticist who taught and researched at Utah State University

and at the University of Utah. As a geneticist, his research into the causes of cancer was focused on families in Utah, notably within the Mormon community. In 1950 he established the existence of a hereditary form of cancer of the lower digestive tract which became known as Gardner syndrome. See http://www.usu.edu/greats/research/index.cfm?article=30847 (visited 8 January 2013) and Gardner and Stephens (1950). The Eldon Gardner papers (1936–1986) are held at the archives of the University of Utah.

Professor Jane Green

PhD Hon FCCMG (b. 1943) received her BSc in Zoology (1964) and MSc in Drosophila Genetics (1966) from the University of British Columbia, then in the late 1960s, moved to Newfoundland and Labrador. From 1978 to 1986 she worked with Dr Gordon Johnson to establish an Ocular Genetics Clinic, studying the distribution and frequency of hereditary eye disorders. They began a cancer genetics screening programme in 1982 after a family with Von Hippel-Lindau disease was referred to the Ocular Genetics Clinic. She received her PhD from Memorial University of Newfoundland (MUN) in 1995, with a dissertation on the development of clinical and genetic screening programmes for hereditary cancer syndromes, in which mapping the first mismatch repair gene, *MSH2*, with Drs Vogelstein and de la Chapelle was an important component. She has been a faculty member at MUN since 1988 and a Professor in the Discipline of Genetics since 2002. In 2008 she received a Knowledge Translation award from the Canadian Institutes of Health Research, and was also made an honorary member of the Canadian College of Medical Geneticists (CCMG). In 2012 she received the CCMG Founders Award for her contribution to developing genetics services in Newfoundland and Canada.

Professor David Harnden

PhD FRCPath FRSE (b.1932) graduated from Edinburgh University BSc (1954), PhD (1957). He was a Scientific Member of the Medical Research Council at the Radiobiology Research Unit, Harwell and then at the MRC Clinical Effects of Radiation Research Unit at the Western General Hospital Edinburgh. He spent a year in the Laboratory of Dr Howard Temin at the University of Wisconsin in Madison, USA. He became Professor and Head of the Department of Cancer Studies in the University of

Birmingham and then Director of the Paterson Institute and Professor of Experimental Oncology in the University of Manchester, now Emeritus. On his retirement he became Chairman of the South Manchester Hospitals NHS Trust. His early research was in human genetics and he was among the first to publish a correct karyotype of human chromosomes. He studied the chromosomes of patients with inherited disorders and discovered the trisomy of chromosome 18 as well as the first double trisomy. His later studies were on patients with an inherited susceptibility to develop cancer.

Ms Christina Harocopos

SRN SCM (b. 1939) studied nursing at St Bartholomew's Hospital from 1958 to 1962, qualifying in 1963. She subsequently trained as a midwife at Freedom Fields Hospital, Plymouth. In 1964 she was a member of a team of European nurses working in Greece with funding from Save the Children. She returned to St Bartholomew's Hospital as a Theatre Sister, before temporarily retiring to raise her two children and also volunteering at St Mungo's charity for homeless people as a project worker (1977–1980). As Professor Brooke's Theatre Sister at St James' Hospital in Balham, she was encouraged to develop her knowledge and expertise in diseases of the colon and rectum and she specialized in stoma care as a clinical nurse at St Mark's Hospital (1980–1986). She was a Genetic Research Assistant and Family Visitor for St Mark's Hospital Family Cancer Clinic (1987–1996), supported by the Imperial Cancer Research Fund. Moving to South Africa, from 1996 until 1998, she was the Family Cancer Coordinator at the Groote Schuur Hospital in Cape Town, a post funded by the De Beers Chairman's Fund (DeBeers Consolidated Mines Ltd-Namaqualand Mines) in support of the South African Hereditary Nonpolyposis Colorectal Cancer Project. Back in the UK, from 1998 until her retirement in 2010, she was a Clinical Nurse for the North East Thames Clinical Genetics service and North East London Cancer Network, based at St Bartholomew's Hospital.

Professor Peter Harper

Kt FMedSci FRCP (b. 1939) graduated from Oxford University in 1961, qualifying in medicine in 1964. After a series of clinical posts, he trained in medical genetics at the Liverpool Institute for Medical Genetics under Cyril Clarke and at Johns Hopkins University, Baltimore, under Victor McKusick. Appointed to develop

medical genetics in Cardiff in 1971, he was Professor of Medical Genetics at the University of Wales College of Medicine, Cardiff, until his retirement in 2004, when he became University Research Professor in Human Genetics, Cardiff University (Emeritus since 2008). At the request of the Chief Medical Officer (England), in 1996 he chaired the working group and authored the report *Genetics and Cancer Services,* more commonly known as 'The Harper report' (Department of Health (1996). He served on the UK's Human Genetics Commission (2000–2004) and the Nuffield Council on Bioethics (2004–2010). He has been closely involved with the identification of the genes underlying Huntington's disease and muscular dystrophies, and with their application to predictive genetic testing. He has also been responsible for the development of a general medical genetics service for Wales. His books include *Practical Genetic Counselling* (Harper (1981)), *Landmarks in Medical Genetics* (Harper (2004)), *First Years of Human Chromosomes* (Harper (2006)) and *A Short History of Medical Genetics* (Harper (2008)). For the past decade he has led an initiative, supported by the Wellcome Trust, to preserve and document the history of Human and Medical Genetics (www.genmedhist.org). He is a consultant to the 'Makers of Modern Biomedicine Project' for the History of Modern Biomedicine Research Group, Queen Mary, University of London.

Professor Shirley Hodgson

DM D(Obst)RCOG DCH FRCP (b. 1945), daughter of Lionel Penrose, she avoided working in genetics for many years, but after training in medicine and working in general practice while her children were young, she did a locum in clinical genetics at Guy's Hospital, and found it irresistible. She went on to work in the field of clinical genetics for many years. From 1983 to 1988 she was Senior Registrar in Clinical Genetics for the South Thames (East) Regional Genetics Centre and Honorary Senior Registrar at Hammersmith Hospital, London. At Addenbrooke's Hospital, Cambridge (UK), she was Consultant Geneticist (1988–1990). She promoted the development of cancer genetics clinics at Guy's and St Thomas', St Mark's and St George's Hospitals in London in the 1990s and ran the regional cancer genetics service at Guy's and St Thomas' Hospital. She has published widely on the subject of cancer genetics, and co-authored several books, including

Inherited Susceptibility to Cancer: Clinical, predictive and ethical perspectives (Foulkes and Hodgson (eds) (1998)) and *A Practical Guide to Human Cancer Genetics* (Hodgson and Maher (1993)). She has an active research programme investigating inherited aspects of cancer predisposition, especially in breast and colorectal cancers. She is particularly interested in international collaborative research. She took up a new post as Professor of Cancer Genetics at St George's, University of London, in 2003. Her current research looks at molecular changes in colorectal polyps in relation to inherited colorectal cancer susceptibility, and she was Principal Investigator of a five-year randomized study funded by Cancer Research UK to evaluate whether the Mirena intrauterine progestogen-releasing system reduces the risk of endometrial cancer in women with Lynch syndrome who are at increased risk.

Dr Alfred Knudson

MD PhD (b. 1922) was educated at the California Institute of Technology and Columbia University, receiving his doctorate from the former in 1956. Primarily a paediatrician, he combined his discipline with clinical genetics research at the Los Angeles Children's Hospital. From 1951 to 1953 he served as a medical officer with the US Army during the Korean War. His service was based at Fort Riley in Kansas where he screened the health of newborns. Subsequently, he was Head of Pediatrics at the City of Hope Medical Center in Los Angeles (1956–1966) where he treated children with cancer and specific genetic diseases and researched their conditions. From 1966 to 1969 he was Associate Dean for Basic Sciences at the State University of New York, Long Island. In 1971 he founded the Medical Genetics Center at the University of Texas Medical School, Houston, becoming Dean of the Graduate School of Biomedical Sciences. The same year, he published his seminal paper which launched his influential 'two-hit' theory of the genes influencing tumour formation (see Knudson (2005)). He was appointed Director of the Institute for Cancer Research at the Fox Chase Cancer Center in Philadelphia (1976–1982), Center President (1980–1982) and Scientific Director (1982–1983). He has since been Senior Adviser for Fox Chase Cancer Center and Special Adviser for the (US) National Cancer Institute.

Professor Alan Lehmann

FRS FMedSci (b.1946) graduated from Cambridge University in Natural Sciences in 1967 and

received his PhD from the Institute of Cancer Research in 1970. He held postdoctoral positions at the Oak Ridge National Labs, Tennessee and the University of Sussex, which were followed by his appointment in 1973 as a senior scientist at the MRC Cell Mutation Unit, University of Sussex. He remained in this position until 2001 and was also made a University Professorial Fellow in 1987. In 2001 he became Professor of Molecular Genetics at Sussex and was Chairman of the Genome Damage and Stability Centre, until 2011. For most of his research career, he has worked on DNA damage and repair and its relation to cancer and other aspects of human health. In particular, he has been responsible for many advances in our understanding of genetic disorders associated with defects in DNA repair. He is consultant scientist for the multidisciplinary xeroderma pigmentosum specialist clinic.

Sir Hugh Evelyn Lockhart-Mummery

MRCS FRCS LRCP (1918–1988), son of Mr John Percy Lockhart-Mummery (see below), became Resident Surgical Officer at St Mark's Hospital in 1950, then Consultant Resident Surgeon 1951–1978. He is credited with making a breakthrough in the successful surgical treatment of polyposis, while retaining the bowel, in collaboration with Dr Cuthbert Dukes, in 1952.

Mr John Percy Lockhart-Mummery

MB FRCS FACS (1875–1957) became Assistant Surgeon at St Mark's Hospital in 1903, Senior Surgeon in 1913, Emeritus Surgeon in 1935 and Consulting Surgeon and Vice-President of the Hospital, in 1940. Among his many published writings are the books *Diseases of the Rectum and Anus* (Lockhart-Mummery (1914)) and *The Origin of Cancer* (Lockhart-Mummery (1934)).

Dr Henry Lynch

MD PhD (b. 1928) served with the United States Navy (1944–1946). He studied at the Universities of Oklahoma, Denver and Texas. From the latter's Medical Branch in Galveston, he was awarded his medical degree (PhD) in Human Genetics, in 1960. He became an Internal Medicine resident at the University of Nebraska where he developed his theories about the hereditary causation of cancer. From 1970 to 1990 Lynch continued his research into the genetics of colon cancer, with minimal funding, and amassed evidence to conclude that the disease could be inherited.

Hereditary non-polyposis colorectal cancer is now more commonly known as Lynch syndrome. Lynch's further research into cancer genetics demonstrated genetic links to some breast ovarian cancers, leading other investigators to locate the breast cancer genes, *BRCA1* and *BRCA2*. In 1984, Lynch founded the Creighton's Hereditary Cancer Prevention Clinic in Omaha, Nebraska. He remains Director of Creighton University's Hereditary Cancer Center and Chair of Preventive Medicine. The American Association of Cancer Research awarded him the Joseph H Buchenal Memorial Award for Clinical Research in 2010. Lynch Syndrome Public Awareness Day was inaugurated in the US on 22 March 2012.

Dr Madge Macklin

MD (1893–1962) was a Canadian medical geneticist who worked at the University of Western Ontario, carrying out research on a wide range of inherited disorders. Post-war, her research into cancer genetics as a Cancer Research Associate at Ohio State University produced evidence of hereditary breast cancer. She became president of the American Society of Human Genetics in 1959.

Professor Eamonn Maher

MD FRCP FSB FMedSci (b.1956) graduated from the University of Manchester in 1980. After clinical medicine posts in Manchester, Cambridge, Leeds and London he trained in medical genetics under Professor Malcolm Ferguson-Smith at Cambridge University. After Clinical Lecturer/ Senior Registrar and University Lecturer/Consultant in Medical Genetics posts at the University of Cambridge he was appointed to the Chair of Medical Genetics at the University of Birmingham in 1996. His main clinical interests are familial cancer syndromes, in particular inherited renal cancers and phaeochromocytoma, and his research interests have been in cancer genetics and epigenetics, genomic imprinting and identification of human disease genes (publishing close to 400 papers).

Dr Pål Møller

(b. 1946) MD PhD graduated from Oslo University in 1971, was awarded an MD in 1973 and, at the same institution, was appointed as a specialist in medical genetics in 1981. In 1982, he was employed as a geneticist to conduct prenatal diagnoses in Norway. He completed his PhD on multifactorial inheritance (HLA B27 and ankylosing spondylitis/

Reiter's syndrome/psoriatic arthritis) in 1984. He set up an outpatient clinic for inherited cancer at the Norwegian Radium Hospital, Oslo, in 1988 and was the head of this unit until 2012. He is now the Senior Scientist, Senior Consultant and Research Group Leader for cancer genetics at all Oslo hospitals which are amalgamated into Oslo University Hospital. He has focused the group's clinical and research activities on preventable and curable inherited cancers. Møller has developed a full electronic medical filing system (CGEN) for clinical and research use holding all information on some 70,000 living and dead patients and their closest relatives who have been seen at the clinic since 1982. He has been Chair of the Norwegian Group on Inherited Cancer since its foundation in 1999 and has co-authored circa 250 published papers.

Ms Kay Neale

MSc SRN (b. 1946) qualified as a nurse at the Royal Free Hospital in 1967 and was appointed as a District Nurse in Islington in 1969. In 1974 she started to work at St Mark's Hospital as a Research Nurse funded by the Cancer Research Campaign. She worked with Dr Michael Hill, who was studying gut chemistry and flora at the Centre for Applied Microbiological Research at Porton Down, and patients with polyposis were part of the group included in their research. In 1984 she was appointed to work alongside Dr H J R Bussey and Dr Sheila Ritchie in the Polyposis Registry, funded by the Imperial Cancer Research Fund. She gained a Master's degree in 1985 in survey research methods and helped with the computerization of data, collected since St Mark's Polyposis Registry began in 1924. This unique database has provided support for both clinical and laboratory based research, including the localization of the *APC* and *MYH* genes. She is currently employed by Imperial College as the Polyposis Registry Manager and Translational Research Co-ordinator. She was a founder member of the Leeds Castle Polyposis Group (1985), which evolved into the International Society for Gastrointestinal Hereditary Tumours (2005), of which she remains the Honorary Secretary.

Professor Robin Phillips

FRCS (b. 1952) graduated from the Royal Free Hospital in 1975, qualifying in surgery in 1979. After a series of clinical posts, mostly with the St Mary's Hospital group of hospitals in London, he finalized his training at St Mark's

Hospital in colorectal surgery and spent a short clinical fellowship in Toronto, Canada, under Dr Zane Cohen. He returned to St Mark's Hospital in 1987 as Consultant Surgeon and Senior Lecturer at St Bartholomew's Hospital. In 1993, while continuing as a Consultant Surgeon at St Mark's, he joined ICRF (later CRUK) and became Director of the St Mark's Polyposis Registry, becoming Professor of Colorectal Surgery, Imperial College in 2000. He was Honorary Co-Administrative Director of InSiGHT (the International Society for the Investigation of Gastrointestinal Hereditary Tumours) until 2012 and has been Clinical Director, St Mark's Hospital, since 2004.

Professor Julian Sampson

FRCP FMedSci (b. 1959) is Clinical Professor of Medical Genetics at Cardiff University and the University Hospital of Wales. He graduated in medicine from Nottingham University (1982) and trained in Medical Genetics at the Duncan Guthrie Institute, Glasgow with Professor Malcolm Ferguson-Smith and at the Institute of Medical Genetics, Cardiff, with Professor Peter Harper. His research interests in tuberous sclerosis have ranged from gene identification to clinical trials, and in colorectal cancer have included identification and characterization of a novel autosomal recessive form of polyposis colorectal cancer, MAP.

Professor Ellen Solomon

FMedSci is Prince Philip Professor of Human Genetics at Guy's Hospital, King's College London. Her current research is focused on the genetics of breast cancer, including molecular analysis of the *BRCA1* gene, and on the mechanisms of acute promyelocytic leukaemia.

Professor Tilli Tansey

PhD PhD DSc Hon MRCP Hon FRCP FMedSci (b. 1953) is convenor of the History of Modern Biomedicine Research Group and Professor of the History of Modern Medical Sciences at Queen Mary, University of London.

Dr Aldred Scott Warthin

MD PhD (1866–1931) studied pathology in Vienna and Freiburg, after which he was appointed Demonstrator in Pathology at the University of Michigan in 1895. Subsequently he became Professor of Pathology at the same institution and director of its pathological laboratories, teaching at Michigan for 39 years. In 1895, a conversation with his seamstress about her family's predisposition to cancer led to his research on 'Family G' and other families with evidence of hereditary cancers.

Henry Lynch suggests that Warthin should be 'the father of cancer genetics', noting that his hereditary cancer studies predated the revival of interest in Mendel's principles at the start of the twentieth century (see Lynch (1985), page 346). His books include *Old Age, the Major Involution: The physiology and pathology of the aging process* and *The Creed of a Biologist: A biologic philosophy of life* (see Warthin (1929) and (1930)).

References*

Aaltonen L A, Peltomäki P, Mecklin J *et al.* (1994) Replication errors in benign and malignant tumors from hereditary nonpolyposis colorectal cancer patients. *Cancer Research* **54:** 1645–8.

Alm T. (1975) Surgical treatment of hereditary adenomatosis of the colon and rectum in Sweden during the last 20 years. Part II. Patients with prophylactic operations, primary and late results. *Acta Chirurgica Scandinavica* **141:** 228–37.

Al-Tassan N, Chmiel N H, Maynard J *et al.* (2002) Inherited variants of *MYH* associated with somatic G:C→T:A mutations in colorectal tumors. *Nature Genetics* **30:** 227–32.

Angler N. (1991) Doctors link gene to colon cancer. *New York Times* (9 August), page A16.

Anon. (2012) Sir Christopher Booth. *The Telegraph* (London), 7 October, online at http://www.telegraph.co.uk/news/obituaries/medicine-obituaries/9592749/Sir-Christopher-Booth.html (visited 18 February 2013).

Austoker J. (1988) *A History of the Imperial Cancer Research Fund 1902–1986.* Oxford: Oxford University Press.

Bicknell D C, Rowan A, Bodmer W F. (1994) beta$_2$-Microglobulin gene mutations: a study of established colorectal cell lines and fresh tumors. *Proceedings of the National Academy of Sciences* **91:** 4751–5.

Björk J, Akerbrant H, Iselius L *et al.* (1999) Epidemiology of familial adenomatous polyposis in Sweden: changes over time and differences in phenotype between males and females. *Scandinavian Journal of Gastroenterology* **34:** 1230–5.

Bodmer J, Kennedy L, Brennan J *et al.* (1985) HLA and genetic marker studies in adenomatous polyposis. *British Journal of Surgery* **72:** S32–5.

Bodmer W F, Cavalli-Sforza L L. (1976) *Genetics, Evolution and Man.* San Francisco: Freeman.

Bodmer W F, McKie R. (1994) *The Book of Man: The quest to discover our genetic heritage.* London: Little, Brown.

* Please note that instances of four or more authors are cited as the first three names *et al.*

Bodmer W F, Bailey C J, Bodmer J *et al.* (1987) Localization of the gene for familial adenomatous polyposis on chromosome 5. *Nature* **328:** 614–16.

Bodmer W, Bishop T, Karran P. (1994) Genetic steps in colorectal cancer. *Nature Genetics* **6:** 217–19.

Boveri T. (1914) *Zur Frage der Entstehung Maligner Tumoren.* Jena: Gustav Fisher. Annotated translation, Harris H. (2007) *Concerning the Origin of Malignant Tumours* by Theodor Boveri. New York: Cold Spring Harbor Laboratory Press.

Bridges B A, Harnden D G. (1981) Untangling ataxia-telangiectasia. *Nature* **289:** 222–3.

Broca P P. (1866) *Traité des Tumeurs*. Two volumes. Paris: Asselin.

Buehler S K, Fodor G, Marshall W H *et al.* (1975) Common variable immunodeficiency, Hodgkin's disease, and other malignancies in a Newfoundland family. *Lancet* **305:** 195–7.

Bülow S. (1986) Clinical features in familial polyposis coli. Results of the Danish Polyposis Register. *Diseases of the Colon and Rectum* **29:** 102–7.

Burn J, Chapman P D, Bishop D T *et al.* (1998) Diet and cancer prevention: the Concerted Action Polyp Prevention (CAPP) studies. *Proceedings of the Nutrition Society* **57:** 183–6.

Burn J, Bishop D T, Chapman P D *et al.* for the international CAPP consortium. (2011a) A randomized placebo-controlled prevention trial of aspirin and/or resistant starch in young people with familial adenomatous polyposis. *Cancer Prevention Research* **4:** 655–65.

Burn J, Gerdes A, Macrae F *et al.* on behalf of the CAPP2 investigators. (2011b) Long-term effect of aspirin on cancer risk in carriers of hereditary colorectal cancer: an analysis from the CAPP2 randomized controlled trial. *Lancet* **378:** 2081–7.

Bussey H J R. (1970) *The Pathology of Familial Polyposis Coli (multiple adenomatosis)*. PhD thesis. Hammersmith Hospital Royal Postgraduate Medical School, University of London.

Cavalli-Sforza L L, Bodmer W F. (1971) *The Genetics of Human Populations.* Mineola, New York: Dover Publications.

Cavenee W K, Dryja T P, Phillips R A *et al.* (1983) Expression of recessive alleles by chromosomal mechanisms in retinoblastoma. *Nature* **305:** 779–84.

Cheadle J P, Sampson J R. (2003) Exposing the MYtH about base excision repair and human inherited disease. *Human Molecular Genetics* **12:** R159–65.

Christie D A, Tansey E M. (eds) (2003) *Genetic Testing.* Wellcome Witnesses to Twentieth Century Medicine, volume 17. London: Wellcome Trust Centre for the History of Medicine at UCL: http://www.history.qmul.ac.uk/research/modbiomed/wellcome_witnesses/volume17/index.html (visited 1 February 2013).

Cleaver J E. (1968) Defective repair replication of DNA in xeroderma pigmentosum. *Nature* **218:** 652–6.

Cotton R G H and participants of the 2006 Human Variome Project meeting. (2007) Recommendations of the 2006 Human Variome Project meeting. *Nature Genetics* **39:** 433–6.

Couch F J and 267 other individuals and organizations on behalf of CIMBA. (2013) Genome-wide association study in *BRCA1* mutation carriers identifies novel loci associated with breast and ovarian cancer risk. *PLoS Genetics* **9:** e1003212.

Crowther S M, Reynolds L A, Tansey E M. (eds) (2009) *History of Dialysis in the UK: c.1950–80.* Wellcome Witnesses to Twentieth Century Medicine, volume 37. London: Wellcome Trust Centre for the History of Medicine at UCL: http://www.history.qmul.ac.uk/research/modbiomed/wellcome_witnesses/volume37/index.html (visited 20 February 2013).

Department of Health (1996) *Genetics and Cancer Services: Report of a working group for the Chief Medical Officer* (The Harper report). London: Department of Health/The Stationery Office Limited.

Department of Health and the Welsh Office. (1995) *A Policy Framework for Commissioning Cancer Services: A report by the expert advisory group on cancer to the Chief Medical Officers of England and Wales* (The Calman-Hine report). London: Department of Health/The Stationery Office Limited.

Devilee P, Cleton-Jansen A, Cornelisse C J. (2001) Ever since Knudson. *Trends in Genetics* **17:** 569–73.

Drewinko B, Romsdahl M M, Yang L Y *et al.* (1976) Establishment of a human carcinoembryonic antigen-producing colon adenocarcinoma cell line. *Cancer Research* **36:** 467–75.

Dukes C E. (1932) The classification of cancer of the rectum. *Journal of Pathology and Bacteriology.* **35:** 323–32.

Dukes C E. (1952) Familial intestinal polyposis. *Annals of the Royal College of Surgeons* **10:** 293–304.

Dukes C E. (1958) Cancer control in familial polyposis of the colon. *Diseases of the Colon and Rectum* **1:** 413–23.

Dunstone G H, Knaggs T W L. (1972) Familial cancer of the colon and rectum. *Journal of Medical Genetics* **9:** 451–6.

Enholm S, Hienonen T, Suomalainen A *et al.* (2003) Proportion and phenotype of *MYH*-associated colorectal neoplasia in a population-based series of Finnish colorectal cancer patients. *American Journal of Pathology* **163:** 827–32.

Felix R, Bodmer W, Fearnhead N S *et al.* (2006) *GSTM1* and *GSTT1* polymorphisms as modifiers of age at diagnosis of hereditary nonpolyposis colorectal cancer (HNPCC) in a homogeneous cohort of individuals carrying a single predisposing mutation. *Mutation Research/ Fundamental and Molecular Mechanisms of Mutagenesis* **602:** 175–81.

Fishel R, Lescoe M K, Rao M R S *et al.* (1993) The human mutator gene homolog *MSH2* and its association with hereditary nonpolyposis colon cancer. *Cell* **75:** 1027–38.

Foulkes W D, Hodgson S V. (eds) (1998) *Inherited Susceptibility to Cancer: Clinical, predictive, and ethical perspectives.* Cambridge: Cambridge University Press.

Fraser G R. (1999) The Oxford Cancer Genetic Clinic: experience of the first seven years. In Utsunomiya *et al.* (eds) (1999): 51–8.

Gardner E J, Stephens F E. (1950) Cancer of the lower digestive tract in one family group. *American Journal of Human Genetics* **2:** 41–8.

Ghosh K, Hartmann L C. (2002) Current status of prophylactic mastectomy. *Oncology (Williston Park)* **16:** 1319–25.

Granshaw L. (1985) *St. Mark's Hospital London: A social history of a specialist hospital.* London: King Edward's Hospital Fund for London.

Green J S. (1995) *Development, Implementation and Evaluation of Clinical and Genetic Screening Programs for Hereditary Tumour Syndromes.* PhD thesis. St John's: Memorial University of Newfoundland.

Grindedal E M, Møller P, Eeles R *et al.* (2009) Germ-line mutations in mismatch repair genes associated with prostate cancer. *Cancer Epidemiology, Biomarkers and Prevention* **18:** 2460–7.

Groden J, Thliveris A, Samowitz W *et al.* (1991) Identification and characterization of the familial adenomatous polyposis coli gene. *Cell* **66:** 589–600.

Gulzar Z, Goff S, Njindou A *et al.* (2007) Nurse-led cancer genetics clinics in primary and secondary care in varied ethnic population areas: interaction with primary care to improve ascertainment of individuals from ethnic minorities. *Familial Cancer* **6:** 205–12.

Harper P S. (1981) *Practical Genetic Counselling.* Bristol: John Wright.

Harper P S. (ed.) (2004) *Landmarks in Medical Genetics: Classic papers with commentaries.* Oxford: Oxford University Press.

Harper P S. (2006) *First Years of Human Chromosomes: The beginnings of human cytogenetics.* Bloxham: Scion.

Harper P S. (2008) *A Short History of Medical Genetics.* Oxford: Oxford University Press.

Harper P S, Reynolds L A, Tansey E M (eds) (2010) *Clinical Genetics in Britain: Origins and Development,* volume 39. London: Wellcome Trust Centre for the History of Medicine at UCL: http://www.history.qmul.ac.uk/research/modbiomed/wellcome_witnesses/volume39/index.html (visited 1 February 2013).

Harris H. (1974) Lionel Sharples Penrose (1898–1972). *Journal of Medical Genetics* **11:** 1–24.

Harrison Cripps W. (1882) Two cases of disseminated polypus of the rectum. *Transactions of the Pathological Society of London* **33:** 165–8. Freely available to view at: http://openlibrary.org/books/OL23467727M/Transactions_of_the_Pathological_Society_of_London (visited 11 January 2013).

Heagerty J J. (1928) *Four Centuries of Medical History in Canada and a Sketch of the Medical History of Newfoundland.* Bristol: J Wright and Sons.

Henderson M. (2007) Tests from gene screening firms condemned as waste of money. *The Times* (1 December), page 29.

Herrera L, Kakati S, Gibas L *et al.* (1986) Brief clinical report: Gardner syndrome in a man with an interstitial deletion of 5q. *American Journal of Medical Genetics* **25:** 473–6.

Hirschorn J N, Gajdos Z K Z. (2011) Genome-wide association studies: results from the first few years and potential implications for clinical medicine. *Annual Review of Medicine* **62:** 11–24.

Hodgson S V, Maher E R. (1993) *A Practical Guide to Human Cancer Genetics.* Cambridge: Cambridge University Press.

Hodgson S V, Bishop D T, Jay B. (1994) Genetic heterogeneity of congenital hypertrophy of the retinal pigment epithelium (CHRPE) in families with familial adenomatous polyposis. *Journal of Medical Genetics* **31:** 55–8.

Hodgson S, Milner B, Brown I *et al.* (1999) Cancer genetics services in Europe. *Disease Markers* **15:** 3–13.

Houlston R S, Murday V, Harocopos C *et al.* (1990) Screening and genetic counselling for relatives of patients with colorectal cancer in a family cancer clinic. *British Medical Journal* **301:** 366–8.

Hunter I, Wotherspoon S; Roberts K B. (ed) (1986) *A Bibliography of Health Care in Newfoundland.* St John's: Memorial University of Newfoundland.

Huson S M, Harper P S, Hourihan M D *et al.* (1986) Cerebellar haemangioblastoma and Von Hippel-Lindau disease. *Brain* **109:** 1297–310.

Imperial Cancer Research Fund. (1979) *Imperial Cancer Research Fund Scientific Report. London: Imperial Cancer Research Fund.*

Imperial Cancer Research Fund. (1985) *Scientific Report to the Council by the Director of Research for the year 1st October 1983 to 30th September 1984.* London: Imperial Cancer Research Fund.

Imperial Cancer Research Fund. (1992) *Scientific Report to the Council by the Director-General for the year 1st August 1991 to 31st July 1992.* London: Imperial Cancer Research Fund.

Jagelman D G, DeCosse J J, Bussey H J R. (1988) Upper gastrointestinal cancer in familial adenomatous polyposis. *Lancet* **331:** 1149–51.

Jones A, Bodmer W F. (1974) *Our Future Inheritance: Choice or chance?: a study.* London: Oxford University Press.

Kerber R A, Neklason D W, Samowitz W S *et al.* (2005) Frequency of familial colon cancer and hereditary nonpolyposis colorectal cancer (Lynch syndrome) in a large population database. *Familial Cancer* **4:** 239–44.

Klein R J, Zeiss C, Chew E Y *et al.* (2005) Complement factor H polymorphism in age-related macular degeneration. *Science* **308:** 385–9.

Kolodner R D, Hall N R, Lipford J *et al.* (1994) Human mismatch repair genes and their association with hereditary non-polyposis colon cancer. *Cold Spring Harbor Symposia on Quantitative Biology* **59:** 331–8.

Knudson A G. (1971) Mutation and cancer: statistical study of retinoblastoma. *Proceedings of the National Academy of Sciences* **68:** 820–3.

Knudson A G. (2005) A personal sixty-year tour of genetics and medicine. *Annual Review of Genomics and Human Genetics* **6:** 1–14.

Lalloo F, Kerr B, Friedman J M *et al.* (eds) (2005) *Risk Assessment and Management in Cancer Genetics.* Oxford: Oxford University Press.

Lamlum H, Al Tassan N, Jaeger E *et al.* (2000) Germline *APC* variants in patients with multiple colorectal adenomas, with evidence for the particular importance of E1317Q. *Human Molecular Genetics* **9:** 2215–21.

Leach F S, Nicolaides N C, Papadopoulos N *et al.* (1993) Mutations of a *mutS* homolog in hereditary nonpolyposis colorectal cancer. *Cell* **75:** 1215–25.

Littler M, Harper P S. (1989) A regional register for inherited cancers. *British Medical Journal* **298:** 1689–91.

Lockhart-Mummery J P. (1914) *Diseases of the Rectum and Anus: A practical handbook.* London: Baillière, Tindall and Cox.

Lockhart-Mummery J P. (1919) Case and complete resection of the large bowel for multiple adenomata. *Proceedings of the Royal Society of Medicine (Surgical Section)* **12:** 43–4.

Lockhart-Mummery [J] P. (1925) Cancer and heredity. *Lancet* **205:** 427–9.

Lockhart-Mummery J P. (1934) *The Origin of Cancer.* London: J & A Churchill.

Logan C Y, Nusse R. (2004) The WNT signaling pathway in development and disease. *Annual Review of Cell and Developmental Biology* **20:** 781–810.

Lord Privy Seal (1972) *Framework for Government Research and Development, etc.* (Cmnd 5046). London: HMSO.

Lovett E. (1976) Family studies in cancer of the colon and rectum. *British Journal of Surgery* **63:** 13–18.

Lynch H T. (1985) Classics in oncology: Aldred Scott Warthin (1866–1931). *CA – A Cancer Journal for Clinicians* **35:** 345–7.

Lynch H T, Cristofaro G, Rozen P *et al.* (2003) History of the international collaborative group on hereditary nonpolyposis colorectal cancer. *Familial Cancer* **2**: S3–5.

Lynch H T, Krush A J. (1971) Cancer family "G" revisited 1895–1970. *Cancer* **27:** 1505–11.

Lynch H T, Lanspa S J. (2010) Colorectal cancer survival advantage in *MUTYH*-associated polyposis and Lynch syndrome families. *Journal of the National Cancer Institute.* **102:** 1687–9.

Lynch H T, Lynch J F (1985) Genetics and colorectal cancer. In Müller *et al.* (eds) (1985): 72–7.

Macklin M T. (1959) Comparison of the number of breast-cancer deaths observed in relatives of breast-cancer patients, and the number expected on the basis of mortality rates. *Journal of the National Cancer Institute* **22:** 927–51.

Maher E R, Bentley E, Yates J W R *et al.* (1990) Mapping of Von Hippel-Lindau disease to chromosome 3p confirmed by genetic linkage analysis. *Journal of Neurological Sciences* **100:** 27–30.

Mannion J J. (ed.) (1977) *The Peopling of Newfoundland: Essays in historical geography.* St John's: Memorial University of Newfoundland.

Mathers J C, Movahedi M, Macrae F *et al.* on behalf of the CAPP2 Investigators. (2012) Long-term effect of resistant starch on cancer risk in carriers of hereditary colorectal cancer: an analysis from the CAPP2 randomised controlled trial. *Lancet Oncology* **13:** 1242–9.

Mayo O, Leach C. (eds) (2007) *Fifty Years of Human Genetics: A festschrift and liber amicorum to celebrate the life and work of George Robert Fraser.* Kent Town, Australia: Wakefield Press.

Mihill C. (1991) Gene breakthrough on breast cancer. *The Guardian* (19 February), page 7.

Miki Y, Swensen J, Shattuck-Eidens D *et al.* (1994) A strong candidate for the breast and ovarian cancer susceptibility gene *BRCA1*. *Science* **266:** 66–71.

Morson B. (1990) Henry John Richard Bussey. *Annual Report St Mark's Hospital* **1990:** 43–4.

Müller H J, Weber W, Kuttapa T. (eds) (1985) *Familial Cancer. First international research conference on Familial Cancer, Basel, September 16–21, 1985.* Basel: Karger.

Neale K, Bülow S. (2003) Origins of the Leeds Castle Polyposis Group. *Familial Cancer* **2:** T1–2.

Overy C, Reynolds L A, Tansey E M. (eds) (2012) *History of the Avon Longitudinal Study of Children (ALSPAC), c. 1980–2000.* Wellcome Witnesses to Twentieth Century Medicine, volume 44. London: Queen Mary, University of London: http://www.history.qmul.ac.uk/research/modbiomed/wellcome_witnesses/vol44/index.html (visited 20 February 2013).

Palladino P. (2002) Between knowledge and practice: On medical professionals, patients and the making of the genetics of cancer. *Social Studies of Science* **32:** 137–65.

Parsons R, Li G, Longley M J *et al.* (1993) Hypermutability and mismatch repair deficiency in RER+ tumor cells. *Cell* **75:** 1227–36.

Patterson J T. (1987) *The Dread Disease: Cancer and modern American culture.* Cambridge, Massachusetts: Harvard University Press.

Peltomäki P, Aaltonen L A, Sistonen P *et al.* (1993) Genetic mapping of a locus predisposing to human colorectal cancer. *Science* **260:** 810–12.

Penrose L S, MacKenzie H J, Karn M N. (1947) A genetical study of human mammary cancer. *Annals of Eugenics* **14:** 234–66.

Peters K, Tansey T, Thompson G. (2012) Sir Christopher Booth: Clinical scientist and medical historian. *The Independent*, (5 October); http://www.independent.co.uk/news/obituaries/sir-christopher-booth-clinical-scientist-and-medical-historian-8198454.html?origin=internalSearch (visited 18 February 2013).

Povey S, Attwood J, Janssen L A J *et al.* (1991) An attempt to map two genes for tuberous sclerosis using novel two-point methods. *Annals of the New York Academy of Sciences* **615:** 298–305.

Prolla T A, Pang Q, Alani E *et al.* (1994) MLH1, PMS1, and MSH2 interactions during the initiation of DNA mismatch repair in yeast. *Science* **265:** 1091–3.

Reenan R A G, Kolodner R D. (1992) Isolation and characterization of two *Saccharomyces cerevisiae* genes encoding homologs of the bacterial HexA and MutS mismatch repair proteins. *Genetics* **132:** 963–73.

Reynolds L A, Tansey E M. (eds) (2000) *Clinical Research in Britain, 1950–80.* Wellcome Witnesses to Twentieth Century Medicine, volume 7. London: Wellcome Trust Centre for the History of Medicine at UCL: http://www.history.qmul.ac.uk/research/modbiomed/wellcome_witnesses/volume07/index.html (visited 20 February 2013).

Richmond C. (2012) Sir Christopher Booth obituary. *The Guardian* (31 August); http://www.guardian.co.uk/society/2012/aug/31/sir-christopher-booth (visited 18 February 2013).

Rowley J D (2003) Introductory speech for Albert de la Chapelle. (2003) *American Journal of Human Genetics* **72:** 233–5.

Sacks O. (1992) Dr Richard Herbert Lindenbaum, FRCP. *Journal of Medical Genetics* **29:** 925–6.

Schiller F. (1992) *Paul Broca, founder of French anthropology, explorer of the Brain.* New York: Oxford University Press.

Seizinger B R, Rouleau G A, Ozelius L J *et al.* (1988) Von Hippel-Lindau disease maps to the region of chromosome 3 associated with renal cell carcinoma. *Nature* **332:** 268–9.

Sieber O M, Lamlum H, Crabtree M D *et al.* (2002) Whole-gene *APC* deletions cause classical familial adenomatous polyposis but not attenuated polyposis or "multiple" colorectal adenomas. *Proceedings of the National Academy of Sciences* **99:** 2954–8.

Sjursen W, Haukanes B I, Grindedal EM *et al.* (2010) Current clinical criteria for Lynch syndrome are not sensitive enough to identify *MSH6* mutation carriers. *Journal of Medical Genetics* **47:** 579–85.

Slamon D J, Leyland-Jones B, Shak S *et al.* (2001) Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *New England Journal of Medicine* **344:** 783–92.

Solomon E, Bodmer W F. (1979) Evolution of sickle variant gene. *Lancet* **313:** 923.

Solomon E, Voss R, Hall V *et al.* (1987) Chromosome 5 allele loss in human colorectal carcinomas. *Nature* **328:** 616–19.

Spirio L, Green J, Robertson J *et al.* (1999) The identical 5' splice-site acceptor mutation in five attenuated APC families from Newfoundland demonstrates a founder effect. *Human Genetics* **105:** 388–98. See also, for the omission of Green R from the original author list, Anon. (2000) Erratum. *Human Genetics* **107:** 294.

Steinbach G, Lynch P M, Phillips R K S *et al.* (2000) The effect of celecoxib, a cyclooxygenase-2 inhibitor, in familial adenomatous polyposis. *New England Journal of Medicine* **342:** 1946–52.

Taylor A M, Harnden D G, Arlett C F *et al.* (1975) Ataxia telangiectasia: a human mutation with abnormal radiation sensitivity. *Nature* **258:** 427–9.

Tulinius H. (1985) Familial cancer registration in Iceland. In Müller *et al.* (eds) (1985):263–7.

Turcot J, Després J, St Pierre F. (1959) Malignant tumors of the central nervous system associated with familial polyposis of the colon: Report of two cases. *Diseases of the Colon and Rectum* **2:** 465–8.

Utsunomiya J, Mulvihill J J and Weber W. (eds) (1999) *Familial Cancer and Prevention: Molecular Epidemiology, a new strategy toward cancer control.* New York, NY: Wiley-Liss.

Varesco L, Thomas H J W, Cottrell S *et al.* (1989). CpG island clones from a deletion encompassing the gene for adenomatous polyposis coli. *Proceedings of the National Academy of Sciences* **86:** 10118–22.

Vasen H F A, Möslein G, Alonso A *et al.* (2007) Guidelines for the clinical management of Lynch syndrome (hereditary non-polyposis cancer). *Journal of Medical Genetics* **44**: 353–62.

Veale A M O. (1960) Clinical and genetic problems in familial intestinal polyposis. *Gut* **1:** 285–90.

Veale A M O. (1961a) *Familial Intestinal Polyposis.* PhD thesis. London: University of London.

Veale A M O. (1961b) Genetics, carcinogenesis and family studies. *British Surgical Practice: Surgical Progress* **1961:** 169–85.

Veale A M O. (1965) *Intestinal Polyposis.* London: Eugenics Laboratory, University College London.

Vogt S, Jones N, Christian D *et al.* (2009) Expanded extracolonic tumor spectrum in *MUTYH*-associated polyposis. *Gastroenterology* **137:** 1976–85.

Waldholz M. (1997) *Curing Cancer: The story of the men and women unlocking the secrets of our deadliest illness.* New York: Simon & Schuster.

Warthin A S. (1913) Heredity with reference to carcinoma as shown by the study of the cases examined in the pathological laboratory of the University of Michigan, 1895–1913. *Archives of Internal Medicine* **12:** 546–55.

Warthin A S. (1929) *Old Age, the Major Involution: The physiology and pathology of the aging process.* New York: P B Hoeber.

Warthin A S. (1930) *The Creed of a Biologist: A biologic philosophy of life.* London: Constable.

Wijnen J T, Vasen H F A, Khan P M *et al.* (1998) Clinical findings with implications for genetic testing in families with clustering of colorectal cancer. *New England Journal of Medicine.* **339:** 511–18.

Wijnen J, de Leeuw W, Vasen H *et al.* (1999) Familial endometrial cancer in female carriers of *MSH6* germline mutations. *Nature Genetics* **23:** 142–4.

Wilding A, Ingham S L, Lalloo F *et al.* (2012) Life expectancy in hereditary cancer predisposing diseases: an observational study. *Journal of Medical Genetics* **49:** 264–9.

Index: Subject

Glossary entries appear in bold

Index: Names

Biographical notes appear in bold

VOLUMES IN THIS SERIES*

1. **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 (1997) ISBN 1 86983 579 4

2. **Making the human body transparent: The impact of NMR and MRI**
   Research in general practice
   Drugs in psychiatric practice
   The MRC Common Cold Unit (1998) ISBN 1 86983 539 5

3. **Early heart transplant surgery in the UK (1999)** ISBN 1 84129 007 6

4. **Haemophilia: Recent history of clinical management (1999)**
   ISBN 1 84129 008 4

5. **Looking at the unborn: Historical aspects of**
   obstetric ultrasound (2000) ISBN 1 84129 011 4

6. **Post penicillin antibiotics: From acceptance to resistance? (2000)**
   ISBN 1 84129 012 2

7. **Clinical research in Britain, 1950–1980 (2000)**
   ISBN 1 84129 016 5

8. **Intestinal absorption (2000)**
   ISBN 1 84129 017 3

9. **Neonatal intensive care (2001)**
   ISBN 0 85484 076 1

10. **British contributions to medical research and education in Africa**
    after the Second World War (2001) ISBN 0 85484 077 X

* All volumes are freely available online at: www.history.qmul.ac.uk/research/modbiomed/wellcome_witnesses

11. **Childhood asthma and beyond (2001)**
ISBN 0 85484 078 8

12. **Maternal care (2001)**
ISBN 0 85484 079 6

13. **Population-based research in south Wales: The MRC Pneumoconiosis Research Unit and the MRC Epidemiology Unit (2002)**
ISBN 0 85484 081 8

14. **Peptic ulcer: Rise and fall (2002)**
ISBN 0 85484 084 2

15. **Leukaemia (2003)**
ISBN 0 85484 087 7

16. **The MRC Applied Psychology Unit (2003)**
ISBN 0 85484 088 5

17. **Genetic testing (2003)**
ISBN 0 85484 094 X

18. **Foot and mouth disease: The 1967 outbreak and its aftermath (2003)**
ISBN 0 85484 096 6

19. **Environmental toxicology: The legacy of *Silent Spring* (2004)**
ISBN 0 85484 091 5

20. **Cystic fibrosis (2004)**
ISBN 0 85484 086 9

21. **Innovation in pain management (2004)**
ISBN 978 0 85484 097 7

22. **The Rhesus factor and disease prevention (2004)**
ISBN 978 0 85484 099 1

23. **The recent history of platelets in thrombosis and other disorders (2005)** ISBN 978 0 85484 103 5

24. **Short-course chemotherapy for tuberculosis (2005)** ISBN 978 0 85484 104 2

25. **Prenatal corticosteroids for reducing morbidity and mortality after preterm birth (2005)** ISBN 978 0 85484 102 8

26. **Public health in the 1980s and 1990s: Decline and rise? (2006)** ISBN 978 0 85484 106 6

27. **Cholesterol, atherosclerosis and coronary disease in the UK, 1950–2000 (2006)** ISBN 978 0 85484 107 3

28. **Development of physics applied to medicine in the UK, 1945–1990 (2006)** ISBN 978 0 85484 108 0

29. **Early development of total hip replacement (2007)** ISBN 978 0 85484 111 0

30. **The discovery, use and impact of platinum salts as chemotherapy agents for cancer (2007)** ISBN 978 0 85484 112 7

31. **Medical ethics education in Britain, 1963–1993 (2007)** ISBN 978 0 85484 113 4

32. **Superbugs and superdrugs: A history of MRSA (2008)** ISBN 978 0 85484 114 1

33. **Clinical pharmacology in the UK, *c.* 1950–2000: Influences and institutions (2008)** ISBN 978 0 85484 117 2

34. **Clinical pharmacology in the UK, *c.* 1950–2000: Industry and regulation (2008)** ISBN 978 0 85484 118 9

35. **The resurgence of breastfeeding, 1975–2000 (2009)** ISBN 978 0 85484 119 6

36. **The development of sports medicine in twentieth-century Britain (2009)** ISBN 978 0 85484 121 9

37. **History of dialysis, *c.*1950–1980 (2009)** ISBN 978 0 85484 122 6

38. **History of cervical cancer and the role of the human papillomavirus, 1960–2000 (2009)** ISBN 978 0 85484 123 3

39. **Clinical genetics in Britain: Origins and development (2010)**
ISBN 978 0 85484 127 1

40. **The medicalization of cannabis (2010)**
ISBN 978 0 85484 129 5

41. **History of the National Survey of Sexual Attitudes and Lifestyles (2011)**ISBN 978 0 90223 874 9

42. **History of British intensive care, *c.*1950–*c.*2000 (2011)**
ISBN 978 0 90223 875 6

43. **WHO Framework Convention on Tobacco Control (2012)**
ISBN 978 0 90223 877 0

44. **History of the Avon Longitudinal Study of Parents and Children (ALSPAC), *c.*1980–2000 (2012)**
ISBN 978 0 90223 878 7

45. **Palliative medicine in the UK *c.*1970–2010 (2013)**
ISBN 978 0 90223 882 4

46. **Clinical Cancer Genetics: Polyposis and familial colorectal cancer *c.*1975–*c.*2010** ISBN 978 0 90223 885 5 (this volume)

UNPUBLISHED WITNESS SEMINARS

1994 **The early history of renal transplantation**

1994 **Pneumoconiosis of coal workers**
(partially published in volume 13, *Population-based research in south Wales*)

1995 **Oral contraceptives**

2003 **Beyond the asylum: Anti-psychiatry and care in the community**

2003 **Thrombolysis**
(partially published in volume 27, *Cholesterol, atherosclerosis and coronary disease in the UK, 1950–2000*)

2007 **DNA fingerprinting**

The transcripts and records of all Witness Seminars are held in archives and manuscripts, Wellcome Library, London, at GC/253.

OTHER PUBLICATIONS

Technology transfer in Britain: The case of monoclonal antibodies
Tansey E M, Catterall P P. (1993) *Contemporary Record* **9**: 409–44.

Monoclonal antibodies: A witness seminar on contemporary medical history
Tansey E M, Catterall P P. (1994) *Medical History* **38**: 322–7.

Chronic pulmonary disease in South Wales coalmines: An eye-witness account of the MRC surveys (1937–42)
P D'Arcy Hart, edited and annotated by E M Tansey. (1998)
Social History of Medicine **11**: 459–68.

Ashes to Ashes – The history of smoking and health
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
Professor Christine Lee and Dr Charles Rizza (interviewers). (1998)
Haemophilia **4**: 769–77.

Witnessing the Witnesses: Pitfalls and potentials of the Witness Seminar in twentieth century medicine
Tansey E M, in Doel R, Søderqvist T. (eds) (2006) *Writing Recent Science: The historiography of contemporary science, technology and medicine.* London: Routledge: 260–78.

The Witness Seminar technique in modern medical history
Tansey E M, in Cook H J, Bhattacharya S, Hardy A. (eds) (2008) *History of the Social Determinants of Health: Global Histories, Contemporary Debates.* London: Orient Longman: 279–95.

Today's medicine, tomorrow's medical history
Tansey E M, in Natvig J B, Swärd E T, Hem E. (eds) (2009) *Historier om helse* (*Histories about Health,* in Norwegian). Oslo: *Journal of the Norwegian Medical Association:* 166–73.

Key to cover photographs

Front cover, left to right
Professor Sir John Burn
Professor Jane Green
Ms Kay Neale
Dr Pål Møller
Professor Sir Walter Bodmer

Back cover, left to right
Professor Gareth Evans
Professor Robin Phillips
Professor Shirley Hodgson
Professor Julian Sampson
Professor Peter Harper (Chair)