GENETICS & HEALTH

Compilation of edited interviews conducted by the History of Modern Biomedicine Research Group, Queen Mary University of London

Edited by E M Tansey and A Zarros

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CONTENTS

THE HISTORY OF MODERN BIOMEDICINE INTERVIEWS (DIGITAL COLLECTION) AND THE CURRENT VOLUME

The History of Modern Biomedicine Research Group originated in 1990 as the Wellcome Trust's History of Twentieth Century Medicine Group, which in October 2000 became a part of the Wellcome Trust's Centre for the History of Medicine at UCL. From October 2010 until June 2017 it was a part of the School of History, Queen Mary University of London, principally funded by a Strategic Award from the Wellcome Trust.

Throughout that period, the remit of the Group has been to develop and strengthen links between medical historians, and medical scientists, and practitioners, and to stimulate and expedite the historical study of contemporary biomedicine, especially by creating material resources to inform such studies. These have included the famous Witness Seminar series, widely available freely online and in print,[1] and more recently a series of in-depth individual interviews.

The History of Modern Biomedicine Interviews (Digital Collection), curated by Professor Tilli Tansey, Mr Adam Wilkinson, Mr Alan Yabsley, and Dr Apostolos Zarros, comprises these interviews.[2] The Collection has been deposited in Queen Mary Research Online (QMRO), the online repository of Queen Mary University of London.[3] The material has been linked to Digital Object Identifiers (DOIs) and can be cited.

The History of Modern Biomedicine Interviews (Digital Collection) contains approximately 700 items including audio and video interview transcripts (as .pdf files), and video interview media files (as .mp4 files; video clips corresponding to the video interview transcripts archived). In addition, each interview entry includes a 'How to cite' file (.docx file) that acts as a guide on how to cite each item.

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[1] See http://www.histmodbiomed.org/article/wellcome-witnesses-volumes (accessed 28 March 2017).

[2] Tansey E M, Wilkinson A, Yabsley A, Zarros A. (curators) *History of Modern Biomedicine Interviews (Digital Collection).* Queen Mary Research Online. Queen Mary University of London, London, 2016–2017; https://qmro.qmul.ac.uk/xmlui/handle/123456789/12359 (accessed 28 March 2017).

[3] For more details, visit the QMRO website at https://qmro.qmul.ac.uk/xmlui/ (accessed 28 March 2017).

Readers should note that video interview transcripts deposited there are edited for clarity and factual accuracy, following the principles of oral history methodology. However, the Collection's audio interview transcripts are in most cases subject to enrichment by the interviewee and further editing. Related material has been deposited in the Wellcome Library.

We now present a further edited selection from that Collection. This, the second of a three volume series of 'Voices of Modern Biomedicine', focusses on genetics and health. Sections have been selected and edited to highlight the broad features of each interviewee's career and contributions, and much detail has been omitted. Readers wanting to learn more are encouraged to read the full interview and other material listed in the 'Related resources' section at the end of the volume. The interviews of Professors Bert Bakker, Malcolm Ferguson-Smith, Peter Harper and Marcus Pembrey are edited down and provided in shorter length than usual, since extensive interviews with all four exist in the "Interview Series with Founders of Human Genetics".[4]

ACKNOWLEDGEMENTS

We are grateful to Professor Sir David Weatherall for writing a comprehensive introduction, and also to the Wellcome Library, London, for permission to use photographs.

We would like to thank Ms Lynda Finn for conducting a number of these interviews; Ms Emma M Jones, Ms Caroline Overy, Mrs Sarah Beanland, and Ms Fiona Plowman for their editorial assistance; Mr Alan Yabsley for his editorial and technical support (including filming and production of several of the original interviews); and Mr Adam Wilkinson for his excellent project management. We are grateful to Mr Jeremey Claridge, Dr Stephen Welburn, and Mrs Sarah Molloy for their time and assistance in setting up the History of Modern Biomedicine Interviews (Digital Collection), assigning DOIs to the interview transcripts, and making sure this Digital Collection is well integrated in QMRO. We are also grateful to Mr Akio Morishima for the design and production of this volume; the indexer Ms Cath Topliff; and Mrs Debra Gee for transcribing the original interviews. Finally, we thank the Wellcome Trust for their financial support.

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[4] Harper P S (2017) Recorded interviews with human and medical geneticists. *Human Genetics* **136:** 149–164.

ILLUSTRATIONS AND CREDITS*

* Figure 6 is a still image taken from a video recording by Mr Alan Yabsley, QMUL, and reproduced courtesy of the Wellcome Library, London. Unless otherwise stated, all other photographs were taken by Thomas Farnetti, Wellcome Trust, and reproduced courtesy of the Wellcome Library, London.

ABBREVIATIONS

ALSPAC	Avon Longitudinal Study of Parents and Children
APC	adenomatous polyposis coli gene
APP	amyloid precursor protein gene
BRCA1	breast cancer 1 gene
BRCA2	breast cancer 2 gene
BrdU	bromodeoxyuridine
CRUK	Cancer Research UK
EEG	electroencephalogram
ENT	Ear, Nose & Throat
FAP	familial adenomatous polyposis
GP	General Practitioner
GWAS	genome-wide association study; GWA study
HCHWA-D	hereditary cerebral haemorrhage with amyloidosis of the Dutch type
HNPCC	hereditary non-polyposis colorectal cancer
ICRF	Imperial Cancer Research Fund
JAMA	*Journal of the American Medical Association*
kb	kilobase
LCPG	Leeds Castle Polyposis Group
MRC	Medical Research Council
MRI	magnetic resonance imaging
NHS	National Health Service
NIMR	National Institute for Medical Research
RFLPs	restriction fragment length polymorphisms
SCA3	spinocerebellar ataxia type 3
SDH	succinic dehydrogenase

SHO	Senior House Officer
SV40	Simian virus 40
THET	Tropical Health and Education Trust
UBC	University of British Columbia
UV	ultraviolet

INTRODUCTION

By developing the Witness Seminar programmes,[1] and later the Voices of Modern Biomedicine series, Professor Tilli Tansey and her colleagues have done a valuable service for medical historians of the future. This is exemplified by the second volume of Voices of Modern Biomedicine, which contains interviews with a wide range of medical geneticists; workers in a field which now touches on almost every aspect of medical research and practice.

On reading the interviews in this volume, one is struck by the extraordinary diversity of backgrounds and other medical activities of those who were interviewed. This observation raises the question of how genetics, and particularly medical genetics, has developed over the years. The founders of genetics, Gregor Mendel and Francis Galton, were both born in 1822. Mendel was a monk, and Galton was a polymath who trained in medicine, but who became an explorer and inventor, and who later observed that talent appears to run in families - particularly those of Lord Chancellors; an observation which led to the field of eugenics.

The undoubted father of medical genetics was the physician Archibald Garrod who was born in 1857. Although he was a busy clinician, he developed an early interest in biochemistry and the biochemical basis of disease. The first disease he studied in this way – accounts of which were published in 1899 and 1901 – described families with alkaptonuria; in both families there was a history of consanguinity in the parents of children with this disease. Although he did not appreciate the genetic significance of these findings, his work was seen by one of the leading protagonists of Mendel's work of the time, William Bateson, who suggested that a recessive form of inheritance for alkaptonuria reflected the pattern of its inheritance in these families. In June 1908, Garrod delivered the Croonian Lectures at the Royal College of Physicians in London entitled 'Inborn Errors of Metabolism'. By this time he had extended his work on alkaptonuria, and added cystinuria and several other conditions to his list of inborn errors. He later published these lectures, quoting Bateson's interpretation of his work.[2] At a later stage in his career Garrod was

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[1] The transcripts of the Witness Seminars have been published as 'Wellcome Witnesses to Twentieth Century Medicine' (Volumes 1–45) and 'Wellcome Witnesses to Contemporary Medicine' (Volumes 46–63).

[2] For more details, see Weatherall D J. (2008) The centenary of Garrod's Croonian lectures. *Clinical Medicine* **8:** 309–11.

appointed Regius Professor of Medicine at the University of Oxford, and during this time he wrote a second book, Inborn Factors in Disease, which was published in 1931. This remarkable and completely neglected book finishes with the words '… diseases are inherent in our very chemical structure and even in the molecular groupings which confer upon us our individualities, and which went to the making of the chromosomes from which we sprang.' Both Garrod's books and work were largely ignored by the medical profession, and their reviewers had not the faintest idea of the significance of Garrod's findings.

For many years after Garrod's work, although a number of important genetic diseases were discovered, genetics played very little role in medical practice. However there was a steady development of related fields such as biochemistry, protein chemistry and molecular biology. After World War II, Departments of Medical Genetics started to spring up on both sides of the Atlantic, but even at this stage of development, it is clear that the success of their founders depended on their mixed backgrounds. There are many examples of this observation. One of the first highly successful Departments of Genetics in the USA was developed at Johns Hopkins Hospital in Baltimore by Victor McKusick. McKusick had trained as a general physician and cardiologist, and specialised on phonocardiography and the study of connective tissue disorders involving the heart and vascular system. He observed that the latter were often inherited, and realising the importance of genetic disease, he persuaded the hospital to develop a new centre for these conditions. This turned out to be extremely successful with many major discoveries in several fields of medical genetics, the training of many young doctors from different parts of the world in medical genetics, and his famous production Mendelian Inheritance in Man. Catalogs of Autosomal Dominant, Autosomal Recessive, and X-Linked Phenotypes; a work that has been reproduced through many editions and later online.[3] Throughout all these developments, McKusick continued to practice and organise general medicine as Chairman of the Department of Medicine and Physician-in-Chief. There seems little doubt that much of his success was due to the recognition of potential genetic diseases through his wide experience of general medicine. In fact, several of the interviewees in this volume commented and reflected

[3] For a comprehensive review of the *Mendelian Inheritance in Man* editions, see McKusick V A. (2007) Mendelian Inheritance in Man and its online version, OMIM. *The American Journal of Human Genetics* **80:** 588–604.

on the influence of McKusick directly or indirectly in their own careers: Malcolm Ferguson-Smith and Peter Harper actually working with him at Johns Hopkins Hospital.

Another example is the career of Sir Cyril Clarke. After qualifying in medicine, he worked for several years in an insurance company, and after serving in the Navy during the World War II, he specialised in general medicine and obtained a post as a consultant physician in Liverpool. There he developed a large private practice and specialised in the management of asthma. His lifelong interest had been in butterflies, and he learned how to hand-breed them and did some interesting work on the genetics of their different colours. Quite late in his career he began to wonder if genetics might have any place in clinical practice. While still continuing his own practice, he developed a team which first began studies of the relationship between different blood groups and particular diseases. Early success in this research led to studies of the Rh blood group system and the mechanisms of Rh haemolytic disease of the newborn.[4] Ultimately, this work led to a successful approach to the prevention of Rh haemolytic disease, one of the major success stories in clinical genetics. Clarke is also cited in the interviews of this volume: Peter Harper worked with him in Liverpool, while Marcus Pembrey reflects on his influence in his career.

Therefore, it seems very likely that much of the success of modern medical genetics results from the mixed backgrounds of the research workers and their teams who were involved. These observations will have implications for the discovery of the genetic component of common diseases by their study at the cellular, molecular and genetic level in the future. Because of the extreme complexity of many of these diseases and their investigation by genome-wide association studies and related techniques, it will be of great importance for detailed analysis of the phenotypes of the populations that are being studied. This will require very close collaboration between the geneticists who are carrying out this work and the clinicians who are able to provide detailed phenotypic information about the population which is involved. As judged by the history of the development of modern medical genetics, it seems likely

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[4] Zallen D T, Christie D A, Tansey E M. (eds) (2004) *The Rhesus Factor and Disease Prevention.* Wellcome Witnesses to Twentieth Century Medicine, vol. 22. London: Wellcome Trust Centre for the History of Medicine at UCL.

that these new approaches to define the role of genetics in common disease will also be aided by geneticists who have maintained their connection with clinical practice.

Readers of these detailed and extremely thorough interviews will have the unusual opportunity of assessing whether the careers of successful clinical geneticists of today have the breadth of their predecessors. Given the extraordinary breadth of clinical genetics, information of this kind may have important implications for training their young colleagues of the future. It will also be of great help to medical historians.

Professor Sir David Weatherall
MRC Weatherall Institute of Molecular Medicine
University of Oxford

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Figure 1: Professor Bert Bakker

Professor Egbert (Bert) Bakker PhD (b. 1951) studied chemistry in Delft (BSc), and continued his studies at Leiden University (1975–1976) where he was also a technician (1977–1989). During this period he worked closely with Professor Peter L Pearson and pioneered molecular genetic techniques, which led to the first prenatal diagnosis of Duchenne muscular dystrophy in 1985. In 1989 he completed his doctoral research on Duchenne muscular dystrophy, and the same year he was awarded the Lustrum Prize by the Dutch Human Genetics Society. In 1990 he became Head of the DNA Diagnostic Section in Leiden University's Clinical Genetic Centre and Associate Professor at the Department of Human Genetics. In conjunction with these roles, he was Head of the Forensic DNA Laboratory at Leiden (1994–2000). In 2000 he was appointed Professor of Molecular Genetic Diagnosis at Leiden University Medical Center, where he continued as Head of the Laboratory for Diagnostic Genome Analysis, till April 2015, when he stepped down as Head of the laboratory and ceased his management duties.

1 Bakker, Bert*

Emma Jones: Can you tell us how your career in genetics started?

Bert Bakker: I was trained as a biochemical technician and I had to do my internship in a place in Rotterdam where they were working with heart perfusion of rats. I didn't like that so much so I went out and looked for another place to do an internship, and it was in 1974. And I found a place in Leiden at the Human Genetics department – at that time it was called Anthropogenetics – in Leiden, and there Peter Pearson offered me an internship and so I started to work in genetics. And it really fascinated me a lot because there was not so much known at that time. It was looking down the microscope at chromosomes, finding out how their replication worked by adding bromodeoxyuridine (BrdU) to cell lines and getting sister chromatid exchange. And it really fascinated me how this whole process worked. After my internship I had to go in the Army. Actually, I knew I had to go in the Army but there was some time left so I started first to study of chemistry but I couldn't finish the first year; I had to go in the Army. And when I came back from the Army I phoned Peter Pearson and said, 'Can I give you as a reference for my new position?' I wanted to get another job somewhere. And he said, 'Yeah, it's fine but why don't you come here. I have an opening for you.' So I could come and work in his lab as a technician, and I started; that was 1977 at that time.

EJ: Your career really developed under Peter Pearson, didn't it? Would you like to describe that period in more detail?

BB: Thinking of the start of my career with Peter Pearson, at that time he was very enthusiastic and trying to stimulate in all kinds of ways the work that we did. When I came in there as a trainee he gave me three articles, and I read all three. There was one in German, French and an English one. I got the three articles, about BrdU incorporation in cells and making these harlequin chromosomes. And there was another article, from the French group of Dutrillaux and they had made these harlequin chromosomes, by adding BrdU in culturing cells, and doing that for 24 hours. You would see that in the

* Edited passages from the interview conducted by Ms Emma M Jones, 27 October 2015, in the Wellcome Trust, London. For more details, see 'Related resources' at the end of this volume.

first replication round everything was doubled; in the second replication, one chromatid of the chromosome was completely incorporated in the other half. So it was a very nice article and you could see changes between the two sister chromatids. And so Peter came back after a few days and said, 'Okay, have you read these articles?' I said, 'Yes, it's interesting.' 'Okay, well that's what we're going to do.' 'Going to do what?' I asked. 'We are going to try to reproduce it. Just order the stuff and start doing it.' So I had to order all kinds of chemicals and start trying to get cells to grow and try to redo those experiments.

EJ: And how did those experiments develop?

BB: At the same time we also used BrdU incorporation for late replication of X chromosomes so if you just add BrdU, for seven hours, and you then harvest the cells, you can see that the one that replicates late is one of the X chromosomes, and you could very nicely see the X chromosome on these spreads. And with assisted chromatid exchange, after 24 hours' BrdU incorporation, you could see very nicely all these exchanges. And with that, people used that kind of technique to look at Bloom syndrome and look at all kinds of chromosomal breakage syndromes to diagnose them. But at that time it was more interesting to see that we could replicate it and reproduce it in the lab. After that we started to work on cell lines. There was a tumour cell line that was called HEK-273. It was a human embryo kidney cell, HEK, and that cell was originally made from a human embryo kidney cell on the floor above us in our building, by the group of van der Eb. And Graham and van der Eb together had done the first transformation of a human cell with Simian virus 40 (SV40) DNA, and this transformation, this cell line, became stable.

That was a stable, growing cell, an indefinitely growing cell, and with that you could actually study these cells. What Peter was interested in, was the question where in this human DNA, is the SV40 DNA, the viral DNA? Where is it incorporated and can you see it? In the lab there was a PhD-student who worked on this topic, and she was working with hybrid cell lines, fusing lymphocytes (actually, the HEK-273 cells) with hamster cell lines, using lymphocytes from the human and ovarian cells from the hamsters. She would fuse them, and grow them and you lose chromosomes. At a certain point you have a set of chromosomes and you can see (via immunoprecipitation) if T-antigen which is expressed by the SV40 gene, if that's in there or not, and you can try to locate it on one of the human chromosomes. That turned out to be very difficult because the cell lines were very dysregulated. When you looked at the chromosomes of these HEK-273 cells, we made karyotypes, and if you look at the chromosome,

104/105 chromosomes, and from each chromosome made, three to five copies, and we found each cell had almost a different composition because there's so much DNA in there, the cell was growing, growing further.

So from these cells Peter wanted to know: where is the foreign DNA located? And because localization by immunotyping didn't succeed with the hybrid cells, okay, he said what we can try is to do that at the DNA level. If the T-antigen is not working for some of the cell lines that we have, we can maybe look at DNA, isolate DNA from the hamster hybrid cell lines and hybridize the probe for SV40 (the T-gene) to that. So it was another difficult job that we had to do and we couldn't localize it, not with Southern blotting, and it was very difficult to get it to work. But on the other hand, from that we learned to do Southern blots, hybridization, and try to get this to work. And one of the first hybridizations that I did at that time was with these hybrid cell lines, so that's how I came into DNA work and to learn Southern blots; that was something that had not been done in our department until then. I had to go to Amsterdam to the lab of Piet Borst, and Dick Flavell was working at that time in Amsterdam, at the Jan Swammerdam Institute, and there I learned to do the first Southern blots and see how they worked. And from that time on we had connection with the people from the Jan Swammerdam Institute and also Dick Flavell, who later moved to Mill Hill in London, and in Mill Hill in London I went there to make the first DNA probes by cloning these pieces of human DNA. So it's all connected.

EJ: So the key thing was learning to do successful Southern blots?

BB: Yes, but those first Southern blots on these hybrid cell lines were really, really difficult. Peter Pearson always tried to stimulate us, and to get the best out of you, and he was very enthusiastic, and if there was something new he wanted to know immediately. 'Oh, what's new? What did you find in this? Let's see.' A disadvantage from that same way of thinking of his was that he was always going for new problems. And the people who were steadily going and working on other diseases in the lab; like Huntington's for example, that was already there, we knew where it was localized, how it segregated in the Huntington families and that was not so interesting to him. But we had a lot of reports on that also, and there was also a PhD-student working on Huntington's disease and trying to replicate all kinds of negative studies on effects on the cells and he got less attention. And that's what happened then. So Peter was always trying to get new things first. I had a very good time working in Leiden with Peter

Pearson and when he left in 1989, he left to go to Baltimore, at that time I did my PhD myself and became head of the DNA diagnostic laboratory, and have run that ever since.

EJ: And from there, you went on to clone pieces of human DNA?

BB: Yes; so if you go back to 1979 when we first started trying to clone pieces of human DNA, it was possible to have plasmid and to digest the plasmid and to ligate a piece of DNA in there. But it was not allowed in the Netherlands to clone pieces of human DNA in bacteria, or to get a small piece of human DNA into a plasmid and put it in a bacteria to grow and to multiply. There was a special committee that was working on genetic modified organisms, and this committee was saying, 'Okay, it's not allowed, we have to clear first of all the bacteria in which it has to be done, and clear the plasmids that have to be used.' And there were a few plasmids known that could be used, for instance to produce insulin, and so the regulatory committee were already working on those. But they were very strict on which cells to use and which bacteria to use and which plasmids to use. So at that moment it was not possible to do this experiment in Leiden, to take these pieces of DNA, because we had no probes, so I had to make the probes. I collected the placenta from hospital, isolated DNA from the human placenta. This DNA was then digested in small pieces, in fragments, in fragments of around 1 kilobase (kb), which was then separated on the sucrose gradient and from these fragments I made the plasmids by ligating this fraction of 1 kb, 2 kb, and 3 kb into plasmids, transforming them in bacteria.

EJ: And where were you doing all this work?

BB: But it all had to be done in Mill Hill in the Medical Research Council (MRC) labs in London, in the lab of Dick Flavell, which we already knew from the time that I first learned the Southern blots. So these difficulties were only for a few years because after, I think 1982, at that time we got permission to do it in our own lab in Leiden and we got a VMT-safe microbiology technology lab to do these transformations. And from then, from that time on, we also could clone bigger pieces and make cosmids and it was Gert-Jan van Ommen actually who came into our laboratory in 1983. He had already experience of making cosmid libraries, which he also learned in Mill Hill but he was at that time working in the lab of Jan de Vijlder in Amsterdam, in the same institute also where Piet Borst was so he worked there and together they, Gert-Jan and Piet

made these cosmids. And because, for the Duchenne gene, we wanted to clone the whole region, so at that time Peter Pearson attracted Gert-Jan van Ommen to come to Leiden to work on Duchenne muscular dystrophy. It was in 1983.

EJ: From all of this genetic research, is there anything in particular you might regard as your proudest achievement?

BB: Proudest achievement? I have been working now for over 40 years in genetics. One of the first things that really was new and that was making the probes to detect restriction fragment length polymorphisms (RFLPs), the small pieces of human DNA cloned in plasmids, and to make these probes to work on Southern blots and see differences between individuals and see segregation in families. And at that time it was really new, that was 1980, 1981, 1982, and I know that the Head of Department, Peter Pearson, came in and almost when I had developed the X-rays he came in and started to say, 'What's new? What's new?' So it was very exciting at that time with these RFLPs; we could start genetic linkage in families, and for Duchenne muscular dystrophy we started to do carrier detection and prenatal diagnosis. And the first prenatal diagnosis for Duchenne was, of course, that was very impressive, that we could do that at that time. That was early 1980s, the end of 1984, and it was published in *The Lancet* (March 23, 1985). That was one of the major things in my career.

One other thing is, a few years later when we had this family where we couldn't work out the carrier status of a woman. She had a son with Duchenne muscular dystrophy carrying a deletion but this deletion was not present in the mother, in her DNA. So she was not a carrier. But on dosage it was difficult and we said, to be on the safe side we did offer her a prenatal test for the next child, 'No, you never are sure if there might be a somatic mosaic or she might be a carrier, which we missed somehow, so she could transmit it a second time.' And we proved that the second child, the second foetus that we tested, was also affected. So there was a germline mosaicism. It was already known from about 1926 or so that that could happen, and it was published in hamsters, guinea pigs. And now, actually we had the proof that it really occurred in humans as well, and we published it in *Nature*, 1987. How frequent it was came a few years later when we could see it occurred more often. That meant that there was really a recurrent risk for these women. So these two things are very new things to be proud of.

And there was another thing: a few years later we had a neurologist in our department in Leiden University Medical Centre that had a family member who had brain haemorrhages, and these brain haemorrhages looked, if you look at the small vessels in post-mortems and you stain them, they looked very much like the same accumulations that you have in Alzheimer's disease. So it was the staining with Congo red, and it was amyloid that was seen, but not in plaques as you see in Alzheimer's, but now in the small vessels. And this huge family was from the area of Leiden; so they asked us to look at segregation, and mainly because there was a geneticist from Antwerp who came to our lab to learn the techniques, and to work with RFLPs, and to work with Southern blots. And our colleague Christine Van Broeckhoven was interested in Alzheimer's disease. She was from the Born-Bunge Institute and she was interested in these families. And she had, together with people from London, John Hardy and his lab, they had the probes for the Alzheimer gene, for the amyloid precursor protein gene (*APP*), which they thought would be involved in Alzheimer's disease. Earlier they had already proven with these probes that it didn't segregate with the Alzheimer's in these Dutch families but we were bound to see how that worked in this family. And here we could prove that the genetic defect segregated fully with the amyloid locus. So the brain haemorrhage, and this is called a very long name, hereditary cerebral haemorrhage with amyloidosis of the Dutch type (HCHWA-D).

And this small family was then linked to this amyloid locus, and with that we could say definitely that amyloid, the gene, is involved. Later it turned out that a Belgian family with Alzheimer's, with early onset Alzheimer's, that in that family the disease also segregated but it had one case of Alzheimer's that didn't fit in this family. They could then show that this was an outlier and was actually having Alzheimer's disease due to another problem. So it was a phenocopy as we call it. This linkage for the amyloid gene was published in *Science* in 1989.

EJ: You mentioned the difficulties when certain types of work were not allowed in the Netherlands. Were there any other difficulties or problems in your career?

BB: Thinking about obstacles in the technologies that we used, then there was in 1982 when we had had this international course for RFLPs; that was an international course that Peter Pearson and I and other people from the States that – Ray White, Web Cavanee and Mireille Schäfer – organized this course to use RFLPs in research and later diagnostics. And so we had nearly 30, 23 or so people, coming to our lab to learn this new technique. And it was all running very smoothly; we had nice Southern blots, we had nice results, and it

all worked fine. But then, when the course was finished we were also running out of lots of chemicals. The membranes ran out, the agarose gel was almost finished, the buffers were gone, so, restriction enzymes were all out. So we had to buy them all new and start again and then for half a year we couldn't get it to work again. So then we also had contact with Ed Southern and asked him what had happened, and he said, 'Oh, I've had that also.' He had also had some problems during the time that Southern blotting didn't work. So sometimes the technique worked and sometimes it didn't work, so it was very frustrating to have half a year to get no proper results. Sometimes it worked and then it didn't work again. It also turned out that the batch of agarose we had was almost run out, so we had a new one, and if we used the new one, then the result or signal on the X-rays, was gone, but if we used the old one again it was working fine. So actually the type of agarose, if you make Southern blotting you have the gel, within the gel you have your DNA, and the gel was pressed so flat that DNA couldn't come out so you got no results in your Southern blot. And it took a long time before we found that out, because we first thought of the buffers, or the enzymes, or the denaturation agent, and all this stuff. At the end we found out what it was, and also later with other techniques where we had these SSCPs, single strand conformation polymorphisms, so by melting out the DNA and hybridizing you get secondary structures if you run it in agarose, or in PAGE, or polyacrylamide gels. If you run DNA there you get different conformations if there's a mutation in there. And that was also a very tricky technique to use but we got it to work, but we only used it for half a year or two years and then it was gone. It was not a technique to use for a longer time.

And so we have seen, during all these years, the "wave" that was a technique also using this hybridization and melting out and DGGE, denaturing gradient gel electrophoresis, a very successful technique, we used it for many years in the lab. But sometimes you have a hurdle that you have to take to get it to work especially if at a certain point, you are going to use it in diagnostics. From 1985 when the first prenatal diagnosis from Duchenne was possible, we were going to move towards diagnostics, and were getting more diagnostic samples. And, at a certain point, we really chose that. I became Head of the diagnostic laboratory and Gert-Jan van Ommen was Head of the research part, and at that time we said, 'Okay, we have to really be sure that we have proper validation of the techniques and quality system and getting all the things in place to do real diagnostics.'

EJ: What do you consider to have been the major changes during your career?

BB: One of the major developments in genetics has been, of course, the new technologies that came along all the time, but on the other hand also the prenatal diagnosis that become possible from 1985 onwards. And then, looking at all the other diseases like haemophilia, ornithine transcarbamylase (OTC) deficiency, HCHWA-D, where we had this large family, we could do segregation analysis. So to offer genetic tests that could be used in genetic counselling, we had a counselling unit quite close to us; to do the carrier detection, prenatal diagnosis, helping families to cope with what's in the family, the disease, and everything else. Of course, you would like to come towards finding therapies, and that's the next step. We have seen over the years that there is the antisense oligos, the oligonucleotides, that people started using. Especially in Duchenne muscular dystrophy there has been very successful research in mice and in all kinds of studies now; and it's now in the first trials with patients. And it will take some time before that really will be implemented but that will be one of the major steps as well. So getting therapy involved has been an important development. Of course, with all the diseases where you do have a substitution therapy like, for instance, Hunter's disease where you miss a gene called *IDS*, the iduronate-2-sulphatase gene, if you have that deleted or mutated, then you end up with Hunter's disease and patients die very early or they get lots of problems. But if you could supplement that early on then they might live longer. But also these therapies are very expensive so having the enzyme made is not really working yet. So, I think there will be some time needed to get all the therapies in place.

EJ: And what would you hope to see happen in the next 30 to 40 years?

BB: If we're going to look at therapies and look into the future and what's going to be the major challenges and the major developments maybe is that with the use of induced pluripotent stem cells, and with the use of changing skin cells towards neurons or towards other types of cells, that you can help to make a change. For instance, now for diabetes patients they can make these Islets of Langerhans and produce the insulin in small packages, and they can do that separately so they can make a kind of membrane part with cells in there that produce the insulin. So there's lots of developments in that area. For the replacement therapy it will be also possible, for instance, the genes like Factor VIII, Factor IX it has been there already made by recombinant technologies and it can be used and can be given to patients. So these replacement therapies are not so difficult but if you want to change a cell producing a gene then you come into antisense, and antisense oligos are fine and you can use them and they work in cell culture, and they work in mice and we can maybe get them to work in

patients, but every patient is different. Their genetic background is different, the reaction to these oligos is different. The outcomes until now are not that great yet so it will take some time before the antisense oligo therapies will work. If you make a change then other changes follow, and that will help, not so easy to get the problem better. So I don't think we can cure Duchenne patients in the next 20 years. That will take some time.

EJ: Thank you so much Bert.

Figure 2: Professor Victor Dubowitz

Professor Victor Dubowitz BSc MB ChB MD PhD FRCP FRCPCH (b. 1931) graduated in medicine in Cape Town (1954). He came to the UK in 1956, and was a Senior House Officer (SHO) at Queen Mary's Hospital for Children, Surrey, where he worked with patients who had muscular dystrophy. He became interested in research on muscular dystrophy and embarked on a study of enzyme histochemistry of normal and dystrophic muscle, completing his MD Thesis in 1960. He returned to clinical medicine and paediatrics, and successfully applied for a lectureship in Sheffield where he spent the next 13 years, becoming Reader in Child Health and Developmental Neurology. There he set up a muscle unit and completed a PhD on the histochemistry of developing and diseased muscle. In 1973 he was appointed Chair of Paediatrics and Neonatal Medicine at Hammersmith, and rapidly established an internationally-recognized paediatric centre for muscle disease with a primary emphasis on the clinical management of patients and their long-term follow-up. He established the multidisciplinary journal *Neuromuscular Disorders*, in 1990, of which he remains Editor-in-Chief. In 1995 he founded the World Muscle Society to provide a forum for young researchers to present their work. Professor Dubowitz published his autobiography, *Ramblings of a Peripatetic Paediatrician*, in 2005.

2 Dubowitz, Victor*

Tilli Tansey: Let's start with why did you become a doctor? Was there science, was there medicine in your background?

Victor Dubowitz: There was nothing in the background and it was purely chance, because I was interested in science at school and I was very interested in mathematics – it was one of my favourite subjects – and so was I going to do something like chemical engineering or was I going to do something like mathematics? And an additional option somehow was going into medicine. Eventually, I got a place for chemical engineering and for medicine, I didn't apply for mathematics. And then more or less spun a coin and said, 'No, I think I'm going into medicine.' So it was just a choice at the time. There was nobody in the family at all, apart from one distant uncle.

TT: Where do you come from in South Africa? What was your school like?

VD: I come from a small country town called Beaufort West, which nobody had heard of until Chris Barnard, the cardiac surgeon, said he came from there as well, so he put it on the map. It was a very integrated schooling system. There was a Catholic school run by some nuns for pre-school and they were very good. I then went to the ordinary school, there was a boys' school and a girls' school separately, and then there was the high school, and that's where I matriculated. We had very good basic teachers who were quite interesting tutors. Although it was a small country town, I think they gave us quite a good education.

TT: You then went to the University of Cape Town to do medicine?

VD: There was a close friend of mine and myself who grew up together and were four days apart in age, and we were always chasing each other academically in a way. We got onto the merit list for the Cape Province, that's all the matriculation, a few thousand, and we were number three and number four. He was three and I was four, and I believe there was one point between us. This gave me a very nice scholarship to Cape Town of £50. And £50 in those days was a good start,

* Edited passages from the interview conducted by Professor Tilli Tansey, 27 September 2016, in the School of History, Queen Mary University of London. For more details, see 'Related resources' at the end of this volume.

and also having had quite a good pass I got into medicine. I was still interested in science, and in second year there was the option of doing a BSc, intercalated, and so I went for that, so it was quite nice. I got interested in hemochromatosis or something to do with iron, and so tried to produce it in rats by making them diabetic and then feeding them iron, trying to look at it.

TT: And you'd already got an experimental bug as well?

VD: Yes, I think so.

TT: And when you qualified, where did you do house jobs?

VD: I qualified in 1954 and did two house jobs in Cape Town, the standard surgery and medicine, six months each. Then I met up with a friend who qualified with me, and he said, 'How about going to England?' So I said, 'Well, that's a good idea.' And so I then went and did two months of General Practice in my home town, as a locum, saved a bit of money for the fare and booked my ticket for a six weeks' trip, all the way to England, for the same price as the direct one, but it was a nice holiday. I came to England in April, I think it was, of 1954 into a pea-souper of a fog, and I nearly got onto the next boat back.

TT: That must have been an awful shock after South Africa?

VD: It was unbelievable. I wanted to see a bit of the world, I wanted to be in London, I wanted to get some general experience, so I was looking for casualty posts. And people said, 'Ooh, you'll never get jobs in London.' Too competitive and all that. In those days, there was the British Postgraduate Medical Federation, which actually controlled the postgraduate institutes and stuff, and there was Sir Frances Fraser, he was the Dean or whatever, and it was customary for colonials to go and meet up with him and then one's chiefs would send him confidential reports. I went to see him and just told him I'm interested in general practice and wouldn't mind doing a bit of casualty and various things, and he said, 'Yes, that's alright, but what do you want to specialise in?' I said, 'No, I don't want to specialise.' So he said, 'What did you come here for?' I said, 'I came for a bit of culture and theatre.' And then he said, 'What job? Hold on, you're looking for some casualty.' He said, 'Let me have a look. Hold on a moment, they're looking for a casualty officer in Lewisham. That's not too far from London. You can get a train into Charing Cross.' So I went for an interview and got the job, partly because the previous casualty officer had been a South African and he'd obviously left a reasonable impression. I was there setting fractures, and playing around, and doing minor surgery and so

on. So that was extremely helpful. I always tell people, it's very important to do what you enjoy doing, it's always been a principle, and always have a go at things. One day out the blue the superintendent called me and said, 'We've got a problem, we've got an ophthalmologist and urologist that do sessions here, and they've got a houseman, and they've said they'd rather have no houseman at all than have this guy. He's a bit of a danger to patients. Would you be prepared to help out?' I said, 'Sure.'

So then I did an ophthalmology fill-in. This ophthalmologist would come along and he'd operate and so on, and it was some amazing experiences, because for instance at Guy Fawkes [Bonfire Night 5th November] there was a kid who put a cracker into the fire, and it didn't go off, and then he went down to look and it blasted both his eyes, and he was totally blinded, and his corneas were totally opaque. I thought, 'Goodness, that's tough.' Anyway by giving him 10-minutely drops and saline and steroid, eventually he walked out with normal eyes. As a result of being friendly with this ophthalmologist, he said, 'What do you want to do next?' I said, 'I wouldn't mind doing a medicine job.' He said, 'I'll check what's going on at Northend Hospital in North London, Hampstead, because I do sessions there.' He came back the following week and said, 'They're advertising a job in about a week's time.' I put in for it, and I got the job unexpectedly, and why did I get it? Partly because Bill Hoffenberg had been the Registrar then.

TT: The South African connection again.

VD: Yes, an ex-South African [laughs]. He had been my Registrar in Cape Town. Not that he gave them a reference for me, but they obviously liked the accent or whatever it was. Then I wanted to do some paediatrics, and out of the blue one day I was phoned 'Can you help out? There's a Registrar at Queen Mary's Hospital for Children in Carshalton, and he's going up to some youth festival in Moscow,' which turned out to be an international festival, this was 1957, and they were looking for a locum. So I went out to Queen Mary's, it was an old army barracks, there were 600 beds or something, and there was tuberculosis and polio and herpes and all sorts of things. He said, 'There's also a muscular dystrophy ward, but you don't need to worry, because if a child has pneumonia, they will call you.' I'd never heard of muscular dystrophy, so the following morning of course I went to the ward. And, as they say, the rest is history. I went for three weeks and I stayed for three years and became interested in muscular dystrophy.

TT: But by this time you'd had, you'd done a wide variety of surgical jobs, got quite a lot of experience. And then specialised surgery, and then the medical jobs.

VD: And this polarised me, but then it also set me off at a tangent, because nobody seemed to know anything about this muscular dystrophy. Nobody was interested in these kids, and the paediatrician said and the neurologist said, 'There's nothing we can do, so we're not really interested.' And then I learnt a bit about pathology so I asked, 'Who is the best pathologist around here?' This was Professor Daniel, who was the neuropathologist at the Maudsley.

TT: Peter Daniel? I knew Peter well. He is largely responsible for me becoming an historian.

VD: He's responsible for me becoming a pathologist, almost. I went out to Peter Daniel, and he was very nice to me. I took biopsies from the children and I took them to King's College, he processed them and then we looked at them together and he taught me about the pathology. In the meantime the pathologist at Queen Mary's, who thought he knew about everything in pathology, biochemistry, he called me one day at lunch and he said, 'What are you dabbling in? Keep your fingers out of the pathology. That's my domain,' or something like. So I said, 'Well, I'm just doing whatever I like doing.' And he said, 'Well, that's fatal you know. You can't possibly do that.' I said, 'I'm single, I've got no responsibilities. That's what I'd like to do.' So anyway that's what I did and then I asked Peter Daniel about some advice about doing some research, and he put me on to Everson Pearse at the Hammersmith. And so I phoned Everson Pearse and said, 'I know nothing about histochemistry, but Peter Daniel thought it might be a good idea to come and talk to you. And I'd like to do some research and I'm interested in muscle disease.'

So he said, 'Would you like to come to lunch on Friday?' So there I went for lunch with all these big dignitaries, you know like McMichael and all the big names of the time. And this was at the Hammersmith. And here I'm a SHO coming from Queen Mary's Carshalton out in the sticks. So, anyway, Pearse took me around his lab and introduced me, one guy from South America, one guy from here, one guy from there, and a very nice Polish guy. And he said, 'There's a bit of bench space there. When can you start?' I said, 'Tomorrow.' So then I took biopsies at Queen Mary's and I took them to the lab and I soon realised there was only one cryostat, so I came at night, and I sat there cutting my things and learning about histochemistry and so on. And I went on with

this for about two years and was thinking, 'Well, I could make a career of this and go into pathology and so on.' And then a few things happened, sidelines, but the main chance was, I was discussing what to do next and then Pearse said, 'Go and talk to John Cumming,' and he was the biochemist, mainly a lipid brain chemist. So I went to chat to him and he was also at the time Chairman of the Muscular Dystrophy Group Research Committee, and so he asked what I was interested in and I said, 'Well, I don't know exactly where I'm going, but I'm enjoying this, enjoying that, I've done some histochemistry and I've got a paper into *Nature*.'

So he said, 'Well, if you're interested in a lectureship here, I've just got a vacancy in chemical pathology.' So I was looking at cerebrospinal fluid samples and doing all the biopsies at Queen's Square. And then I got a bit fed up, because these eminent neurologists would send a form with the muscle biopsy and the most erudite of clinical details, it would say, 'Query muscle.' [Laughter]. So I'd write back and say, 'This is indeed muscle. I'm sure it's not liver or kidney. Can you tell me something about the patient?' you see. And it went on, and then I realised that my heart was really in clinical medicine, seeing the patients. I missed them.

TT: Can we go back a little, Victor. What has struck me so far is how generous some people were. Sir Francis Fraser, Peter Daniel, all generous with their time to a young chap who has just arrived.

VD: And who speaks with a foreign accent, yes. They were very supportive and very helpful. They all were open and trying to encourage me, and I've done that myself ever since with young people.

TT: Yes, a very good role model. So can we go back, you're taking biopsies. What biopsies did you take?

VD: I took from the gastrocnemius mainly just under local anaesthetic or sedatives, and then I'd take these biopsies, and then I'd freeze them. We didn't use liquid nitrogen initially, froze them with CO_2, the gas. And then I found the samples were full of artefacts, and so discussed this with Pearce and he said, 'Well, it needs more rapid freezing.' And so we introduced liquid nitrogen as rapid freezing, which hadn't been used at that time, and then we got beautiful sections.

TT: And what were you looking for? Enzyme histochemistry?

VD: Enzyme histochemistry. I looked at muscle and there was a nice checker board pattern in human muscles, and the physiologists were, of course, talking about slow and fast, and white and red, fibres. And so I said, 'Well, I can't see anything white or red here, and I can't tell if it's fast or slow here, but I can tell you there are some fibres that are strong and some are weak reacting.' And then what we observed, it was quite useful that I had David Hill next door, a physiologist. I used to chat to him quite a lot and he said, 'Ah, human muscle. What happens in the frog Sartorius is…' [laughter]. That was days of the frog sartorius muscle, and I couldn't talk frog sartorius with them. But, anyway, I then started doing a bit of comparative things, and I looked at the breast muscle of the pigeon and the breast muscle of the chicken, which is white – the pigeon's is red – for long distance maintenance, and various animal studies, and histochemistry. I learnt quite a lot about development of muscle and so on. But the important thing we noticed from the dystrophy muscle first – which was obvious – was these very big fibres were one type, but there was a reciprocity between oxidative enzymes and glycolytic enzymes in individual fibres.

So this meant it was meaningful, that actually different fibres had different function within a mixed muscle. So we got a paper into *Nature*, reciprocal activity, a one page paper, which took about a month to write. If I'd written six pages it would have taken one evening. So, anyway, that was a milestone for me. And then we then published a comparative study, so I looked at all these animals, looked at fish and frog and then the slow type of muscles, all different animals.

TT: What enzyme were you staining for?

VD: There was succinic dehydrogenase (SDH) that was standard, and then there was NADH-TR [nicotinamide adenine dinucleotide tetrazolium reductase] or whatever the nicotinamide thing was called, which was a more general one. And then we also looked at other oxidative enzymes, lactic dehydrogenase and a few others. We eventually realised they were all parallel, and we could just do one or two and that was enough. So SDH became a standard, and then of course cytochrome oxidase became a standard, so all these things eventually evolved. So that became very important in relation to people believing, and even David Hill said, 'Yes, I think there's something there.'

TT: It must have been such an exciting time to be in muscle, when you think, because Andrew Huxley was looking at nerve muscle fibres, and Krebs' stuff on glycolysis and muscle enzymes, it must have been so exciting.

VD: I was learning a new language all the time and I was learning to communicate with these guys. When I went there, NADHT or whatever, diaphorases and you know, what the hell's this language they are talking? Then I made great friends with people, because the guy, Niwelinski, was a zoologist, I went to visit him subsequently in Poland. We also had an experience once. I came one morning, and the biopsies I had, they had all thawed out, and if you refreeze them they get a lot of artefact. What had happened, the cryostat had failed or something. And then Niwelinski came to me and he said, 'You know, I had a phone call last night while I was working at the lab, and the machine was making a noise.' We called the machine "Wheezy", because it was very temperamental. 'And I switched it off in order to talk on the phone, and I forgot to switch it on.' And everything had thawed inside, and I had left all my specimens there for storage, you see. So he was terribly sorry and every time I used to meet him subsequently he used to say, 'I'm terribly sorry.' Anyway, we became very good friends, and so it was basically a very nice team, it was very good. And Pearse had an ability to encourage young people. He'd say, 'Get on with it and this is what you do,' and so I was thrown in the deep end. But then I thought, 'No, I'm not really a pathologist at heart, and I really would like to go back to children.'

I spoke to David Lawson, who was the chief paediatrician at St Mary's. In those days there was one superintendent physician. There was one superintendent nurse and there was one hospital secretary and they ran a very efficient hospital, 600 beds, and everybody was friendly and interactive. I spoke to David Lawson and I said, 'I'd like to get back to paediatrics.' He said, 'What I suggest is go and see Alan Moncrieff.' He was the first Professor at Great Ormond Street, of Child Health. And that was when the Institute of Child Health was developed. Lawson said, 'Let me just warn you: he's very abrupt, he's seemingly very rude. It you get 10 minutes with him you've done pretty well, don't feel discouraged. He's always in a hurry and he's always got a lot to do.' So, anyway, I phoned his secretary, I made an appointment. David Lawson also phoned and he said that I was coming to see him. And so I went to see him, and he interviewed me and said, 'What are you doing? What's this? What's that?' And I, in the meantime, also wrote an MD Thesis in six weeks or eight weeks or something, and that was a different story. He suggested I should apply for the Lecturer post in Child Health in Sheffield.

TT: The MD – you submitted that through Cape Town?

VD: Yes, that's right. What happened was actually, in the midst of all of this, I met a girl on a picnic, I helped a friend of mine who was taking her out for the day and then his car broke down. He had an old Riley. He phoned me up, 'Can you help?' I said, 'Oh yes, it would be a pleasure to take her out. I'll chauffeur you.' Virginia Water and Windsor Park. Anyway, 10 days later we got engaged. So it was, and so we had a long partnership. And then we went on honeymoon to St Ives and so on, and then we were discussing meeting up, her mother was in Australia, my parents were in South Africa, and although my father had come out for our wedding, we decided we would try and visit. And then I thought, 'Well, a good excuse for getting there is to present an MD Thesis,' and at that time I hadn't written anything down. So, anyway, we got down to it, and my wife was very systematic with things. She said, 'No, get this, get this, get this. We need all these family trees up.' I had 60 patients that I had seen altogether.

TT: Was Lilly already a doctor by then?

VD: Yes, yes, she was going to be an endocrinologist. She was sent out by the Professor of Obstetrics to train in endocrinology with Russell Fraser at the Hammersmith. And then she was going back to a new Department of Endocrinology, Obstetric Endocrinology. Then her course changed a bit as well, and that's a different story. But anyway, so we thought perhaps if we do this thesis, we'd have an excuse. And so in about six weeks, I contacted Cape Town and they said, 'That's fine for graduation in November/December. It's got to be in by the end of August.' I said, 'Fine.' We got married 10th July, so we got back from honeymoon in the middle of July, which left us just the six weeks, so we just got on with it. In the meantime, I went to see Moncrieff, and why I told you about the MD Thesis was, it became relevant. He started talking about this and that, and asked, 'Have you applied for the lectureship in Sheffield?' And I said, 'No, because it said you need a Membership.' And I thought I'm not eligible. And he said, 'You've just done an MD Thesis. That's just as good as a Membership, I think. I think you should put in.' Obviously Moncrieff was interviewing me, because he spent about three quarters of an hour. And I thought, 'What the hell am I still doing here? This guy's supposed to get rid of me.' And so he phoned up Illingworth and said, 'You know I've just seen this guy and I think he might fit your lecturer post.' The closing date was that day, that Friday, so I put in. Of course Illingworth being Illingworth, on Saturday morning he gets my application, on Monday I get a reply, 'Come for an interview on Wednesday.' And the rest is history, as they say.

I went up to Sheffield and they were looking for somebody to replace Rendell Short who was going off. I came along and they said, 'When can you start?' or something. And I remember Illingworth saying to me, with the committee there, 'You will be getting the Membership, won't you?' So I said, 'Yes.' Of course, in those days there was a 7% pass rate out of 300. I did the adult, not paediatric, Membership and I had one or two goes and didn't get anywhere because I had patients, or I just didn't know all the stuff. And then I had a go when everything went fine with the papers and things, and then in the exam I had interesting cases and interesting short cases. Then I got the next letter, which was the pathology *viva*, in those days. You either got a thick letter or a thin letter. A thin letter you hardly bothered to open it, because it meant you'd failed. I went to the pathology *viva* and they asked me all sorts of questions and I remember a picture of a girl with anorexia nervosa, and I knew all about that, and so on. Anyway, so then I got another letter, a thick one, for the final *viva* and in those days there were 25 to 30 people getting a final *viva*. So I read through the whole of the textbook of medicine in the course of that week, and I was in a terrible state, really worked up; came down from Sheffield. And you get shown into this big room with the President there and the censors, and I'm sitting there petrified and the chief censor says, 'No questions.' And the President said, 'There are no questions.' So I sat there and he said, 'You can go now.' So is said, 'But I came for my final *viva*.' He said, 'You've passed.'

TT: I've never heard of that for anybody.

VD: Yes, I scored enough bonus points not to need any questions in the final *viva*. I'd passed. So I was going to write to the College, but I didn't – perhaps I should have – because they send you a letter at each stage and if you don't get an initial pass, it's a thin letter, 'We're really sorry to inform you that you've not done well enough in the papers,' or whatever, to justify a further thing. And then if you go through the pathology *viva* and you get a final *viva*, but if you don't get a final *viva* it's another thin letter they say, 'Sorry, you haven't reached the appropriate level for a final *viva*.' But then you get the thick one which says, 'Can you come for a final *viva* at the College on this and that date,' and it doesn't tell you anything more. And so I thought I'd write to them that if they are calling you for a final *viva* and they're not going to *viva* you, they should have at least the courtesy to say, 'Don't worry about it, because however badly you do you've already passed.' People now wouldn't understand it, because Membership now is 30 to 40% pass, it's like an ordinary exam. Then it was a knock out competition. It was a major hurdle.

TT: Going back to you going to Hammersmith and Tony Pearse saying, 'Well, this is your bench space.' How did you do that? Because nowadays you'd have to apply and have a grant and pass security and all that stuff.

VD: The world has changed. If I came here to the UK now I'd probably have gone back into general practice, because they would have told me, 'Look, you've got to do this, and seven years of this and five years of that.' Britain was a wonderful place, because they somehow always accepted the eccentric or the deviant or the whatever; they liked the maverick, or whatever you call it. And as long as you didn't have too much of an English accent.

TT: It's just fascinating to modern youngsters that you turned up and Pearse just said, 'There's a bench, get on with it.'

VD: People took you, you know, if they thought, 'Well, this guy's reliable, he wants to do something and I'm sure we can depend on him,' then it's okay. And it was just me as a Lecturer in Sheffield and one Houseman. I had no Registrar. So if the Houseman couldn't do something, I had to go in and help him. And I was succeeding Rendle-Short who was interested in cardiology and he'd set up a weekly session of paediatric catheter work for cardiology. I came along there was told this was what he did, so I thought, 'This is very interesting, I know nothing about cardiology. I might as well learn a bit of cardiology.' So I did cardiac catheters every Tuesday. I did about 400. I've still got a box with all my detailed reports, and it was great fun because you clinically make a diagnosis and then you find it's something different. I felt I couldn't let that go when the guy had established it, and it was something which was beneficial to the paediatric work. Much as in Lewisham I did a locum in dermatology and I did a locum in obstetrics. I was on call for obstetrics for about six weeks when they were short of someone, because I was just interested in getting experience.

TT: A vast portfolio. You would be regarded nowadays as being dangerously unfocused.

VD: Yes, so there you go. But you know it's just the principle: just enjoy yourself. Well, people used to ask me, 'What are you specialised in? Or what are you accredited in?' I said, 'Nothing.' [Laughs].

TT: So when you got to Sheffield, Ronald Illingworth was Professor?

VD: Professor Illingworth, yes. So I came as Lecturer, and then I was Lecturer plus a Houseman and equivalent I suppose to a Senior Registrar, in a sense, but having a little bit more autonomy and independence, because Illingworth took

people on trust. There was John Lorber then who was doing spina bifida work and there was Holt who was doing cerebral palsy. I started a muscle clinic and that sort of thing. And then I went for a year to the States. I was going to work with a chap called David Clarke who was a general paediatric neurologist, and I'd fixed this up with him at the Johns Hopkins. And then about a month or two before he wrote to me and said he was leaving Johns Hopkins, he was going to Lexington Kentucky, and if I wanted to come out to Lexington Kentucky, I was very welcome to join him. So I took up my fall-back option which was going to the Muscle Institute in New York which was linked with Cornell Institute and Hospital, so I had an outpatient clinic, some position of Visiting Consultant to outpatients or something, for a year.

TT: You were allowed to see patients?

VD: Yes, I did biopsies on patients, and I taught the residents, and then I got interested in orthopaedic people, and there was the hospital for special surgery next door. They were treating congenital scoliosis and so I started to combine meetings with them. That was very useful in getting them to do some spinal fixations.

TT: How did you organise that because, again, now you'd have to have a grant, you'd have to have permission to take leave. How did you do that?

VD: I got a sabbatical from Sheffield. I was entitled to that after five-six years, whatever, and I don't think I got a salary, because another South African came and did a locum in my place. So I was away for a year. Well, in those days the BTA [Been to America] was a very important degree for most people. Now, of course, they do their five year training and they're totally introspective and their horizons are about 200ft. But this was nice for me and a lot of people did this year of research in the States and it was really very good because you learnt a different thing and, of course, American medicine is different.

TT: Coming back to Sheffield you still had a focus on muscular dystrophy?

VD: I was focusing on muscular dystrophy but I did a general outpatients in general paediatrics, and I got interested in the newborns who were having fits, and there was somebody – a biochemist – who was measuring levels of anti-epileptic drugs.

TT: And what was Lilly doing at this time?

VD: She was training to be an endocrinologist. We went up to Sheffield. So Illingworth spoke to the Professor of Endocrinology who said 'Yes,' he'd be very happy to take her on board. She applied for transfer of her animal licence and applied to the MRC for transfer of her grant. The Home Office said they couldn't transfer the animal licence until the grant was transferred, and the MRC wouldn't transfer the grant until they knew she was getting an animal licence.' There was another paediatric unit running in parallel with the Illingworth firm, and their Senior Registrar who was going off to a Consultant post, and so they asked Lilly if she could help out, because they needed somebody almost immediately. She said, 'Yes, fine.' She became a paediatrician. She always had a research bent and a biochemical interest, and then eventually she found, when we had four kids, that basically it's a bit difficult doing a full-time research job with four kids, but she made sure the kids were always first, always collect them from school and fed them and topped them up, and then once they were asleep, she'd go in to work at night. And the only people who didn't mind her coming at night were the newborns, so she actually got interested in neonatology as a practical area. And then, of course, she got totally fixated, and was really very good at handling newborns.

TT: This was the start of the Dubowitz scale?

VD: In the 1960s, when we came back from the States, I was interested in neurology of the newborn, at that time there was no real, proper neurological examination of a premature baby. I had a picture of a premature baby and the knee hammer, which was a little bit longer than the baby. An adult approach to the examination of a newborn was pretty useless. We started with various neurological signs that were used for maturation and doctors were saying, 'Well, if this sign is present it's 32 weeks, and if that sign is present it's 36 weeks,' and this didn't seem to be quite right. Then Allie Moosa, a South African who was doing a job as Registrar in Sheffield, and with Lil and I looked at some babies and we just objectively looked at their gestational age and what stage they developed particular signs at. And we found there was a range. As a result of that, we evolved into not relating a sign to a particular age, but just grading it from minimum to maximum, we thought, 'Well, let's just grade them from 0–5, or 0–3, whatever number.' So you take the maximum, you take the minimum, and you see how many stages you can find between. So we then tested all these neurological signs and the ones that were easy to do and seemed to relate, we just retained. We ended up with 11 neurological signs, and then Lil did a very carefully, meticulously controlled study of 400 successive newborn babies at the

Jessop Hospital in Sheffield; no knowledge of the gestation of the babies, just looked at the babies blind and scored them. After she'd finished the 400 she went to the mothers and went through all the obstetrical data, their last period etc, all this, and there were about 167 mothers who were certain of dates and had regular cycles, and those she analysed. And then she found that the superficial signs were a bit better than the neurological, which was very disappointing, but then she had a brainwave because that was the most important thing. She then added them together and she got something that was almost equivalent to nature, I mean it was such a close fit that you couldn't do better than that on the last gestation or last period and so on. That was the basis of the score, and it suddenly caught on like wildfire because it was practical and it was simple. You didn't need machines and you didn't need calculations; you just needed to look. And the charts were there, you would just put circles around the equivalent on the chart. So in no time they were doing it in Tanzania and they were doing it in Thailand, where she went out a few times to assess babies, and New Guinea and so on.

TT: You both had your hands full. Burgeoning careers, growing family, lots of challenges. Not only your research career in muscular dystrophy, but also a full paediatric load.

VD: I just enjoyed clinical medicine. I had a big clinic of cystic fibrosis; I was treating these kids very actively and in fact we may not have been the first, but certainly we intuitively started giving combined antibiotics. Some of them were not fully sensitive to either antibiotic, but clearly you got the synergy. This was already in the 1960s. But I was just interested, I wrote up a single case report, people these days wouldn't write a case report. There was a baby born at the Jessop Hospital at full-term and was about 3 lbs or 4 lbs, and had a funny face. I still remember her name. And the mother said that her previous child had looked the same, but had been born prematurely and didn't survive. I looked up all the syndromes of dwarfism and it didn't quite fully fit, it wasn't clear. So I just wrote a case report in the *British Journal of Genetics*. I said, 'Here's a genetic thing that's recessive and it's an unusual face, with odd ears and a particular nose, and doesn't quite fit in.' And then Opitz, who became a very well-known geneticist in Salt Lake City in the States, he was then in Germany and he read this, and then he published an identical case. He said, 'I've seen exactly the same case,' and in fact they looked like sisters, you couldn't tell the one from the other. He started calling it 'Dubowitz Syndrome' based on a single case. And it got into the textbook of malformations. So basically on the single case report

there, I've got my name attached to a disease. Even to this day, I still get people coming along and sending cases, and I've seen quite a few, and then somebody thought they had a gene for it in the States, but I'm still not quite sure exactly.

TT: And what is it?

VD: Well, they've got slight retardation, they're very small, low birth weight, underdeveloped, and then there's a propensity, what I didn't notice actually because they were using sunlight in those days for vitamin D, this child became quite red and then I tested actually with UV, ultraviolet, and found they were hypersensitive to sunlight or to UV. It's mainly their faces and it's not directly recessively inherited, but there is some genetic component. It's a small world, of course, I was visiting San Francisco, where one of our sons was at Caltech, and then I was going to Utah to meet up with a neurologist there, because they had a muscle clinic and they wanted to discuss some patients. And I went out there and who should I bump into in the corridor, but Opitz. He was the geneticist there, and he said, 'What are you doing here? I've been trying to get you on the phone! I phoned up the Hammersmith and they said you're not there at the moment. We're having the first meeting next week of the Parents' Support Group for Dubowitz Syndrome. And we've got about 50 families coming from all over the States. Can you come back?' I said, 'Yes, I'll fly back next week. I'll just ask my wife.' We were in Los Angeles for about two to three weeks, and so I flew back and saw all these kids, and they all looked pretty similar. Some of them were not quite typical, so they probably were not the same, but those that were typical – and then there were some odd ones, because there was one family where an aunt or somebody had the condition and then another child was born subsequently, so there was some link, but it wasn't a straight genetic link. Every now and again I look up if anything recent has been developed.

TT: In Sheffield did you also have a research lab?

VD: In one of these old buildings was an extension of the children's hospital. It was originally a tuberculosis ward in Lorber's day, because he did a lot of early pioneering work with streptomycin and they were saying in Sheffield that this building was kept together by the tubercle [laughter]. Anyway one of the wards was there and there was a long corridor and there was a wash basin at the end, there were two separate taps. And this was supposed to be the isolation ward for infection. I set up the muscle research, and then I wanted to set up some histochemistry and I got a grant from the Muscular Dystrophy Group, £500 a year or something, advertised and got a chap. I trained him and then I got

money for a cryostat, and it seemed difficult trying to fit everything into the Department building. John Emery, the pathologist, said, 'Oh fine, the guy can come and work here in my lab with the cryostat,' but this guy and was always behind with things and nobody was pushing him. I think, he spontaneously decided to leave, which I encouraged. Then I had a technician who was an absolute gem, came with her mother from school, just finished school and she just had that spark, so I did an Everson Pearse and I appointed her. She was wonderful.

Eventually it wasn't going to work like that, so we put the cryostat in my office, and so in my office I had a small desk with the cryostat and she was doing sections. That's the first part of it. Then that building was knocked down and they built a new Department. I went to see Illingworth and I said, 'I'd like to have an animal house in the basement.' 'Don't be ridiculous, what are you on about?' So I said, 'Well, we're doing some research and we're starting to tissue culture muscle.' We were the first actually to tissue culture human muscle, because they were saying at that time it was not possible.

TT: When was this?

VD: In the 1960s. This shows the flexibility of the system. Basically, when I arrived in Sheffield and I was trying to get some money for technical staff and so on, there was nothing available immediately. Then I found out that every department in Sheffield was entitled to a technician, as a general helper. I spoke to Illingworth and he said, 'No, we don't need that.' Then I spoke to a friend of mine who was in Fuel Technology. Of course they had several technicians. So I went to Illingworth and I said, I'll just bring you a word of thanks from the Fuel Technology Department, from my friend, and he's very grateful that you haven't used your money, because he's spending it very wisely for you. Now how's about spending it on our Department?' [Laughter]. So then I spoke to the Registrar and he said, 'Oh yes, we've got that money set aside if you want it, but don't exceed it.' Then a geneticist came to see me, she'd been working with Eric Blank, who was a senior geneticist, and she was looking for part-time stuff in research, and so I interviewed her and appointed her half-time. And that was fine, and she was very good, and started with a culture of muscle.

Then out of the blue I got a call one day from Alan Roper who was Professor of Genetics, and he said, 'We've got a bright young thing here who is bouncing all over the place, and we've offered her a job that we've got and she says we're very nice people, and she's very interested, but she doesn't really like the work we are

doing,' which was on yeast genetics. 'She'd like something human-related. Have you got anything you can offer her?' I said, 'Send her along.' A breath of fresh air. She qualified from Manchester, a medical BSc or something. And she was full of ideas and tissue culture, fantastic, very excited about tissue culture. I phoned up the Registrar, in those days you could talk to the Registrar directly. And I said, 'Remember we had the technician post? You remember I appointed this geneticist half-time? I've just got a very bright postgraduate student, done her BSc and things, and I think she's just what we're looking for, for some research. Any possibility of using the other half?' He said, 'Oh yes, no problem, as long as you don't exceed the total.' So I appointed her full-time as a Research Fellow, she did a PhD Thesis, and she was just absolutely phenomenal. Between the two of them they cultured human muscle, they got engaged with nerve muscle preparations interactions. I sent her to New York to go and see Silverman who started her nerve muscle preparations, and so it went on. I hear from her from time to time, in fact she phoned me up about a year ago and came to visit me in London.

TT: There's somebody who did come to apply to do a post-doc with you, I think, and that was Jan Witkowski. He's going to write the introduction to the muscular dystrophy Witness Seminar book.

VD: Oh, fantastic. Jan Witkowski is very interesting. Jan was working at the MRC centre in London in Hampstead, doing basic research and he came up to Sheffield and we interviewed him and he said, 'To be quite honest, I'm very interested in coming to Sheffield, because I like mountaineering. The mountains around Derbyshire, in fact.' We appointed him as a Post-doc Fellow and he was great, because he also started all the tissue culture stuff and all that. Then it was a matter of months after that, I got offered the post in London, which was a different story. I was in Australia travelling around on my way to New Guinea actually, and I get a call from Illingworth. And he says, 'Why haven't you put in for the Chair at the Institute in London?' I said, 'Because there's a Reader in the Department, worked with Tizard, and I'm sure it's all fixed.' 'No, no, Otto Wolff, Head of Paediatrics at the Institute of Child Health phoned me up and said, 'Why hasn't Dubowitz put in?" So I put in an application, was shortlisted and offered the post. But there were numerous problems with research facilities and bringing my team along.

I didn't want to leave Sheffield, but that's another story. I said to Illingworth, 'If I can get a personal Chair here, I'd prefer not to go to London,' because there were all sorts of difficulties with housing. He sent me to the Vice-Chancellor

and he listened out my story and said, 'Well, we have a policy in Sheffield that we don't give personal Chairs to people who deserve it.' I said, 'What do you mean?' He said, 'Well, our policy is that if you can get a Chair on the open market, we wish you well. I mean we sent off Edward Mellanby and we sent of Howard Florey and we sent off Hans Krebs, and we wished them all well, you see [laughs]. And that's our policy. The only people we give personal chairs are the people who are stuck in a *cul-de-sac* and they can't get a Chair outside.' So anyway I said, 'Well, I'm terribly sorry about that,' because we were very happy in Sheffield. We had our kids there in school, and so who wants to go to London, you know, for the rat race? So there we were. So that was that part of the story.

TT: Poor Jan missed out on his climbing?

VD: So then, I said to Jan, 'Look, I'm terribly sorry, Jan, but we're going back to London. If you want to stay here in Sheffield, I'll find something.' He said, 'No, no, I'm coming with you.' And so he came with us and then we got money from the Muscular Dystrophy Association of America to put up our labs. Anyway Jan Witkowski came with us to London and we set up the lab. I found out there was some space on top of one of the roofs, which was flat, of the hospital. And I went and got all the original plans out and there was nothing that said you can't build another floor. We actually got permission to build, we got money from Action Research, and so we put up the lab up top there. But the Hammersmith was a very competitive place.

TT: Who was at the Hammersmith when you went back?

VD: The Professor of Medicine at that time, was your friend, Chris Booth. Keith Peters became Professor later. Now I remember Booth very well, because I went to see him soon after and asked him for advice about a member of staff. He said, 'I never worry about the people who leave. I only worry about the people who stay.' A very important thing because I was saying, 'This guy leaves, that guy leaves, what do we do, or whatever?' Never worry about those people, it's the people who stay. He said, 'If somebody good leaves, you always get another person good to put in their place.' A very important principle from Chris Booth.

TT: Where did the link with Jerry Lewis come in? Was that part of that lab?

VD: Ah, Jerry Lewis. Basically, I had nowhere to do research, and so initially we had some facility in what was called the 'labour yard', and it was awaiting destruction, but there was an old lab there that was still available. Originally when it was a poorhouse hospital, they used to take in people who were indigent, they had a labour yard there where these people actually did work and chopped up things and so on. That was at the turn of the last century. The Rheumatology Department had use of some of the building that was connected with it, but it was now condemned and it was going to be cleared. I found this building and they said, 'No, it's the labour yard, it's unfit for human habitation.' So I said, 'Well, I'm sure it's alright for us for a little while.' [Laughter]. And we actually settled into this labour yard, and that's where Jan came along. And of course Jan very happily came, and then he got interested in tissue culture and the nerve muscle culture and stuff as well, and he was doing some very interesting time-lapse photography of movement of cells and comparing dystrophic and normal cells, you know, so it was quite an exciting time.

So we were in there and I spoke to various people and there was Richard Edwards, a very close colleague and a long-standing friend, and he was interested in respiratory medicine mainly, but he was also interested in muscle biopsies in order to study physiology of muscle, and had worked with Bergstrom in Sweden who was developing this type of needle biopsy in athletes. He was in the Department of Medicine, and was also interested in coming into a muscle lab and doing some muscle work, so we had a combined interest. And then David Hill personally knew one of the people who was on the Executive Board of the American Muscular Dystrophy Association, Gibson, Vice-Chancellor at University of Victoria Vancouver Island?

TT: British Columbia, Vancouver? I think you mean Bill Gibson, who knew Sherrington?

VD: Yes, and we went to visit him on a number of occasions subsequently. A delightful person. He worked with Sherrington at the turn of the century in physiology; he was a great physiologist. Basically, he engineered it for us because the Americans were very insular and they weren't going to give money to anybody doing research outside America. But he said, 'This is very important, we have to promote international muscle research, and that's what the Muscular Dystrophy Group of America is collecting for. We can't just be insular and stick to ourselves.' They gave me a grant of $300,000 with the stipulation this is just for the building, that they would not support any research in it, and then we would find our own research fund. So we took it up and we told them we'd

like to give it some connotation, and so we called it the 'Jerry Lewis'. And Jerry Lewis actually came out to open it, and it was rather tough for Jerry Lewis actually, because his agents also set up a Jerry Lewis concert or something and, in my youth, I remember he was the mad doctor with Lewis and the other guy.

TT: Dean Martin?

VD: Yes, Dean Martin and Jerry Lewis. And so he had this big concert planned in Hammersmith, and it fell absolutely flat and he just couldn't communicate with this audience of middle aged people or whatever, who should have remembered Jerry Lewis. So he wasn't in very good spirits. But he was the guy who had the telethon already every year in the States and collected millions, and he went flat out for three days raising money and was talking about his kids and he personally became very involved, so this was very interesting.

TT: Did he have a personal connection? A child with muscular dystrophy?

VD: No, no, I think the muscular dystrophy, they had just engaged him as a comedian and as a guy who could run the appeal, the annual telethon, because they started the telethon system, which was a television marathon. And so it went on for three days with this marathon on television, collecting. And then, of course, the French did the same, and then the Italians. So that was him coming out to see us, and in fact Richard Edwards was also developing mechanical things for measuring force of muscle and so on, because he was more interested in the physiology side, and he gave Jerry Lewis one of these constructed pressure measuring things as a memento. I remember him going in the lab and he even looked down a microscope and tried to see what was going on.

TT: Do you know the story, I'm diverting here, but it's a story about someone you mentioned earlier, Peter Daniel. And it was the opening of new labs down at the Institute of Psychiatry. The Queen Mother went to open the labs. There is a picture in I think the *Daily Express*, of Peter Daniel in a pristine white coat, explaining something to the Queen Mother. In the *Daily Express* it says, 'Queen Mother talking with the head chef about the patients' dinners.' [Laughter].

VD: That's absolutely lovely. Well I had an experience when the Duke of Edinburgh came to open up our new child health department. We built out on the roof of one of the outbuildings there and got money from Action Research and the Duke of Edinburgh came along to open it. We took him round the wards and he started talking about injuries that give you calcification and stuff, you know, gun injury, but he was worried mainly about muscles, of course polo

players apparently get this calcinosis. Anyway there was a picture of him and myself with my white coat, and then there's one or two of the dignitaries from the institute who came along to be part of it, and this came on the cover one of the nursing journals. I sent a copy to my mother and she jokingly said to my brother, 'Who's that guy with Victor?'

The Muscular Dystrophy Association: they were very political, there were a few people who influenced them politically outside, and, basically, Jan was doing a lot of different types of research and things and then we were trying to get him some long-term support. They said no, basically we needed to send him to the States to get some training in molecular genetics or whatever. And he went to the States and he never came back, but he went to various places. And then the guy who was appointed at Cold Spring Harbor died shortly after appointment and Jan was approached and he's been there ever since. He was great actually, we had a great team. He's been here recently or you've been to Cold Spring Harbor?

TT: No we've been on e-mail. I've just done a Witness Seminar on National Institute for Medical Research (NIMR) technicians, and he sent me an e-mail saying, 'It's a long time since we met at Cold Spring Harbor. Do you remember I started at NIMR?' I remembered him telling me the story of going to work with you in Sheffield, because he wanted to go climbing. And so I thought to ask him to write the introduction to the volume.

VD: That's amazing, that's very good. He's done some interesting books. He invited me along when they had the DNA book at the Wellcome Trust, there was the whole crowd of all these big scientists. And he's done a very good one on DNA and the Watson story and all the background.

TT: Coming back to the Hammersmith, Victor. You move there and you're Head of the Department?

VD: Yes, what happened was I got this call from Illingworth when I was in Australia and I put in for the job and then there were four of us shortlisted. They were prodding me for all sorts of details and what would I do with this and that. And the rumour immediately went around after they announced my appointment via Tizard and his group saying that I was going to close the Neonatal Unit and start a Muscle Unit there, and I had said nothing of the kind. I gave them an assurance that we wouldn't reduce anything, if anything we'd expand the Neonatal Unit, which is of course what we did. What the Institute of Child Health really wanted, why they were interested in me, was they wanted to expand paediatrics at the Hammersmith, because Peter Tizard

actually had a personal Chair. There was no established Chair there, so now they established a Chair of Paediatrics and Neonatal Medicine within the University at the Hammersmith.

TT: And that was you?

VD: That was me. They offered me the post and then, Logan was the Vice-Chancellor chairing the interview, and I asked a few embarrassing questions like, 'What is the Department's annual grant, or departmental grant?' They said, 'What?' I said, 'Don't you have a departmental grant?' Nothing. Then they offered me a second class return rail fare for my interview. I said, 'Well, in Sheffield, even as a Lecturer they give you a first class fare even if you don't use it and travel ordinary class, it doesn't matter.' There was nothing in place for helping you, moving expenses or anything. So it took me five weeks actually before I accepted the post, and that's when I went to see the Vice-Chancellor in Sheffield. But anyway it's worked out okay.

TT: They were expecting it was such an honour to be in Hammersmith that you had to pay for it almost?

VD: Yes. The Hammersmith was an outpost of the Institute and so I was actually on the Boards and panels at the Institute of Child Health, but also at the Hammersmith, of course, as I was Professor of Paediatrics and Neonatal Medicine of the Institute at the Hammersmith, so therefore on the Clinical Board there as well. Eventually when Hammersmith became an independent School, outside the Postgraduate Federation, we had to make a decision whether to stay part of the Institute or part of the Postgraduate School, and it seemed obvious that we should be part of the Postgraduate School then, which we did. And so, basically, we severed the link at that time.

TT: What changes did you find moving from Sheffield back to the Hammersmith? You'd already had links with Hammersmith, but now you're coming in as the boss, so you have a clinical load, a research load, you were teaching?

VD: Well, it was very different, because when I was there originally it was a great era at the Hammersmith for development. I used to go to all the grand rounds on Wednesday mornings, which were in a small lecture theatre down on the ground floor. Of course now with the new building they were on Wednesdays in the big lecture theatre. Once you get at a place like the Hammersmith and you've got a Chair there, there's a little honeymoon period, but then you're battling with everybody else and everybody's needs are much greater than your

own obviously. So you've got to make a few friends. It was a different world but it was interesting. I was officially Professor of an academic Department and also Director of Service. These days, and even then at most universities, the Director of Clinical Service was separate from a Professor. And I used to go around the Neonatal Unit every Friday morning, see all the babies, discuss them and so on, although I wasn't involved in the intensive care of the newborns. Lilly of course became interested voluntarily, and she did a lot of work on the ultrasound and so on. We started doing continuous electroencephalograms (EEGs), Tizard's original work was doing standard EEGs on all these babies. Loads and loads, they had a room full of all these EEGs, which nobody was ever going to look at or do anything. So I had to tell Tizard either we'll have a bonfire or come and collect them.

We gradually started expanding research and clinical research, and then we started doing continuous EEGs. Then I went to see Pampiglione who was the guy at Great Ormond Street, who was the EEG king, and I said, 'We're doing this stuff on the newborns and we'd like somebody to train up in this area, and would you be prepared to have them as secondment? It would be one of our Registrars.' And he said, 'Yes, that's fine. Just arrange for them to come for nine months and I'll teach them all about EEGs.' So I came back and I spoke to Lil about the nine months. She said, 'I'll have a go.' We also had a guy, John Connell, one of the registrars or fellows, and between him and Lil, they started just doing it, putting things on, connecting the leads, and a week or two and it was up and away. The same happened with ultrasound, you see. In America all the ultrasound, all the babies' heads were being done by the radiologist, and they'd send their technician in to do the ultrasound and they'd look at the pictures. Lil was going around with a bloody machine on every baby in the Unit, every morning of the week. No official appointment or payment or anything, but she just enjoyed it. Neena Modi who is now President of the College of Paediatrics and Child Health, spoke at Lilly's memorial and she said, 'The most amazing thing was Lilly going around and everybody going around with her, and just doing these ultrasounds, and seeing there's a haemorrhage and there's this and there's that.' You just get on and do it. Nowadays there's politics and there's this, and health and safety, and that. I don't know how I'd survive in this environment [laughter], because you know what was nice in those days was just the freedom of doing what you wanted to do, in a sense.

TT: What was the main stimulation when you got to Hammersmith with your new colleagues? Was there something new that really took your imagination? You'd already been pioneering tissue cultures.

VD: We were already doing newborn stuff and already had the Dubowitz score, which, of course, they weren't doing at the Hammersmith, because they were still doing their old fashioned things. There was Pamela Davis, she was Senior Lecturer there. Everybody was on grants apart from the Reader, he had a permanent post. The first thing I had to do, I managed to establish one or two extra posts, and get people some security. But I had to assure people that we weren't going to infringe or run down whatever was going. Pamela Davis' was doing long-term follow ups, which she was pioneering, seeing these babies from prematurity right through to five, six, seven years of age, that went on. And so, basically, I encouraged all this, and then we just started gradually adding on, and then the muscle thing was entirely separate, there was no infringement. Then we also tried to develop general paediatrics, so I got linked up with the haematologists and the anaemias, and then there was the cardiology and there was Dr Hallidie-Smith, the niece of, I think, John MacMichael, the cardiologist. She was doing all the paediatric cardiology, and was doing these catheters.

I went around all the wards in the hospital collecting children. I said it's not appropriate for these kids having tonsillectomies to be on the adult Ear, Nose & Throat (ENT) Unit. They need paediatric nursing. And the same with the surgical wards. I said, 'We're getting them all back to the Paediatric Department and then you can look after them in the paediatric ward. They are still your patients.' I used to go around the general wards every Thursday, and then I'd come to a patient and the resident would say, 'That's ENT, that's only tonsils.' And I'd say, 'What do you mean it's only a tonsils? Is it medical tonsils or surgical tonsils?' So they'd say, 'I don't know.' I said, 'Well, get the notes and just check why is the child having his tonsils out? If that's a surgical tonsils, it's ENT. If the child's got obstruction and recurrent infection, well then that's medical tonsils, you know?' So they gradually started getting the point. Then one day we're going around and they said, 'That's only a dental case.' Once a week the dentists came in from the Institute of Dentistry and they did any tooth stuff that needed doing on the Paediatric Unit. So I said, 'What do you mean it's just a dental? Why is the child here?' So they said, 'We don't know.' So I said, 'It's your ward. Can you get the notes? What's he having?' 'Clearance of teeth or something. Got six bad teeth,' I'd be told. 'That's interesting. Are they doing it under local or are they doing it under general.' 'General anaesthetic.' 'Okay,

will you go and phone the dentist and tell him that I've cancelled this case and I'd like to chat to him, because the child's got myotonic dystrophy. And if you give it an anaesthetic it may not wake up again, because they're very sensitive to relaxants.' This child had a drooping face and a weakness and so I made a diagnosis, which was quite obvious. That taught them the lesson.

TT: What about your own research at the Hammersmith?

VD: I was doing this histochemistry and I defined the fibre types in human muscle and there were people at that time who were dividing into 12 fibre types and six fibre types and red muscle and white muscle. And I said, 'I can't see the colour of the muscle when I do biopsies.' You can tell the enzyme stuff, but you've got to use the language appropriate to the technique. And then in 1972/73 – just about the time I came to the Hammersmith, I was at a meeting in Denver, Colorado, on muscle and I was giving a talk on histochemistry. And met this very nice guy there, Mike Brooke, ex-British, who was a neurologist in Denver, and we were having a glass of beer and he was also interested in this histochemistry in muscle and he'd set up a lab. And so we started talking and we said, 'How about doing a book?' We started exchanging material, putting it together, and then we started arguing on interpretation and so we did a chapter on how to interpret the biopsy. And eventually it was published and Saunders published it in the neurology series and it was called "The Blue Bible"; just small, blue and it sold out in a year, and they said they'd wait for the second edition, they weren't going to do another reprint. But, anyway, that was the start.

And for the second edition Mike wasn't interested, he was now interested in steroids and Duchenne disease, so I wrote around to 60 people, do we need a second edition, what do you think, or whatever? And they all said, 'Yes, it's very useful.' So I did it on my own and it nearly killed me. Then for the third edition Saunders was now taken over by Elsevier, and I asked Caroline Sewry who had worked with Pearse, she came to work with me and she converted all the black and white pictures to colour, which meant starting from scratch again. And then the fourth edition we needed somebody extra because it was expanding and so we got Anders Oldfors to come on board, and it's now become quite a well recognised book. We're now working on the fifth edition, which they weren't really very keen to do because nobody thought it would need a fifth edition, but I managed to convince my two colleagues, 'We're not writing a new book again like we did before, we're just going to change about 20%, a bit of window dressing.'

TT: You mentioned the muscle meeting in Denver, Colorado. I'd like to ask you about societies and meetings and the role that they have played in your career. Looking through your CV there's such a range – from some very precise, clinical ones to some really heavy-duty research ones.

VD: I became a Member of the Physiological Society shortly before I took up my clinical post at the Hammersmith, and got in on the strength of the cross-innervation work I'd done. When I was in the States for a year I followed up the original stuff that Eccles had developed of crossing nerves together with the Professor from Bristol, Arthur Buller. I thought it would be interesting to look at this histochemically, because they were arguing whether it's a change in tropism or whether it's a change in speed. We showed that if you take a muscle like the soleus, which is mainly type one fibres, and a mixed muscle, and you cross the nerves, then in the mixed muscle you suddenly get big areas of the same muscle fibre, type one. So the nerve from the soleus is actually influencing the muscle fibre type.

TT: You started talking about The Physiological Society.

VD: Yes, so I was a Member of The Physiological Society because of the cross innervation stuff, and I gave a paper there and they said, 'It's okay, we'll make you a Member.' You know, you had to apply.

TT: It was a terrible performance in those days.

VD: Well, it's the same in the Neonatal Society, because there was McCance and Widdowson who used to sit in the front row at meetings. And McCance used to tear everybody apart who wasn't a Sheep physiologist, saying that wasn't proper physiology etc. And there were always one or two people who knew better who asked you about the statistics. But the interesting thing was, that soon after I got to the Hammersmith, The Physiological Society asked me if I would host a meeting of The Physiological Society there. So I said, 'Yes, sure.' And then, 'What are we going to do?' So I said, 'Okay, we'll get together the basic scientists, and we'll get together the clinical scientists,' and I think it was a combined meeting with the Medical Research Society or some group from both directions. That would have been around 1973, 1974, because I know we had one guy over from the States who had done some work about innervations and stuff. And it was very nice because I was given a free rein more or less on the things.

One small anecdote: I did a paper for The Physiological Society for *The Journal of Physiology* in 1965, and I had all my cross-innervation stuff there and I did some biochemistry as well at the Institute in New York, because I met up with Barkany and he was a very good histochemist, and Sandow who was a physiologist, so we did some good stuff on the muscle. Anyway, we wrote this paper for *The Journal of Physiology* and got no bloody response. And after about eight months I said, 'Look, if you're not interested I'd just like to publish this somewhere else.' They said, 'No, no, we're expecting a reply soon.' And then after another month we got it, and it was Arthur Buller who was actually reviewing it. But he was so anti all the results, because he was so fixed in his original ideas about the cross-innervation that he was trying to block it. And then – eventually – the, whoever the Editor was or whoever, said, 'You know, it's okay, it's been accepted now,' and then they published it. But it took them about 18 months from the time I'd done the work.

TT: And talking about time, I've been interrogating you now for over two and a half hours, so perhaps we should stop. Thank you very much Victor.

Figure 3: Professor Malcolm Ferguson-Smith

Professor Malcolm Ferguson-Smith (b. 1931) is Emeritus Professor of Pathology, University of Cambridge. He graduated in medicine at Glasgow University in 1955 and, while undertaking postgraduate training there in pathology, was introduced to research on sex chromatin under Bernard Lennox. An interest in Klinefelter's syndrome in 1957 to 1958 led to his appointment as Fellow in Medicine at Johns Hopkins University, Baltimore, in 1959, where he established the first chromosome diagnostic service in the USA, and undertook cytogenetic research into Turner syndrome. Research interests include molecular cytogenetics, karyotype evolution, vertebrate sex determination and comparative genomics. He is joint author of *Essential Medical Genetics*.

3 Ferguson-Smith, Malcolm*

Emma Jones: How and why did you become a medical geneticist, Malcolm?

Malcolm Ferguson-Smith: Well, it was really by accident because when I graduated from medicine and had done my internships, I decided that the best thing to do, was to train for being a general physician in medicine, and that I had better learn something about the science of medicine. So I decided that to spend some time in pathology would be a good idea. So I went into pathology with the idea of training for general medicine. And while I was there one of my teachers in the department, a man called Bernard Lennox, who was a very great character, he invited me to join in his research. And he told me that as I wasn't doing very much of interest, I might as well come and help him. In actual fact we were all working very, very hard at training in pathology but I was very glad to come and work with him.

EJ: What kind of work did you get involved with?

MFS: He had decided that the best way of studying individuals with paradoxical sex anomalies would be to use the buccal smear as a screening tool to search for patients with Klinefelter's syndrome. So my job was to make buccal smears of, first of all, children with undescended testes and then when we didn't find any Klinefelter's syndrome among the children with undescended testes, I said, 'Oh, well I know that Klinefelter's syndrome is associated with infertility so why don't I go to the infertility clinic?' And so I went to screen patients in the infertility clinic and the eighth patient I found was a patient with Klinefelter's syndrome. So, to cut a very long story short, I found that about 11% of the males in this infertility clinic with severe infertility problems had Klinefelter's syndrome. And some of these males had learning difficulties, some of them had been at special schools, so I thought, 'Perhaps learning difficulties might be a part of this syndrome, so perhaps we should screen in children with learning difficulties?' And we screened both children and adults with learning difficulties using this buccal smear test. And the result was 1% of the males that we screened had this same condition and of course afterwards we learned that Klinefelter's

* Edited passages from the interview conducted by Ms Emma M Jones, 6 June 2015, in Glasgow. For more details, see 'Related resources' at the end of this volume.

syndrome was quite common; it was between 1 in 500 and 1 in 700 of the general population, but this was a definite increase in frequency among those with a handicap. And one of, I'm sorry this is so long a story, but the story is quite good, so one of these patients turned out to have spermatogenesis and I should explain that the urologist who was in charge of the infertility clinic, part of his workup for the infertility male patients was to do a testicular biopsy. And as I was in the pathology department I had access to all the testicular biopsies from these patients so I did a general review of these, first of all of these testicular biopsies, and found a great deal more patients with Klinefelter's syndrome among them. And that was, it interested me greatly.

EJ: Can you say more about the patient with spermatogenesis? Why was that significant?

MFS: That one patient interested me particularly because he had in his testes, he had a tubule that had full spermatogenesis. And patients with Klinefelter's syndrome are sterile and don't have any spermatogenesis. And the fact that they had female sex chromatin meant that the prevailing view was that these individuals were sex reverse females. So in looking at the spermatogenesis in the testicular biopsy, I found this tubule in which there was sperm, but more important there were cells in which I could recognize the XY pair, the XY bivalent pair. So this man had a Y chromosome.

So I said to myself, 'This is very interesting. Nobody knows about this.' So I went off to the genetics department and I said to Professor Pontecorvo, 'Please could somebody in your department study the chromosomes of this man and find out whether in actual fact he has a Y chromosome?' because I didn't know anything about how to look at chromosomes. And he said, 'Oh, well we're not terribly interested in cytogenetics.' He referred me to his colleague who looked at the chromosomes of *Aspergillus,* Charles Elliot, and he said to me that he really wasn't very interested, he didn't know anything about mammalian chromosomes but he knew a chap who did. And so he put me in touch with a man called Charles Ford, and Charles Ford, this was in 1957, and in 1957 Charles Ford was just about to publish a method for looking at human chromosomes which involved taking a sample of the bone marrow. And Charles said to me, 'Well look, I haven't published the method yet, we're still working it out, Pat Jacobs is with me, we're working this together with a man called Dr Lazlo Lajtha', who was a hematologist, hence the bone marrow. And 'so I'll let you know when the method is ready. But meanwhile what you can do, is you can, if you've got any more of these interesting people, I've never heard of them before, but you can

look, if you can take a little bit of bone marrow from them, you can look at the chromosomes yourself.' So he said, 'This is how you do it' and so on. And so I tried, and every time my urologist friend, who was doing these biopsies, every time he did a biopsy on a Klinefelter patient he gave me a little bit of tissue so that I could look at the chromosomes in the testes. And they also allowed me, after permission from the patient of course, to make a little hole in the patient's sternum so I could remove with a syringe some bone marrow.

EJ: So you learned how to look at chromosomes that way?

MFS: Actually my bone marrow preparations were terrible, were absolutely awful. I could see chromosomes occasionally; I didn't know how to count them. One chromosome looked much the same as another and there was a lot of dust in the preparation, and it was really very difficult. So my professor said to me that, 'Clearly you need time to do this, you can't, while you're training at pathology with us, you are busy doing post-mortems and looking at surgical biopsies and working hard to train to be a pathologist' – although I wasn't going to be a pathologist – 'I'll see if I can find a place where you can have time to do this.' So, to cut a long story short again, he knew somebody who knew somebody called Victor McKusick, who knew that Victor McKusick was recruiting medical specialists to form a new division of medical genetics in Johns Hopkins Hospital. It was in the summer of 1958, I was interviewed by Victor McKusick in Liverpool, in the Adelphi Hotel in Liverpool, and Victor was able to offer me a job immediately, said he'd like me to come and be a Fellow immediately. And I said, 'I'm sorry, we're working on these Klinefelter patients, I have to get my work published, but I hope to be finished by December.'

EJ: You went to the States to work with Victor McKusick. What kind of work did you do there, did you continue with the Klinefelter research?

MFS: In January I set sail for Baltimore in the SS Carinthia and when I arrived in Baltimore, I arrived simultaneously with the publication of the result of Down syndrome from the French group. They found this extra chromosome in Down syndrome. So I arrived in America just at the time that everybody suddenly was presented with the fact there were abnormalities in chromosomes in certain individuals. And just shortly after that Pat Jacobs was able to look at a patient with Klinefelter's syndrome and was able to show there was in fact Y chromosome there, it was two X's and a Y. So I felt, you know, this is great, this is what I said it would be but I hadn't done it myself and so I got into cytogenetics that way. That's how I started in genetics. And, of course,

I never went back into general medicine. I left pathology several years later and became a medical geneticist running both diagnostic laboratories and also teaching medical students, running a clinic in medical genetics, and counselling women who had had abnormal children. And this fascinating, wonderful area was something that I never, never left.

EJ: How was genetics regarded at the time when you started?

MFS: At that time nobody believed that genetics had anything to do with medicine at all. Genetics played no part in medicine whatsoever. When I told my colleagues that I was going to go into medical genetics in the United Kingdom, they said, 'Why are you going to do that? There aren't any jobs. There are no jobs for you.' So you had to take a risk. And I took a risk and went into a subject where there were no jobs and so I'm very glad I did.

EJ: When you say you were glad that you did develop you career in this area, is there anything in particular you are proud of?

MFS: Well, I think the thing that I'm most proud of, basically, was being able to set up a system for providing the services to patients who had problems with genetic disorders and their children, and setting up a clinic to provide advice to individuals at risk, couples at risk of having an abnormal child about the risks in future and what we might do about them. And, of course, also many, many people came along and said, 'Look, we have these abnormal children, could you please look at their chromosomes and see if you can find a diagnosis and abnormal chromosomes.' So quite a lot of our work was setting up a chromosome diagnostic service and providing these diagnoses for families who had, children with disabilities. So at that point, I should have said that in the United States, I set up the first cytogenetics clinic, the first chromosome clinic; that was in 1959. I set up the first diagnostic clinic in the United States for chromosome abnormalities and that meant that lots of patients were referred with chromosome abnormalities or potential chromosome abnormalities for diagnosis to our clinic.

And in Johns Hopkins hospital where I was, there was a wonderful paediatric endocrinologist called Dr Lawson Wilkins and he was a pioneer in paediatric endocrinology. And he had a particular interest in children with ambiguous sexual development and so he referred his patients, he was happy to refer his patients, or at least blood samples from his patients, to my little diagnostic lab to see if they had chromosome abnormalities. And with that material I was able to collect many cases of patients with Turner syndrome and with ambiguous

genitalia in which it was possible to determine what type of chromosome abnormality, particularly what type of X chromosome or Y chromosome abnormality they had. And out of that grew a research conclusion which was very valuable, which was that those patients that had lost a short arm of the X chromosome, developed the full-blown Turner syndrome with infertility and short stature and various malformations, and those that had lost the lower part of the X chromosome were infertile but not short in stature, did not have the features of Turner syndrome. I should explain that most patients with Turner syndrome, have a single X chromosome and no other chromosome. They don't have a Y chromosome and they don't have two X's, they have one X. So from that we were able to come to the conclusion that the things that matter for Turner syndrome must be in the short arm of the X chromosome. Individuals with full-blown Turner syndrome with only one X chromosome, were short in stature and had these multiple malformations. I thought to myself, 'But males have only got one X chromosome and they don't have any of these features, so there must be something on the Y chromosome that stopped these individuals, that stopped males, from getting Turner syndrome.' And so my idea was that there were genes that were expressed on the X chromosome that had copies on the Y chromosome that had the same function; they were expressed on both the X and the Y chromosome and prevented Turner syndrome. Therefore Turner syndrome was due to haplo-insufficiency of genes on the X chromosome, and that mapped the Turner genes to the short arm of the chromosome X and its corresponding region on the Y chromosome. So that was a bit of science that came into it.

EJ: Having made these discoveries, and running your chromosome clinic, were you tempted to stay in the States?

MFS: No, I came back to the United Kingdom, back to Glasgow in 1961, I was offered jobs in America at the time but as I said I was going to come back to Glasgow when I left, and my idea was that I would try and introduce medical genetics to medical practice in Glasgow and that was my kind of aim, as well as doing some research, continuing the research that I was doing. So it's been a wonderful experience for me to see the period change from where genetics played no part in medicine to where genetics is the actual basis of medicine, is the fundamental science that's underlying all of medicine. So that's been a wonderful journey for me and I guess I'm very happy that I happen to be involved. I think the most important thing for me, because I was trained as a

doctor, the most important thing for me was to be able to provide these services for people who needed them and I guess that's probably the most important thing that I was involved in.

EJ: You've been closely involved in that major transition, that recognition of the importance of genetics. What were the problems in your career, the obstacles along the way?

MFS: I suppose the first one was, the biggest obstacle was finding somebody to look at the chromosomes of these people that I wanted them to look at. Of course everybody was busy with their own work and nobody wanted to be bothered with something they'd never heard about, so I had to realise at a very early age, if you really wanted to do something, if you want something done you have to get on and do it yourself. And the second obstacle was, well, once you made that decision then there was the trouble of getting the technology working. And to be perfectly honest I didn't get the technology working until I met two important people in the United States, and one of them was a Swedish geneticist called Albert Levan. Albert Levan was one of the two people who had discovered the correct chromosome number in man. They had shown that it was 46 and not 48. He worked with his junior colleague, Joe Hin Tjio, and Tjio and Levan discovered that humans had 46 chromosomes, and that was in 1956. And in 1959 I was in Baltimore in the United States, and I had to give a lecture in Atlantic City to the physicians, the American Physicians meeting in Atlantic City, in the Steel Pier in Atlantic City. It was a memorable occasion because there were 5,000 people in the audience, 5,000 physicians and I was talking immediately after Albert Sabin, who was talking about his vaccine for polio. So, of course, everybody came to listen to Albert Sabin and fortunately they didn't get up when I came next. So they had to listen to this Scottish boy telling them about the new discoveries in Klinefelter's syndrome. And I guess that was an exciting time for me but at the time, at that time, I met Dr Hsu, who was a cytogeneticist who worked at Houston, and I told him my problems about how I was hopeless at making chromosomes. So he invited me down to Houston and to see what they did. And in fact at the same meeting I was invited to give the same talk as I'd given in Atlantic City to somebody in the Baylor College of Medicine. So I said, 'Oh, I'm going to come down to Houston anyway, can I come in and spend a few days with you?'

So that was the most important two days in my life, up to that time, because both Levan and Hsu showed me how to make cell cultures and how to make chromosome preparations, and Albert Levan showed me how to draw pictures

of chromosomes using a *camera lucida* on my microscope. That was before the days of cameras perched atop the microscope. Anyway, armed with this new information, when I got back to Baltimore, my first bone marrow preparations in chromosomes worked beautifully because I followed the directions that I had been given. And my little lab didn't look back after that time, because we could make chromosome preparations and all sorts of things, and that's why I was able to make these chromosome preparations in the Turner patients that I just described earlier. So that was a big problem to actually get somebody to make and I couldn't find anybody to make chromosomes. I had to struggle to make chromosomes myself. It worked, and so these are what I remember as some of the big problems in my life too.

EJ: And it was when you were in the States that you also met your wife, wasn't it?

MFS: Yes, one of the most important things that happened to me when I spent my three years in the United States was to meet my future wife. And she was actually working as a student, doing some student work while she was going through college and this was clerical work for Dr Victor McKusick, who was my boss at Johns Hopkins. And every time I went into my office to look down my microscope at chromosomes I would have to pass her desk. And after saying 'good morning' to her a number of times, I eventually, I had the temerity to invite her out and so we got to know each other very well and eventually we married and our first child was born at Johns Hopkins. And that first child, I'm very proud to say, is a professor of genetics at Cambridge so there must be something good about that experience. Anyway, Marie my wife, was detailed off to help in some buccal smear surveys that I did when I just arrived in Baltimore. I mentioned previously that I'd been doing this in Scotland and so as we did the same thing in the mental institution in Maryland, near Baltimore, and it wasn't the least bit like a National Health Service (NHS) institution, it was really a very depressing place. But that's another story.

What we had to do was to go through the wards in this particular asylum, with permission of course, to collect smears from inside the cheek in these handicapped children, and it was quite a sort of mass production thing because we had to do very many, several hundred people, and Marie was there to mark the slides and write down the numbers and to make sure that we didn't get patients muddled up, we got the right sample from the right person. And during that exercise we discovered several new, different types of chromosome abnormality, and individuals with Klinefelter syndrome that had three X chromosomes as well as a Y chromosome, and we found female individuals that had three X

chromosomes instead of two. And this was all apparent from the buccal smears. But anyway, Marie was involved in doing that, and when we went with our baby back to Scotland in 1961, Marie joined me in my lab. I had a grant from the United States to continue some research and so Marie was employed on that grant. She was an American citizen and I was funded by the University of Glasgow, because I had a lectureship. So we were not funded by the same people. We had quite different bosses.

Anyway, so she joined in the work of chromosome analysis with me, which she had already been involved with in Baltimore, of course. And so we've been working together ever since, you know. That was 1960 to, well, 2015. No, she stopped work actually in 1993, but up 'till 1993 she was working in cytogenetics alongside me. We'd been working all that time together and it worked out quite well. We didn't divorce and we had many, many, many arguments of course but we brought up four children and we had a very happy career together.

EJ: You have seen enormous changes and advances in genetics during your lifetime and career, are there any other areas you would like to comment on?

MFS: I'd have to say of course chromosomes is only one part of it and for my purposes, I was also counselling children and parents and families with other genetic disorders, a wide range of genetic disorders at my clinic. We developed slowly, over two or three years, developed a service for all of the west of Scotland and this was a population of about five million. So we formed the West of Scotland Regional Genetic Service, so that was the basis of the genetics programme for that part of the world. This is one of the earliest regional service groups. And so while we were there of course the opportunities developed and it was possible to make the diagnosis of chromosome abnormalities and other genetic disorders from 1967/68 onwards, from samples of the amniotic fluid in pregnant women, so that we were able to make the diagnosis in some of these conditions, severe genetic conditions, in the foetus, and this gave parents who wanted this the opportunity of interrupting the pregnancy and trying at a later time to have another one. So my wife had joined me at that time and we were, or by then – several years before that actually – to work in cytogenetics, and she got involved in doing this, in developing this prenatal work with amniotic fluid cell cultures.

And we were able to collect a number of diagnoses, in fact I think I recall, 70 diagnoses of women who had wanted their pregnancies tested. And some of these women came from Ireland and some of these women were in Scotland.

But the result was that in the majority of cases we were able to reassure these women that they were carrying a normal foetus. I think out of the 70 only one individual had a pregnancy that was affected with Down syndrome and that was the only, there was another genetic condition that was terminated as well, but there were only two pregnancies that had to be stopped. And so the general benefit was that women were encouraged to have pregnancies whereas they wouldn't have had these pregnancies had they known that there was no test.

EJ: Was this work universally welcomed?

MFS: We felt that there was a lot of criticism about what we were doing; my wife and I were accused of being Nazis by the Archbishop, the Roman Catholic Archbishop of Glasgow, and various other people were very much against what we were doing. It was particularly ironic because my wife spent part of her life in a concentration camp in Germany and so she knew what the Nazis did and perhaps rather better than the Archbishop did. And she didn't like being told that she was behaving like a Nazi because she was providing a service for people who genuinely had a big problem and one we could help them with. So one of the other difficulties I had, if you like, was to try and convince the Archbishop and various other people that what we were doing was needed and was the right thing, in fact was part of pastoral care which they should have been providing, but I never was able to persuade the Archbishop, I have to say, nor the Pope or anybody else in the Roman Catholic hierarchy. But that didn't stop us. I was convinced by the needs of parents and I didn't approve of abortion for social reasons but I certainly was sympathetic to women who had these very big problems with having severely handicapped children. And that's what happened. And of course when prenatal testing came into the business, when we were able to give prenatal diagnoses, and my wife's paper on this subject was the first published in the United Kingdom, when we were able to provide this service, it increased the amount of genetic counselling that was done throughout the country and suddenly there was something genetic counselling could achieve through testing pregnancies. So suddenly genetic counselling became very much more important than it had been and genetic clinics were enlarged.

EJ: Did you have good relationships with the obstetricians in Glasgow?

MFS: Yes, also associated with prenatal diagnosis was ultrasound and in this town, in Glasgow, the pioneer of ultrasound was Professor Ian Donald, a friend and a colleague of ours, our next door neighbour actually. And he was also very strongly against social termination of pregnancy but the first patient that

he terminated a pregnancy in was a pregnancy where there was a very severely abnormally affected child. So although he was against social terminations he helped to convince other people that this was a correct part of obstetric practice. And the fact that we needed sonar ultrasound examination, we used it first of all to determine the age of the foetus and to make sure there weren't twins, to locate where the placenta was so that we didn't hit the placenta when we were sticking a needle in. Ultrasound developed as a result of prenatal diagnosis so companies made better machines and so on and that led to the better visualization of the foetus *in utero*.

So abnormalities could now be seen in the foetus, and I trace the start of all that to the work that we were doing with Ian Donald with amniocentesis in these very early days in 1969/1970/1971, these were the years that that was happening.

EJ: And how do you think genetics will develop in the future?

MFS: Well, you're recording this interview at a meeting discussing human gene mapping. This is another area I haven't mentioned, which I have been closely involved with since I left the United States and I think I came to the conclusion at this meeting that human gene mapping was now a thing of the past, and the mapping that we do now is with mapping, looking for similar sequences in animal chromosomes and other vertebrates, and that's a different story. What is ahead of us in human genetics that's important? Well, you know, if we were to stick with looking at chromosomes, we still don't know an awful lot about chromosomes; in particular we don't know about the 200 different proteins that are involved in the structure of a chromosome. We know about a few of them. And I think there's a great deal to be learnt from looking at the proteins. We've spent a lot of time looking at DNA, and DNA is very important, but we haven't spent enough time looking at the other proteins – not "other" proteins because DNA isn't a protein it's a nucleic acid. Anyway, I think a lot has to be learnt from looking at the proteins in chromosomes, that's one thing. It will help us to understand about how chromosomes pair during meiosis and how, and all the problems of combination. We know that chromosomes pair and recombine with double strand breaks, but only a tiny number of these double strand breaks produce crossovers, for example. And we don't know why that should be. So there are lots of questions about chromosomes that we need to learn and we only can learn about them if we would spend a bit more time studying the chromosomes. That's one thing.

Another thing that interests me greatly is the area called epigenetics. These are factors which influence the expression of genes in tissues, and one of the aspects of that, which is particularly interesting, is that there can be environmental effects which have transgenerational effects, you know, from one generation to the next, which we don't totally understand. We know about things that modify DNA but we don't totally understand all about epigenetics.

And the third thing that we could learn a little more about is how genes are regulated. We know a little bit about how genes are regulated, but there are a lot more DNA sequences which are involved in gene regulation than there are actually genes that make proteins. So we should learn a bit more about that. Then I have a particular interest in non-coding DNA because I believe that much of the rest of DNA, which has been regarded as junk up 'till now, I never believed in junk and I would plead with people not to talk about DNA junk. They should study it a bit more and find out what it does, it's not junk. Anyway, I believe that non-coding DNA is worthy of a lot more study because it will tell us a bit more about the natural history of chromosomes and how chromosomes behave.

Then finally, perhaps a little touch on something that's very, very topical and that's the possibility of editing genes. In other words, looking at a type of gene therapy in which you can actually correct abnormalities, mutations, in genetic material in living people. At the present moment this has been started just recently and the trouble is at the moment we edit lots of things that we don't want to edit and we have to be a bit more specific about what we're editing to get it right. But I mean clearly the method is very promising and there will be a way of doing this properly in the future. So I think that's something that people can quite, with advantage, go into and study in the future because I think it has a lot of potential.

EJ: Thank you so much for your time Malcolm, it's been fascinating.

Figure 4: Professor Peter Harper

Professor Peter Harper Kt FMedSci FRCP (b. 1939) is Emeritus Professor of Human Genetics at Cardiff University. 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. He is a Consultant to the "Makers of Modern Biomedicine" project for the History of Modern Biomedicine Research Group, Queen Mary University of London.

4 Harper, Peter*

Tilli Tansey: Thank you for agreeing to answer a few questions, Peter. First of all, why and how did you develop your career in clinical genetics?

Peter Harper: I think I'd been interested in genetics for a very long time scientifically and I'd always wanted to try and combine it with medicine. At the time I was in medical school there didn't really look much chance of doing that but then I found that things were becoming possible. Then, I was lucky enough to be able to work first with Cyril Clarke in Liverpool, who was a practising physician who very much was a pioneer in early medical genetics. And then from there I went on to Baltimore to work with Victor McKusick, and that really gave me the skills with which I was able to come back and practise as a clinical geneticist. But at the same time I'd trained in adult hospital medicine, internal medicine, and so I kept that up as well because at the time I began clinical genetics it was far from clear whether there would be any long-term jobs in the field. And also before my medical degree was finished, I'd actually been at Oxford where I worked with basic geneticists. When I was at Oxford I was able to spend a lot of time in the zoology department where there were very good basic geneticists in population genetics working. And the scientific aspects really enthused me very greatly, and so I wanted to carry on something scientific as well as something medical, and genetics gave the opportunity to combine the two.

TT: Are there any particular contributions you are particularly proud of?

PH: Well, in terms of which contribution I may have made, would I feel was/has been the most valuable, or at least valuable in my own view, there have been two diseases which I've worked with for well over 30 years, more like 40 in fact, which have kind of interacted. One of them is myotonic dystrophy, one of the muscular dystrophies. The other has been Huntington's disease, a serious brain degeneration. And I started off by doing my thesis on myotonic dystrophy. That work began in 1969 and it's never really stopped. And in terms

* Edited passages from the interview conducted by Professor Tilli Tansey, 6 June 2015, in Glasgow. For more details, see 'Related resources' at the end of this volume.

of Huntington's disease, my work began almost immediately after I came back to Britain from being with McKusick in the States in 1971, and again it's gone on pretty continuously since then.

What I had no idea about when I started was that these two disorders, which at a clinical level don't seem very similar, one a brain disease, the other a muscle disease, proved to be due to the same genetic mechanism. And I feel extraordinarily fortunate to have been able to follow the story and the development of these two diseases right through from the clinical description and the study in families through to the mapping of the genes involved, and then to the discovery, which I and my colleagues were very much involved with in both disorders, of the basic molecular defect. And even more remarkably, this turned out to be the same type of molecular defect in both, a trinucleotide repeat of unstable DNA. And that the two had the same mechanism so the two have interacted. And then from there I was able to apply the new discoveries in terms of the gene to helping families in terms of prediction of those who did and didn't have the gene, and now that work has gone on with others to the stage where trials for therapy are in progress. So I feel very fortunate to have seen this progress from beginning to end.

TT: And what about your other contributions, not directly from the lab or the clinic?

PH: Apart from any of the research and actual practical and clinical work which I've been involved with, I would perhaps rank my book *Practical Genetic Counselling* as being a valuable contribution mainly because it's spread around the world, and for more than 30 years seems to have been the book most used by people giving genetic counselling. And that it's really had an influence in a number of countries where really genetics was very undeveloped, like Russia and China and many other countries. And I have always been amazed that it's continued to be useful for over 30 years, and so I feel that has been a contribution and I've enjoyed meeting the very many people who have told me that they found it useful in their work.

TT: Is there anything that went particularly wrong, or was a major problem, in your career?

PH: You asked me what the greatest problem or mistake I've encountered, or made, has been. Nothing actually stands out individually and I don't regret having worked in the places I have worked, first in America and then very largely

in Cardiff, more recently, over a long time. Yes, a few missed opportunities but nothing sticks in my mind as being particularly problematic, more a question perhaps that if I had done something, more might have come out of it.

TT: What do you think have been the main changes and developments in medical genetics over your career?

PH: How have I seen things change over my career? A huge amount has changed. If I stop to think about it, when I began in medical genetics, well first of all medical genetics hardly existed as a specific field. It's just beginning to. And what one could do was very limited. One could spend time with families, give good genetic counselling, listen to people, and help quite a lot in those general ways. But when you got down to the question of what specific things could you actually do to help with a genetic disorder, there was virtually nothing. And then I've seen it change so that now one cannot only offer genetic counselling and give good, accurate ideas about risk, one can very often now tell whether somebody is or isn't carrying a harmful gene, equally predict whether or not they are they likely to develop a disorder. And then now there are beginnings increasingly of effective treatment as well as good management. So there's a lot basically one can offer which just was not possible before.

TT: And what about changes in the future? What do you think might happen, or would you like to see happen?

PH: I'm not going to try and predict what will happen in the next 20 years. I hope that there will be sensible advances, advances which are driven by people's needs and wishes, rather than purely by technology or industry or any of the other things which seem to be rather powerful drivers at present. Whether that will be the case remains to be seen but I would hope that the sound principles that are present now in medical genetics practice will progressively spread through all clinical specialties and that people will become more educated. And that those involved in promoting the field do so in a responsible and not an exaggerated way, and will show a reasonable amount of humility as to what they are trying to offer people.

TT: Thank you so much Peter.

Figure 5: Professor Shirley Hodgson

Professor Shirley Hodgson BSc BM BC DM D(Obst)RCOG FRCP DCH FRSB (b. 1945) began her career as a Paediatrician and General Practitioner. She became a Registrar in Clinical Genetics at Guy's Hospital, 1980, and worked with Professor Victor Dubowitz at the Hammersmith Hospital on muscular dystrophy whilst doing the work for her DM Thesis. She became a Consultant in Clinical Genetics at Addenbrooke's Hospital in 1988, and Consultant/Reader in Clinical Genetics at Guy's in 1990. She specialised in cancer genetics from 1989, working with the Imperial Cancer Research Fund (ICRF; now Cancer Research UK, CRUK), developing regional cancer genetics services at Guy's, St Mark's and St George's Hospitals in London. In 2003 she was appointed Professor of Cancer Genetics at St George's, University of London, now Emerita. She has published widely on cancer genetics, and co-authored several books, including *Inherited Susceptibility to Cancer* (Foulkes and Hodgson (eds), 1998), and *A Practical Guide to Human Cancer Genetics* (Hodgson and Maher, 1993), now into its fourth edition with W Foulkes and C Eng as co-authors (Springer).

5 Hodgson, Shirley*

Tilli Tansey: Welcome, Shirley, and to begin with I just wanted to ask you why you thought of going into medicine, or did you think of science first?

Shirley Hodgson: Well, I wanted to be a ballet dancer for a long time and then suddenly I thought it wasn't using my brain enough. But then after that I didn't think there was really any question about it; I'd always been interested in biology anyway, and I wanted to help people and that was the driving thing, I suppose. When I was a little girl, when our pets died, I'd bury them in the garden and then I'd dig them up later and put their bones together on bits of wire. So that's the sort of person I was.

TT: So how old would you have been when you were disinterring your pets?

SH: I did wait till they died [laughs]. I don't know, seven or eight I suppose.

TT: Were you helped by your family, your friends?

SH: Well, my dad was rather well known so I don't know whether it helped or hindered me really, but he was very interested in science. All my brothers are a lot older than me so I was rather a solitary child; I mostly looked after myself, found my own interests. My dad was Lionel Penrose. He was a geneticist and he was quite a pioneer. Having started off as a medical student, then took a post in Colchester doing what became the 'Colchester Survey', and looked at huge number of patients in Colchester Mental Institution – they all had mental retardation, as it was known then, and he was the first person to examine and analyse them all very meticulously and find out what he thought the causes were, or possibly were. He took the family histories, he identified things like the fact that the ones who were very retarded were more likely to have normal parents, and the ones who were mildly retarded were more likely to have somewhat retarded parents, so there was a big difference. Just before the Second World War he moved to work in Canada, where I was born, and then he came back to take up the Chair of 'Eugenics' at University College London. But he

* Edited passages from the interview conducted by Professor Tilli Tansey, 4 November 2015, in the School of History, Queen Mary University of London. For more details, see 'Related resources' at the end of this volume.

was very much against eugenics because he thought this was absolutely wrong, and particularly in the climate as it was in 1946. So he changed the name of the Department to 'Genetics', and made sure that the emphasis was not on eugenics, but on genetics, which was quite a different emphasis. He was an inventor really. He invented all sorts of things and ideas, and he just never stopped thinking and inventing things.

As a father he was very fond of me, I think, but he didn't spend a lot of time with me because he was very busy with his various projects. One of the things it resulted in though was my being very interested in the way things worked. He had a Quaker background which meant that he was also very keen on this idea of helping people, and he was a pacifist – it being a part of the Quaker ethos – and that was very much infused in me. One of the things he taught me was never to take anything at face value. Don't just accept what people say; think about it and decide what you think yourself. I suppose this made me somewhat unconventional. He was also rather unconventional, never accepting the norm just because it was the norm. He was also very musical, he was very artistic, it was just ridiculous that he was so good at so many things! Sometimes he did things with me, for instance we made a crystal set, a radio out of crystal and a cat's whisker, and did photography, and things like that, which was very, very exciting. What else? We had a lot of friends. He'd spent a lot of his childhood, or junior life, in Bloomsbury and we knew a lot of very interesting people, like J B S Haldane, and they often used to come to stay.

TT: And what about your mother?

SH: That was one of the things about him that was not so good, he didn't like her working. So she didn't work although she was a doctor and she was popular and clever. My mother was an only daughter. I guess she must have been a bit frustrated by not having her own medical practice. She did things like help edit the MAPW, Medical Association for the Prevention of War journal, which was founded by my father and a few other like-minded physicians at the end of the war to try and stop it all happening again. She used to edit the journal and run the meetings, and things like that, and of course, look after the children, but I think it must have been a bit frustrating.

TT: Do you think perhaps that part of your mother's frustrations were expressed with helping you in your scientific career?

SH: No, I don't think she did. It's funny, I remember my childhood as being rather 'self-propelled'. I was rather left to myself quite a lot, since she was an older mum so maybe had less energy? She was 44 when she had me, and my youngest brother was 13 or something, and we were living in Canada, and so I was born in the local hospital and my father went in after I was born, concerned that I might have Down syndrome because of his observation that older mothers had a significantly increased risk of having children with this, and he looked at my palms and instead of saying, 'What a nice looking baby,' he said, 'I don't think it's an imbecile,' because my palms didn't have transverse palm crease.

TT: You were interested in science. What kind of school did you go to?

SH: I went to an ordinary primary school. In fact, in those days I used to walk about a mile when I was about six to this school on my own every day. Then it came to the 11+ exam and I failed it, and it was just terrible. I felt really devastated, and then I took it again and I failed again. I remember doing it on my own in the classroom and just crying. And my dad said, 'We'll have to send you to private school. It's expensive.' So I went to this school called 'Channing', which was not very academic in those days. It's a good school now; it's been turned around. They did have science, although I remember the science was not very well taught, and the chemistry teacher was a bit unstable. But I remember I was mostly top or second in the science classes. Then, when it came to Sixth Form, when I was 16, they said I could go to the local co-educational grammar school, which was not very far from us, and it was very, very good: Hendon County Grammar. The students were mostly Jewish, and they were all incredibly bright and there were mostly boys in the science classes. When I went into the science class, instead of being top I was not anywhere near top because they were all much better than me so that was a bit of a shock to the system. But, nevertheless, I managed to get through the A levels alright.

TT: And you went to university to do medicine, or physiology?

SH: I went to study for medicine, and also did an intercalated BSc in physiology. I'd given up my ballet when I was about 15, I suppose, and I think there was never any doubt that I wanted to be a doctor.

TT: What did your parents think about your career choice? Do you have any memories of them influencing you at all? You seem to have been a very self-sufficient child.

SH: I'm sure they encouraged me. I can't really remember the details. I would have thought they were probably rather pleased I wanted to be a doctor, yes.

TT: So why physiology?

SH: Well, it was a good course, with Professor Andrew Huxley as Head; he was a very sweet man! This was University College London.

TT: And then you got your medical degree from Oxford?

SH: Well, I did the clinical bit in Oxford. It was the wrong way around really.

TT: Yes, it's usually the other way.

SH: I hadn't thought I would get into one of the Oxbridge colleges as an undergraduate, because I didn't think I was bright enough. I went to University College London, but I thought it would just be nice to get out of London really for clinical. The Radcliffe Infirmary was then rather a small clinical school, and it was really very nice. And actually it was a really good place to go, because in London there were masses of students and you'd have 10 students to a patient, whereas you had 10 patients to a student in Oxford! Not quite that perhaps, but it was so much better.

TT: So you had a much wider variety of clinical experience?

SH: I think we probably did; it was really good then – lovely living there as well.

TT: You've done physiology, then you've had your clinical training. What ideas were you developing, if any, as to where you might go?

SH: Well, I then went to see a careers advisor person, and I remember she said, 'You're a woman so you'll have to do general practice. In order to do general practice, you have to do paediatrics, you have to do obs and gynae, in addition to the ordinary training.' I'd done my house jobs in Oxford, but I did rather lonely ones. I did geriatrics, and I did chest surgery with a terrifying man as my boss. So I decided I'd better do paediatrics and obs and gynae as instructed, so I did a paediatrics House-Officer post at Chase Farm Hospital and I did obs and gynae at the North Middlesex Hospital.

TT: But you also spent some time in Iran? How did that come about?

SH: Well, we wanted to do a bit of travelling, and I hadn't done an elective abroad – apart from obstetrics at the Rotunda Hospital in Dublin – because I'd crammed my degree into my six-year course, I didn't feel I had the time to

spend doing an elective. At that time, I had fallen in love with Humphrey who was in London because he'd done the conventional thing; he'd been at Oxford to do his pre-clinical because he was very bright and got all the top scholarships and everything. He'd gone to London to do his clinical training, and we met after bus journeys between Oxford and London all the time. Anyway, he did an elective in Algeria, and I guess when we first got married we thought it would be nice to do some travelling, and there was a doctor at St Thomas' Hospital where Humphrey worked, who had links with Iran, and so we went as part of that exchange.

TT: So that was 1971–1972 you were there?

SH: That sounds about right, yes. Yes, it was still Persia with the Shah still there. It was very fascinating and I suppose it got me interested in international medicine, and obviously made one realise there were huge differences between English medicine and medicine in different countries, relatively resource-poor countries, and all the cultural inferences as well in terms of what you could and couldn't achieve.

TT: Coming back to Britain, you did obs and gynae, and paediatrics; then you become a trainee General Practitioner (GP)?

SH: That was largely because of babies, because I had my first baby, Julian, in 1973. I didn't want to be away from my kids at all really, but I also wanted to work. I always used to do part-time jobs, and so the first one I did was just baby clinics when Julian was a baby. I went to the Whittington Hospital to do some part-time work on children's asthma. It was research on the effectiveness of Becotide, so that was fun but it was only part-time.

TT: Was that your career pattern while your children were small?

SH: Yes, I stuck around with them really for 10 years or more part-time, which is quite a big chunk of my career time. I don't think anyone would do that nowadays.

TT: I think it would be very difficult to then develop a career if you were to do it for that length of time. But then you went as a Paediatric Fellow to America: how did that come about?

SH: Humphrey was awarded a Fulbright Scholarship, with a year in America in Boston, at the Mass General Hospital. We went over for a year and stayed in Boston, without having any job fixed up for me. In fact, I'd been quite ill for

about six months previously, with fevers, and nobody knew what it was, and that was quite debilitating. I ended up in Addenbrooke's Hospital, and eventually, when I had some dental treatment I had a lot of intravenous antibiotics given to me because of having a tooth out, because it was some embedded tooth or something was wrong with it. After that I was perfectly healthy, and a few years later I had a scan for some other reason and they saw this little oak leaf calcification in my liver, and I knew exactly what that was: it was a hydatid cyst. So I think it probably was hydatid disease, which was then cured by the high doses of antibiotics. Nobody knew for sure, of course, but it was very probably the diagnosis.

So I wasn't in a great state when we first went to America, but I pepped up, but didn't enjoy it terribly to start with. Then I found a job in the Psychosomatic Unit of the Boston Children's Hospital, and I was incredibly lucky to get it because the number of doctors there per patient is ridiculously high. There weren't many jobs around but I got the job, and I worked there for six months at least.

TT: And had you taken the children?

SH: Yes, Julian was four and Anna was two and a half, and so they went to little morning playschools nearby and they seemed quite happy there, and so I worked part-time, and it was fine.

TT: You then came back and resumed your General Practice?

SH: Yes, and I went on being a GP for quite a long time. I finished up the training, and then went into a very religious practice, a puritanical practice. Of course, I'm not particularly religious; if I were religious I'd be Quaker. They were Methodists. They had big posters in their rooms saying, 'Jesus never kept anyone waiting,' things like that. Of course, people would be waiting for hours. And they were okay and they obviously worked very hard, and so on. I enjoyed the work, and I enjoyed the visiting, I always found that very interesting.

TT: Was it very much the human contact and social context that you found stimulating?

SH: Yes, it was interesting but then they caught me prescribing the 'Pill' to unmarried girls, and they took a serious dislike to this idea and they threw me out [laughs]. So I was without a job and a bit distressed about this. I remember

once they had a Christmas service, and we went, and one of them gave a sermon. They were lay preachers, and he said, 'Will you be there at Judgement Day? Will I see you there?' This made Humphrey very angry, and we left the service!

Humphrey, such a wonderful man, looked in the newspaper and he saw an advert saying, 'Locum, Polani Department of Genetics in Guy's Hospital.' So he said, 'Oh, go on, try that.' So I went and did this locum, and I just thought it was completely wonderful. I was so interested in it. I'd tried not to be interested in genetics because of my father, and I just thought it was completely fascinating. But the problem was, because I'd been part-time for so long, I didn't have the Membership qualification, and you couldn't be a proper Registrar without having Membership. So I had to go back to Chase Farm Hospital on, I think, one of the very first women's retraining schemes. So I did two or three years in paediatrics again to swot up enough to do Membership. I remember walking into the exam and looking at the paper and feeling terribly sick and thinking, 'I can't do this.' And then I thought, 'What will the children say if I got home and say I've flunked it?' So I stayed and passed it, it was fine.

Then I went back to Guy's as a Research Registrar. I worked on Duchenne muscular dystrophy with Victor Dubowitz at the Hammersmith Hospital. I worked part-time at Guy's and I did my thesis, which was on Duchenne. It was only part-time because the kids were still too young for my liking to be left alone completely. I enjoyed it very much. I then got the substantive Registrar's job at Guy's, which was pretty responsible because I remember it was just me and Caroline Berry, who was the Consultant. It was just the two of us. So when she was on holiday it was just me in charge of the clinical genetics work. It was quite a responsible thing, and I used to get very exhausted, I remember that. If you didn't know something you had to find out, so it was quite challenging. And it was very good, and I loved it there.

TT: And these were NHS positions? You said you went as a Research Registrar?

SH: First of all it was Research Registrar. It was Paul Polani's Unit, but I think Martin Bobrow was the Head of the Unit by that time. I think that was research funding initially, and then NHS. But then when I got the job as a Registrar that was just NHS.

TT: And at this time your responsibilities were clinical, teaching, research?

SH: Mainly clinical. Yes, I didn't do a lot of research then, although there were always cases of interest that came up, so you just published the case reports – certainly my bibliography is full of case reports [laughs].

TT: All 60 pages of it. It's really interesting the way it shows how science changed. From early papers with just one or two authors, and then suddenly in the 1980s we start getting these huge multi-authored papers. Can we continue to talk about your career: you became a Senior Registrar at Guy's; then you became a Consultant?

SH: Yes. Then I got the Consultant job at Addenbrooke's. It was a bit silly because obviously Humphrey wasn't going to move house, so I had to commute. But by that time my dad had died and my mother was on her own, living near Cambridge, and getting quite arthritic, and so on, needing a bit of help. So it was rather nice that I could go and spend a night or two there. And by that time the kids were more grown up so I could leave them for short periods. But it was always quite difficult. On Sunday evening I'd start getting all nervous about it, but it was a very nice job. When I was there, Eamonn Maher turned up as Registrar – very bright. Somebody from Cambridge University Press came round and asked if we wanted to write a book. At the time I was becoming interested in cancer genetics but this was very early days in cancer genetics and not much was known about it. There was Joan Slack, who ran a clinic with my great friend Vicky Murday in London, associated with the Polyposis Unit at St Mark's Hospital. And she was running a cancer genetics clinic, one of the first; there was Bruce Ponder who was running one at Guy's, but they were all very new and based on family history of cancer.

TT: Can I just ask for clarification? When you say family history, these would be constructing conventional pedigrees?

SH: Yes. The way it all started was in the 1980s at St Mark's there was this nurse who got interested in the family histories of the patients with cancer and she took family histories from all the cases with colon cancer in the hospital. Richard Houlston had done some analysis to show that the degree of family history of colorectal cancer that you had dictated your own risk. Joan Slack saw people in the population who had a family history of colon cancer, and if the family history was sufficient, you arranged for them to have colonoscopies and they would have a higher yield of polyps and cancer than average. That

could be correlated with the degree of family history and the ages at diagnosis. She was busy setting up clinics to assess family histories and then arranging for colonoscopies for appropriate people.

Then Lynch syndrome was described, mainly in the 1980s by Patrick and Henry Lynch in America, a susceptibility to colorectal cancer, associated with uterine and ovarian cancers. I was becoming aware of Lynch syndrome, and screening individuals in these families. In the late 1980s Humphrey, a gastroenterologist, had a patient who had colon cancer who was quite young. He was talking to her and it turned out she'd already had uterine cancer, and he thought this was a bit unusual, and he also thought she looked a bit familiar and he eventually found out that she was the mother of my cousin's wife, who was a very gorgeous person. I thought about it and then started thinking, 'Oh my God, perhaps she's got Lynch syndrome; should I tell my cousin's wife?' It took me several months to screw up courage to do this. So eventually I rang her, and she was actually very pleased to have this discussion, and she didn't seem at all bothered after me getting so nervous about approaching her. In those days Joan Slack used to see people like that, and she used to arrange screening for ovarian and uterine and colon cancer for people with such family histories. My cousin's wife, Suzanna, went to see her. She said she should have screening, and this was arranged, but it turned out that Suzanna was pregnant, and so she postponed it. After she'd had the baby she was very sadly diagnosed with ovarian cancer, and she died. This was a terrible thing. We knew subsequently that actually screening for ovarian cancer is really not at all good in this situation, so in a way that was a relief to me to know that. I kept feeling really awful about that.

TT: Understandably.

SH: I felt that I must really do something about cancer genetics and increase knowledge about it, so when we were visited by someone from Cambridge University Press asking 'did we want to write a book?' Eamonn and I agreed to write a book about cancer genetics. So we did, and it was probably one of the first clinical cancer genetics textbook for clinicians. And we dedicated it to Suzanna. That was really when things became fast moving. Genes such as the breast cancer 1 and 2 genes (*BRCA1* and *BRCA2*) and the Lynch syndrome genes were all being identified in the 1990s.

TT: There was a period when your clinical experience, but also your research experience, because you'd done your thesis on Duchenne, meant you were already moving in that direction? Can you just say something about what it was like at that time? It was almost every week you picked up *Nature* or *JAMA* [*Journal of the American Medical Association*] and there was a new test or something.

SH: Yes it was. My research was never really very molecular but I kept up with all the molecular discoveries. I should have spent time working in a lab when I was doing my thesis because I was very involved in all the molecular work, I knew about deletions in the Duchenne gene, for instance, and I was very puzzled about the different sizes of the deletions and why they didn't always have predictable effects on disease severity. It was really exciting but I should have spent at least a year probably working in the lab. I just didn't want to go away from the patients. So, in a way, my education was not very good in that sense but I still knew how to apply the information and it was, as you say, it was just incredible the way it was going, and really exciting.

TT: Did you feel optimistic that you really may be able to do something to help your patients? Was it just another step in improved diagnosis but not necessarily therapeutic?

SH: I was quite cynical about the possibility of therapeutics for Duchenne for a long time. I suppose I didn't see the discovery of the Duchenne gene leading to therapeutics so much as diagnostics, but in cancer genetics you can actually save lives by screening. If I look back on 'lives saved' in my career, I remember I diagnosed a small melanoma in a young patient when I was a GP, which was removed and everything was fine, but I suppose most of the times when you may have saved lives is when you arrange screening for people, having identified that they're high cancer risk, and you do pick up early malignancies. I remember, when I was deciding that I must go into cancer genetics, one of the things I found difficult about clinical genetics was prenatal diagnosis, and I used to have a bit of emotional trouble with that. You might find that somebody had something very mildly wrong with their baby and they'd say they had to have a termination. I used to find that quite hard, and so I preferred something that was more positively helpful, if you see what I mean?

TT: Yes, yes; did this all start when you were in Addenbrooke's?

SH: Yes, well really when I came back to Guy's but it was joint with St Mark's because the Head of the ICRF, Walter Bodmer, supported me. I received grants from ICRF, and used it to fund a series of Registrars. They've done some really

interesting work, I've always needed help in overseeing the molecular work so I always used to have to partner with somebody else. When I was at Guy's, Marc Tischkowitz was one of my Research Fellows, but the person who directed him in the laboratory sense was Chris Mathew who supervised him with the molecular work. And then I obtained various other grants doing psychosocial and other work as well.

TT: More into genetic counselling?

SH: Yes. One of the interesting things was when you gave people results that were not clear cut and you couldn't quite understand, and what did they make of it? So we wrote quite a lot of interesting papers about the way people perceived the sort of thing you were telling them, especially when you didn't completely understand it yourself.

TT: Was that quite usual at the time? Would clinicians be involved in looking in that kind of aspect of things?

SH: Well, I suppose it was all fairly new, it was all starting up. There was some cancer genetics counselling going on, but I guess apart from Joan Slack's clinic, mostly at the Royal Marsden in London but also the Christie Hospital in Manchester was always way ahead with everything, and Southampton probably too.

TT: Were you still working part-time at this stage?

SH: No, I think I must have been full-time by then but I was running backwards and forwards between St Mark's and Guy's. I think I used to do three days at one place, and three at the other.

TT: Was St Mark's out in Northwick Park then?

SH: No, it was in City Road. It did go to Northwick Park later but it was City Road then. I learnt so much there. You'd see Peutz-Jeghers syndrome, familial polyposis, juvenile polyposis. I remember one time Nick Wright asked me if I knew a patient who had polyposis and had a mosaic cell line. And I said, 'Yes,' because we had all these patients. He had an XY/XO karyotype, and so they did some really rather important work on the clonality of his tumours, his polyps, predicated on this. Without having the clinical link you wouldn't have been able to do that. So I suppose, if you want to describe my research, it's always been translational. I've been the person who went with the information to the patient and came back with the patient data to the molecular people.

TT: A key role really. You could see the two sides moving ahead almost independently.

SH: Yes, it was exciting. I spent quite a long time at St Mark's doing that, and then I gave up St Mark's, mainly when it went to Northwick Park because it was a long way. Also, they got more of their own staff there. But one of the important links I made then was with Ian Tomlinson who was a great ally all along and, again, my Research Fellows used to go and work with him in the lab, and liaise with me for the clinical side of things.

TT: These are really important links you're making between the lab, which is burgeoning with exciting developments, by feeding into the clinics more information about the families, the genes. It's almost synergistic – having somebody like you in the middle to translate and talk to both sides was really very important.

SH: Exactly, yes, and I suppose being able to understand what was going on. I still felt that I should have known more about the laboratory work but my heart was in the clinic really, and I found it really hard to drag myself away. When I finished there, I became more of an academic, I got an academic post with an honorary clinical post as Senior Lecturer and then Reader. The medical schools merged again and became King's, Guy's and Thomas'. I did a bit of teaching as well. I remember having students assigned to me, and I did some student mentoring as well.

TT: And then the move to St George's?

SH: That was 2003, and that was quite serendipitous. I'd been great friends with Vicky Murday for many years, because, I did a degree module in genetics at the Galton Institute. When was that? I suppose it must have been when I was with Polani the first time, or perhaps when I'd just done Membership. I did it part-time in order to make sure I knew all my genetics, probably when I was starting in the substantive Registrar post; it was a sort of diploma. But Vicky was there getting the full diploma and so I got to know her. I remember she looked terribly pre-Raphaelite with long flowing red hair and she was just great fun to be with and we got on very well. She got a Consultant job at St George's and was working there with Mike Patton, and was a cancer geneticist, having been at St Mark's as well. We worked together on some research projects, both at St Mark's and St George's. Then her husband moved to Newcastle so she went with him there and found a job, and then they moved again, to Glasgow.

When she moved away from St George's her post remained and Mike Patton made it into a Chair, so they offered me this Chair. So I went there and I really enjoyed it. I went on working there until I retired.

TT: When you say they offered you a Chair, did you then become a Head of Department?

SH: Well, it was a personal Chair, but on the other hand there wasn't anyone else doing cancer genetics. When I was at Guy's beforehand, I was running the South East Thames Regional Genetics Service for cancer. So when I went to St George's it became logical that I'd run the South West Thames Regional Genetics Service for cancer, so I did as much as I could. Cancer genetics by then was quite involved because it not only meant doing clinics but it also meant deciding on what level of risk to do what screening, and negotiate with the 'powers that be' in order to decide which groups of people should have what kind of screening, and so on. And also going to multi-disciplinary team meetings, which tended to be at some awful hour in the morning like 7:30, so I had to go to these from Muswell Hill to Tooting by bicycle, and I was always late.

TT: It sounds like an awesome full-time responsibility.

SH: It was quite a responsibility but then you did it as a team; there would be clinicians from other disciplines, registrars, nurses, genetic counsellors involved and so you would do things as a team. Ros Eeles and I set up the Pan-Thames Cancer Genetics Group, we used to meet once every three months, and we used to talk through cases. That's the way it started. We would develop screening and get management guidelines sorted out. Ultimately there was a need to liaise with the Department of Health, and help develop the NICE [National Institute For Health and Clinical Excellence] Guidelines. My job was on all sorts of levels.

TT: So your responsibilities were: the hospital, the hospital Medical School; you've got the regional obligation?

SH: Yes.

TT: What about the Colleges?

SH: Oh, I see what you mean. Yes, that's right, and of course I got my MRCP in paediatrics, but I'm a Fellow of the ordinary College, the Royal College of Physicians. They have a specialist committee for genetics and I was on that for a while. We used to go and meet at the College of Physicians and thrash out

procedural things, very much under the umbrella of the College of Physicians. Although a lot of genetics is paediatric, the aspects I was involved in were mostly about adults, because thankfully most children don't get cancer, although some do.

TT: You've spoken quite a bit about your overwhelming desire to be involved with patients, clinical work. You also mentioned you'd found prenatal testing troublesome.

SH: Yes, I had a bit of trouble with that.

TT: It almost comes back to what you talked about your father and eugenics; there have always been some of the ethical concerns, those grey areas that have to be negotiated at the coalface as a clinician with the patient. I just wondered whether you could reflect on that?

SH: I remember my father was really, really strongly anti-eugenics. When he was coming back from Canada in about 1946 he was on his own, pretty much, to start with. I'd always been aware of this being very important to him, and I felt very supportive of his ideas. I remember he used to love Down syndrome people, and he always used to really like being with them – I suppose they're not very complicated, they don't have all these ambitions and things that 'ordinary' people sometimes have. He was very caring of them and I, I guess it rubbed off on me, really. I remember him saying, 'Oh, you can always tell how advanced a society is by the way it treats its Mongols and imbeciles and disabled people'; this is what they were called in those days. So I guess that was very much part of what I believed. I'd always thought, although I couldn't have had prenatal diagnosis when I was pregnant, I'd always thought that if I had known that I had a Down's baby, I probably wouldn't have been able to bring myself to have a termination. Although, thankfully I didn't; I would have found termination quite hard.

Although, I could appreciate why, particularly with Duchenne for instance, I could absolutely understand people having a termination if their baby was going to have Duchenne. It is just such a terrible illness, really terrible. And so, there are obviously gradations; I remember talking to Paul Polani about it, and what he felt about terminations and he said, 'It's not really quite a person yet, is it? It's only part of a person.' It's difficult but there clearly isn't going to be a hard and fast line that you should never have a termination – I don't believe that

at all – but, as I say, I just found it quite difficult. For instance, when people wanted to terminate a foetus with Turner syndrome, and people with Turner's can have a very fulfilled life.

TT: Could you please describe Turner syndrome?

SH: Turner's, well they have an XO karyotype so they are usually infertile, tend to be a bit short, they may have some physical disabilities and they may not be quite as bright as their peers, so they have various problems, but they don't usually have many serious problems.

TT: What about this question of giving bad news? How did you face that?

SH: No, you're never taught those things are you? You just do it by the seat of your pants. You try and empathise with the people, and you don't whack them with things, you just try and get cues from them as to how they're feeling, how they're going to handle it and that sort of thing.

TT: You mentioned multi-disciplinary teams: that must have been quite a transition during your career, the creation of multi-disciplinary teams?

SH: Well, they are usually already in existence in other disciplines such as breast cancer management teams, in order to arrange the best way of treating the patients. They need a social worker, they need a nurse, they need a doctor, they need a surgeon – all the different people who are going to have a say in what their management is. So it was only quite recently that geneticists were included in those meetings. In fact, I used to find them quite difficult because most of the meeting was naturally about the treatment of the tumour, and I had to wait for the appropriate moment to discuss any relevant genetics issues, such as whether and when to test the patient for a *BRCA* mutation.

TT: Were there more nurses and genetic counsellors to help you as a geneticist giving and discussing bad news?

SH: No, in those meetings the patient wasn't there, and you wouldn't do much except alert people to the genetic issues, and the counselling would then be done later. You would get the patient referred to you. People would then suggest that this family ought to see the geneticist, but there are serious problems. Usually we used to see people on our own although sometimes, like the other day for instance, at my Leicester clinic, I had a difficult situation where there was a young woman who wanted to have a *BRCA* test, and her mother had breast cancer and she'd had it from a young age but she was still alive and she didn't

want to be genetically tested. She was the one I ought to be testing, but the daughter was very firm, she wanted to be tested. After a long chat with her about all the relevant issues, she said she'd talked to her mum, and so I did test her, and she had a mutation. So then the question was how to go back and deal with how to give this information to her mother. I talked it through with the team, including nurses and other doctors and genetic counsellors. Then I saw the young woman again with her boyfriend and with one of the nurses so that we had the backup – if I wasn't there on a future occasion she'd be able to deal with it.

TT: How did you get involved in Leicester?

SH: There is a lot of serendipity in my life. I was examining a thesis, and the other examiner was Julian Barwell, who had been one of my Research Fellows, now working in Leicester. And at the time, I didn't really particularly want to retire, but in 2011 we'd been approached by the Dean of the new Namibian Medical School to help with setting up a new Medical School, and so we were going to be spending one month in three in Namibia helping with that, and so I wasn't going to go on doing a full-time job at St George's. I wanted to work there part-time and they felt this was not appropriate, quite reasonably. So I'd stopped seeing patients, but then I came up for revalidation with the General Medical Council (GMC), and if I wanted to be revalidated with the capacity to see patients, I had to be seeing patients currently, because you need their feedback. And I was on the train with Julian Barwell telling him about this, and he said, 'Oh well, we need a Locum Consultant at Leicester,' so he found me a job. I went up for interview and was accepted there, and saw the patients and got revalidated. Currently I'm still doing it. It's really nice, I enjoy it. I work there just one day a week.

TT: There's one thing you mentioned there: 'we' were invited to go to Namibia to set up the Medical School. Who is 'we': you and Humphrey?

SH: Yes, I've always been interested in international medicine, and perhaps going out and helping people who are less well off than we are. I'd always had this desire at the back of my mind that I'd like to go and do that, and so I told various people, including THET, the Tropical Health and Education Trust.

TT: I know Eldryd Parry, who founded THET, very well.

SH: The Dean of the Medical School in Namibia had written to Eldryd. Namibia is a huge country with a small population, and they didn't have a Medical School. They'd been independent since 1990 and they wanted to start training their own doctors. They had a University, but they didn't have a Medical School, so they set up a Medical School to try and get their own doctors, because the doctor per patient ratio is terrible there. They'd started, and got as far as the third year, and they had beautiful buildings and everything was lovely, except they didn't have any clinical curriculum or any established liaison with the clinics or hospitals. So the Dean wrote to Eldryd asking whether he knew someone who could come out and help develop the clinical curriculum. Eldryd got in touch with Humphrey because he knew of his interest, and his specialism in internal medicine. We had lunch with him and he told us all about this so we thought perhaps we'd give it a try.

We went over to visit the Namibian Medical School in Windhoek, and they asked me what I trained in, and I said, 'paediatrics'. They immediately said, 'Right, well we haven't got a paediatrician' [laughs]. So I had to write the paediatric curriculum, and Humphrey wrote the internal medicine curriculum, which was a bit hard for me because I hadn't done paediatrics for about 30 years. But you can get lots off the internet and the back of your brain usually. We went there one month in three. At the time there was one paediatrician who turned up about a year after I started, and so what I would do is set out what I thought the curriculum ought to be, and try to organise things even when we were in the UK. One of the problems they had when developing the clinical curriculum was that nobody had really talked to the hospitals or to the clinical staff about medical students coming to learn medicine in their hospitals, so we had to spend a lot of time talking to people and trying to explain why this was needed and how we could collaborate. And then, eventually, all that started to work and the students went to the hospitals and it all did start happening. But there were very few medical staff around in the afternoon because they'd all be off doing their private practice.

There were very few faculty in the Medical School and the problem is the faculty were paid much less than doctors in the Health System would get paid and they also couldn't do private practice, so they were very much worse off than the local clinicians. One poor chap, who was only a Reader, ran out of money; he wasn't being paid enough and he had a wife and children to support, so he went off to do a clinical job in Rundu, which is in the north of Namibia. I was left with nobody in the faculty again, and so I brought in a few people from outside who

had taught in Africa before, in Malawi. At the moment there still isn't anybody so in two weeks' time I've got to go back and run three lots of exams, three lots of OSCEs [Objective Structured Clinical Examinations] and mark them all single handed – pretty ridiculous.

TT: You're there and negotiating Medical School and hospitals, you're in a completely different environment.

SH: A challenge, yes. But we are fading a bit. I mean partly because last year we were attacked and, although it's mainly a peaceful country, Humphrey was quite badly injured.

TT: You were mugged?

SH: Yes. I'm not so comfortable going there as much, although it's still much safer than South Africa. We used to go on lovely walks and now we feel we can't go on them. It takes a lot of the fun out of going there.

TT: Have you had much dealings in other international collaborations?

SH: Yes, I have. We went to Burma a bit, a couple of times, to do some teaching, but I didn't get a long-term relationship with them. I went to Nepal a few times. That was because at St George's there was a student group doing electives in Nepal, they used to go out in the summer for two or three months, to do clinics up in the mountains in Nepal. I was put in touch with the Medical Schools in Kathmandu, and I went over two or three times to teach there, mainly genetics, to try and set up links. We thought maybe we could set up a collaboration through THET. We did set up a link through THET, mainly with the students, but then that didn't work terribly well; Humphrey didn't like it. Every time we went there were different people involved, and you'd turn up to give a lecture and there wasn't a lecture theatre and they didn't know you were coming. Everyone was terribly enthusiastic but when you went away they disappeared into a puff of air.

Then there was India. I've done quite a bit of teaching in India together with a geneticist in England who is Indian. We went to Mumbai and we went up north as well giving mainly cancer genetics courses and things. And we met this chap Rajiv Sarin, who then invited us over another time to run a cancer genetics course. There is a very good centre there in Mumbai, a fantastic lab, really brilliant students, very high quality stuff. I'm now on the board of their new genetic counselling/nursing syllabus, setting it up, because they don't actually have any

established cancer genetics counselling as such in India. There's somebody in Bangalore who used to work in England who runs ordinary clinical genetics, but there's very little clinical genetic counselling in India.

TT: Why is that, is that just lack of recognition of its importance, or lack of personnel?

SH: I think they're faced with people who are really ill with tuberculosis and diarrhoea, and really serious things; so genetics seems of secondary importance. But with cancer genetics, they're beginning to see the importance of it even with all the other confounding issues. China, similarly, I've been invited by a colleague Yiming Wang who worked in the UK for many years. Exactly the same, in China there are no genetic counsellors, but they have fantastic labs, they can dissect anybody's genome, no problem. It seems they haven't the facility to use this in the clinical context.

TT: Is the clinical backup there? Are oncologists and others involved?

SH: Yes, there are oncologists, and there are all the medical and paediatric doctors that you need but again, in terms of getting a genetic result and explaining it to somebody and working out what the family tree means to them and what genetic tests are needed etc., etc., they haven't done that yet. It was very interesting talking to them because I would give a talk about whatever, cancer genetics, and they'd say, 'I've got a case of so and so, they've got Peutz-Jeghers syndrome, but they haven't got a mutation in the gene.' And I'd say, 'What are the clinical signs and symptoms?' 'Oh, I don't know, they told me he had Peutz-Jeghers syndrome.' So I'd say, 'Well, tell me more', you know and There is a sort of complete disconnect between the clinic and the molecular stuff; they are very keen to get that link back.

TT: Talking about international collaborations, what about some of the major research consortia that you've been a part of?

SH: It's one of the things that happened to me, and I always sort of stumble into these things rather without noticing. I got a phone call from my friend, Neva Haites in Aberdeen. She'd just got a grant or was about to get a grant in one of these European Union-funded studies to look at genetic counselling for cancer genetics in Europe. Would I like to be involved? So I became the Guy's link for that research project and I was on the Board of the European Society of Human Genetics, and again I got to know lots of people that way. It's just these links and connections, and you get to know people, and you do research

with them. And of course a lot of the research now is on these huge genome-wide association studies (GWA studies; GWASs); you've got to get millions of patients with this and that, and millions of normal controls. I get printouts each week of references that might be of interest, churned out by St George's, and I run through them. There are many dull papers on GWA studies, because they just say, 'This gene is slightly involved with…' and I just think it's not very intellectual doing those things, but you have to do them because then you learn from what you do find out which genetic pathways are involved in certain diseases, and then you can go off and do more interesting research.

TT: Looking at the transitions in your career, one of the other things that I did wonder about, is patients and patient expectations, and how they have changed because one's bombarded in popular culture about a gene 'for' this or that, and doctors 'solving' this or that?

SH: You do get exposed to things like '23andMe', and similar things. I remember my first patient who turned up with a print out about that, and saying, 'Oh God, I'm going to die tomorrow because…' and I had to say, 'This is a variant which gives you a 1.15 per cent increase in risk of colon cancer, forget about it.' That kind of relative risk is perhaps quite difficult for people to understand but, in genetic counselling we're mainly dealing with the strong genes, such as mutations in the *BRCA* genes, which really do make it quite likely you're going to get breast cancer. But the ones that are beginning to be pushed up in the news, and if you do happen to get your saliva tested by 23andMe, you end up with a whole lot of these very minor genetic variants each with small effect but which may be additive.

TT: The other thing you mentioned that I was intrigued by, is when you say you chummed up with people because you didn't know enough or you felt you didn't know enough. How did you find them?

SH: I'm a Member of is this thing called 'the Mallorca Group', which is a group of cancer geneticists who are mainly involved with colon cancer, and we meet up once a year and I suppose you just get to know so many people that you're bound to know somebody who is appropriate to your needs, really. It shows, I suppose, how important the social side of one's scientific career is. You don't just work in your little hole, you make friends with people, and you suddenly find that you're collaborating on something.

TT: Can you say a little more about the Mallorca Group?

SH: It was started by Hans Vasen, a very energetic Dutch cancer geneticist, and it's mainly research collaborations. Recently it has also become a body which organises guidelines because the people within that group are pretty good at what they're doing, they're pretty high up in their own countries, for instance. There's Pål Møller from Norway and he's the only representative from Norway, so you get a lot of expertise from the different countries. They have quite a lot of nous to be able to set up potential guidelines for screening for Peutz-Jeghers syndrome or polyposis or the rare diseases.

TT: Some of these little groups and connections are so important. They're often below the radar.

SH: Yes, that's right. Well, they start off below the radar, yes, but they are terribly important.

TT: Looking back on your career, what would you say you were proudest of, or what are you pleased about achieving?

SH: I suppose writing the book, and I suppose pioneering clinical cancer genetics, because that's what it did. I know Joan Slack had been doing it but it perhaps put it on a more firm footing.

TT: Anything that went particularly wrong?

SH: I've mentioned the various times when I thought one could have done better, and I should have done more real academic hands-on molecular research. Because I've always felt I'm not a real, proper researcher. That's why I've always had to get the expertise of other people, I've never been able to really run a project all on my own because I haven't known enough about the laboratory side of it. I've never felt I'm a great researcher in any way, because I couldn't be without the molecular side, and I don't have the drive either, really.

TT: But you understand it and can make the connections, which is a very important skill.

SH: Yes, but if you want me to do basic, cutting edge research I'm not going to do it.

TT: Yes, well you're using the word research in a very defined way, aren't you? You're just thinking of research as lab research?

SH: Yes, of course, there's lots of other research too.

TT: What do you think have been the major changes over your career?

SH: Well the huge change was finding the genes, the *BRCA* genes and the Lynch syndrome genes; that was a huge, huge change. And then understanding then the way tumours develop and all this new stuff now with Mike Stratton showing that different tumours of the same type are completely different from each other. Two breast cancers can be molecularly completely different, and this fascinating stuff about finding that they have a mutation signature showing that in things like melanomas, all the genes that seem to be "broken" are the ones that you would expect to be broken, the ones that UV light break, and the ones that lung cancers are caused by the mutations in the genes that are caused by the carcinogens in smoke. Once you get an idea about how the cancers develop and why they are initiated then you can get better ideas on how to treat them. It's a real watershed.

TT: What do you hope might happen in the next 30 or 40 years?

SH: Well, I would hope that they would be able to get much better treatment for cancer and I'm sure they will. All this GWAS work is allowing us to find out a lot more about the minor alterations in your DNA. There are lots of different genes that affect your susceptibility to things, which are of lower penetrance. It's mainly personalised medicine that's going to be the big change.

TT: But then personalised medicine comes at a cost, doesn't it? It's First World luxury compared with what you were talking about previously.

SH: I know. I think some of the tests may be relatively easy to develop once we know what they are. Some of the molecular markers may involve quite a cheap test to see is this gene turned on, like melanomas – certain mutations are only present in some melanomas but if it's there, and if the drug can be made cheaply enough then you can use the therapy much more effectively, and then you save a lot of money, of course. You don't waste money by treating cancer with something that won't work.

TT: You've used the word 'serendipity' a lot. I think we all look at our CVs and say, 'Oh, that happened by chance.'

SH: There was a lot of chance. Humphrey finding that advert, a tiny little advert that Polani wanted a Locum, otherwise I'd have gone on being a GP. It's as simple as that, I think.

TT: Shirley, that's been fascinating, thank you very much.

Figure 6: Professor Patrick MacLeod

Professor Patrick MacLeod (b. 1940) is a Clinical Professor of Medical Genetics at the University of British Columbia and an Adjunct Clinical Professor in the Centre for Biomedical Research, Department of Biology, University of Victoria, British Columbia. He trained in Medicine at the University of British Columbia before going on to train in Paediatrics and Medical Genetics at the Montreal Children's Hospital under the direction of the late F Clarke Fraser PhD MD OC. He is a Fellow of the Royal College of Physicians and Surgeons of Canada, and a Fellow of the Canadian College of Medical Genetics. He has initiated research in various paediatric neurological disorders, contributed to the mapping of the gene for what is now known as spinocerebellar ataxia type 3 (SCA3; Machado Joseph Disease), and the natural history of Rett syndrome in a large cohort of Canadian families.

6 MacLeod, Patrick*

Tilli Tansey: Can you say something about your early childhood please Patrick?

Patrick MacLeod: I came to consciousness on a beach on a small island on the west coast of Vancouver towards the end of the Second World War. My father was an anti-submarine pilot in the Royal Canadian Air Force, and Japan had been launching fire balloons from submarines hoping to start forest fires in British Columbia. When they realised that there were 300 forest fires in British Columbia that nobody fights, the Japanese had plan B, they moved progressively down into the States, and these anti-submarine bases moved onto Vancouver Island. I lived with my family there, at the north end, Victoria. I grew up in Vancouver, went to school there. My mum and dad had three more children, my sister, my middle brother and my younger brother. I went through the traditional boy scouts, air cadets type of thing, and eventually went into the regular Air Force to fly for a couple of years as a jet navigator.

TT: Was there national service in Canada?

PM: No.

TT: So this was, you weren't conscripted, you volunteered?

PM: I skipped Grade 4. I was about eight or nine? I was a problem child in Grade 3, I know that the nuns had me sit outside the classroom. My mum being a teacher negotiated, next thing I know I go back to school in Grade 5. Skipped Grade 4, I have no idea what my problem was, but that didn't serve me well later on. But I got through it. And then I went to UBC, the University of British Columbia, and I just wasn't ready for it, I was too young, and decided to go as aircrew for a couple of years, which served me well later on. Came back, wanted to go into Medical School – had always wanted to go to Medical School. Went into Medical School at UBC, graduated. I started off down the road to do neurosurgery, basically because of a patient. I went off to do an internship in the States in New Hampshire, at Dartmouth Medical School, because it was a two-year programme that had extensions to the Boston circle

* Edited passages from the interview conducted by Professor Tilli Tansey, 6 June 2015, in Glasgow. For more details, see 'Related resources' at the end of this volume.

of training programme. So that made a lot of sense. Then I got this career path change from neurosurgeon to paediatric something or other. In the United States, in that period of time, the National Foundation for the March of Dimes was collecting dimes to cure polio. Once the Salk and Sabin story was played out, the effective vaccines for polio, they were going to dismantle this. But somebody, and I don't know who it was, convinced them they should keep the momentum going, but raise money for birth defects. And to this day there are birth defects meetings funded under that rubric. They also made available training scholarships and things like that, so when I got to Montreal I must have qualified for a birth defects fellowship in paediatrics. There was no formal curriculum for medical genetics, you just learned on the job and followed your interests, and serendipity has come to town on many occasions: things have just fallen into my lap without any effort at all, and helped that.

I suppose I became a clinical geneticist quite by accident. I graduated from the University of British Columbia with a career path in neurosurgery, and along the way I met a man at my internship who dissuaded me from being a surgeon. He said, 'MacLeod, you're not a surgeon,' which completely changed my whole tack. So I had to take a year out and do something, so I did a year of paediatrics thinking, 'Well, paediatric neurosurgery is still an option.' But the more time I spent with him, the more I got interested in congenital malformations and birth defects, and he indicated this was a prime time to get into this new field. So I had two options as far as he was concerned: I could go to Boston or I could go to Montreal. So I interviewed at both, and my wife and I decided to go to Montreal. And I joined up with Clarke Fraser at the Montreal Children's Hospital. Now back then there wasn't such a thing as a career path in medical genetics, it was a Certificate of Special Competence in Paediatrics. So I did my paediatric fellowship from the perspective of a medical geneticist, like 'Why are we doing this heart catheterisation on this child, what syndrome does she have?' Or 'Why does this family have a collection of that?' And then, eventually, when I qualified I was recruited back to the UBC as a junior staff person in 1973.

TT: Can I just go back to when you were at school, because you just gave me this throwaway line, you'd always wanted to do medicine. Do you know why?

PM: Oh, sure, I can tell you. We lived in central Vancouver and the family doctor did house calls and night calls. I got a job at the local pharmacy being the delivery boy. And one of the deliveries was to deliver things to his office. I got to know him and his wife, who was his nurse. One thing led to another and he started taking me on house calls. Leo Friesen was his name, he had a very profound

influence on me. Another event had happened, I'd forgotten, and that was the nuns had me all lined up for the seminary. I still remember Grade 11; I had an interview, and in Canada the large missionary priesthood of the oblates, they do a lot of work in the North, this chap interviewed me and I got this impression, 'Don't call us, we'll call you.' It just was terrible.

TT: You must have been a bright, inquisitive boy, because family doctors don't take every delivery boy on house calls, do they?

PM: Well, there was an ulterior motive for doing that. He wanted to get to know me so I could babysit for their kids. I'm in their second family as a consequence. But Leo was quite a good thing. And eventually when I was serious about going to medical he said, 'I don't think you should go to Medical School. Medicine is changing so much, it's going to be tough and you're not going to enjoy it.' Certainly I remember that. There was always this pastoral component, I guess, from the nuns and everything else. And medical genetics offered that kind of opportunity.

TT: Far more than, say, neurosurgery? Because you engage the patients in a much more direct way?

PM: The wonderful benefits of being a medical geneticist over the years, you meet every conceivable belief system or non-belief system on the planet, and you get to learn all kinds of things. And there's the art of medicine, the science of medicine, but there's also the pastoral aspects of being with people.

TT: You're also an educator training future generations of doctors, is there any way you can teach that?

PM: By example. In our situation at UBC, Vancouver Island, all the paediatric rotations involve a rotation through medical genetics, and they have no idea what you do. Because when I was a boy in first year medicine we had 30 hours of lectures, labs, a week. Now we have a problem-based oriented curriculum, and you get a smattering here and a smattering there, and you really don't know that genetics is even a career until it's too late. And so we give them an opportunity to sit in, in anything from a tough prenatal case or listening to some family struggling with the realities of Huntington's disease. The beautiful thing about being a medical geneticist is that the system gives you 90 minutes per patient. Wonderful chunk of time, and you can get so much more done in that sense, you know? So it has that opportunity to get involved and I have stories that would go on for a month of people and families, it's such a benefit. I try and

encourage these young students to consider a career in medical genetics. The problem is with the training programme in Canada, they're trying to look to change this now, and you're basically forced in fourth year, which is early on, to make a career choice. They haven't done any of these rotations yet, you know? And so one of the things I've really tried to do is get exposure to the pre-med curriculum, and so at the University of Victoria, we have a core programme in human genetics. It's a requirement for honours biology and now a requirement for honours biochemistry and microbiology. I do this dog and pony show where one of the basic scientists teaches the course, and have me come in and say, 'Well, why is this relevant?' And it's like a recruiting poster, because every time I do that someone will take me aside at the end and want a career in genetic counselling or in medical genetics, they've never heard about this before. And so time and time again it's a recruiting opportunity to get them involved. The medical students, they're so differentiated by the time they get into Medical School that they don't have time to think a lot about these things. So now there's a movement afoot to try and change that to a five-year programme where in the fifth year you work and are paid in family practice.

TT: This is at the end of the training before the internship?

PM: Yes, before your internship. So that you get out and see some things. I've had more people over the years that never heard of this career in genetics and are now two of my colleagues that I work with, both heard me talking and here they are now, side by side, colleagues.

The other thing about this, and I don't know where this fits in, but for 10 years I was a founding member of the Department at this big academic centre in Vancouver, which is right smack dab in the middle of pretty expensive real estate. Then I moved to Kingston to do this linkage project, and they had two hospitals – one is really primarily an administrative building and outpatient, the other is a full ocean-going hospital. And I began to look at the fact that every time you went up on the ward there was some mother who was caring for a baby with croup or something, and you could just know that she just struggles a bit. And then over labour and delivery you'd always go up, there was some mum you would interact with, or the family members, and you knew these were struggling families. So I asked a question about this after I was there for a year and I was given this typical 'It's the north of Highway 7 syndrome.' In the old days the road went from Toronto to Ottawa along Highway 7, which is the Canadian Shield, there's about half an inch of topsoil and then there's the Canadian Shield. So these families north of Highway 7 eke out an existence

that's sort of Appalachian. So I dug around and I came across a white paper in 1961 – this is now in the mid-1980s – where they did a national survey of children's needs and they used Frontenac county, where the Kingston General Hospital is, one of the bellwethers, and they collected all this information from this county. And the consanguinity rate was no different than anywhere else in the country. So I wondered, 'What's going on here?' So it finally dawned on me. At the British Columbia Children's Hospital, you don't see whoop and croup, because they're in the community hospital. Yeah, there are some in the very expensive part of Vancouver but not many. What you see are fourth level, rare complicated cases of everything. In Kingston you see them all. You get a much better feel for the burden of genetic disease in a community. When I came back, that's why I didn't want to go back to Vancouver because it was a case of, 'I am the Consultant, here's what the GP will do for you.' It was a totally different level. And so I adopted this community genetics approach. So we did house calls and we did outreach, we did all these things, you know, and you get a much better take on genetics in a community, and what it says than spending your life in a really academic centre where you're just seeing the rarest of the rare.

TT: Was that easy to set up because that sounds like quite a big step, in the Vancouver situation, to start doing house calls?

PM: Yes and no. Historically, let's dial back 20 years, when a corn cytogeneticist was recruited to the University, into biology, to teach genetics. His wife, also a corn cytogeneticist, didn't have a job, so she persuaded the pathologist in the hospital that he should have a chromosome lab. Now in those days there was a national survey of needs of Medical Schools, and it was decided we needed five more Medical Schools. Well, four of them were built, the fifth one in Victoria, was resisted by the people in the community. They didn't want any of this town and gown stuff, 'We have this nice community here, forget the Medical School, we don't want University people telling us what to do.' So they resisted this. So there was this friction dynamic between Victoria and Vancouver Island, and the chromosome lab was started up there.

TT: The chromosome lab was on Vancouver Island?

PM: Yes, they set one up, there was a big one in Vancouver but there was nothing on Vancouver Island so she set it up and I began to go over every three months. Eventually that just fell apart and I moved to Kingston and it lost its accreditation and nobody would go near it because there was no Medical

School. So coming home, there was nobody there doing anything. The first thing I did was I travelled five hours north of the city to a community to establish an outreach and so we would commute, you know, three times a year up the island to see patients, and it just grew from there. So that was quite easy. But the problem was that the person who recruited me is a pathologist and the manager is looking at 29 units on the island, one of which is medical genetics and it doesn't fit. Over the last 15 years we've been the low-hanging fruit for any cuts. That's been the downside. And we struggled to exist, we've had a couple of real serious attempts to shut us down and send everything to Vancouver.

TT: And is that a very local situation or is that mirrored across Canada?

PM: It's a bit of both. For example in the province next door, Alberta, they followed the British Columbia example. They had I forget how many, 52 Health Hospital Boards in British Columbia, so that's a terribly large number of Vice Presidents and whatever. So they eventually amalgamated it down into six Health Authorities. And Alberta did the same thing. And they downsized and took down that hospital, and three years later they made a mistake, they were going to build the hospital up again. So it just stumblebums on one after another, and people come roaring in with great ideas. Newspaper headlines are the same, exactly the same problems, everywhere you know. Wait times, and bureaucracy, and red tape.

TT: You mentioned the word 'accreditation'. What's the situation in Canada?

PM: Well, we have a long history there, because the Royal College accredits these training programmes in paediatrics and neurosurgery and internal medicine. We petitioned them for many years to allow us as medical geneticists to join the Royal College and bring our PhD colleagues with us. And that was anathema, we don't give accreditation to PhDs. So we established our own college in 1975, the Canadian College of Medical Geneticists, which at that time was two-thirds basic science and one-third MDs. It led the way, it was the first in North America to do that. It accredited individual persons to the exams, and it accredited the training programmes.

TT: How did you negotiate that and who did it, where did you get the funding?

PM: I was junior to this but my department head, and his mentor, who was my mentor, John Hamerton, they were key players in that, in petitioning, I'm not sure how they went through the process to get a thing called a 'College'. I was on the Credentials Committee for 10 years and there were the cytogeneticists, the

medical geneticists, there were the biochemical geneticists, and then there were the molecular geneticists. Now we have these robust training programmes, and so if you're a young person interested in human genetics you can do your PhD and a two year post-doc in one of these training programmes in molecular or cyto, or both now, molecular cytogenetics. Less and less for clinical geneticists, because although the people who established the College were primarily PhD counsellors, there is the whole issue of funding. So if you're a physician they can bill the programme, your Department can bill for physician service, you can't bill for PhD services. So Dorothy Thompson, whose *Thompson & Thompson Genetics in Medicine* textbook was universally used across Canada, was a PhD who began genetic counselling at the Sick Kids in Toronto. Irene Uchida was the same: a cytogeneticist in Hamilton. But, eventually, it became lab sciences for PhDs. And then clinical geneticists for the rest. It's a pretty rigorous process to sit your exams and it's not an easy thing, you really have to be top of the game. So much so that you get reciprocity with the American Board of Medical Genetics, because that's the standard, you know, against which we compare them.

TT: So you get Board-certified?

PM: Yes. Some of my colleagues in programmes who were involved with the Royal College petitioned them and, eventually, in 1992 the Royal College gave in and recognised medical genetics had long ago outgrown its traditional home in paediatrics and yes, it's a freestanding specialty. So I've written every exam that was offered along the way to be qualified, including the Royal College exam and I have a dual qualification, paediatrics and medical genetics. For reasons I don't understand we have not been able to persuade the genetic counsellors to follow suit. And I'm not quite sure what the problem is. But I see they're trying to get provincial recognition for genetic counselling as all these people have Masters degrees. They should be able to get accredited for counsellors. I remember in Vancouver I have a colleague who runs the marriage and family therapy credentialing process, and in some respects genetic counselling is marriage and family therapy, you know so it would fit, but nobody seemed to really go after that. We find ourselves in this funny situation, I have to sign all the letters of my genetic counsellor. When I went to Victoria I recruited two people, a cytogeneticist to build up the lab and a senior genetic counsellor, who was a Canadian living in the States, and she came and had a clinic. Once in a while she'd come and ask me for advice or what I think she should do, but I didn't see her patients, I didn't read her letters, she just went on with it, you know, got on

with it. In fact I kept telling people she is the most knowledgeable person on this island when it comes to hereditary cancer, because she was. And then new people come in, 'Well, we're concerned about liability and stuff,' and I said, 'I've been practicing 35 years and I've had no problems, I'm not about to start now.' But, oh no, it's creeping credentialism. Vancouver has this training programme and they have 15 genetic counsellors. One of them came to work with us when her husband's job moved and when his job changed he had to leave and go back into the old job, and she couldn't stand it, because she had no authority and no autonomy whereas in Victoria, these were her patients and she ran with it. So I wasn't much appreciated around the Department for seducing away some of their key partners. But part of my strategy was, 'Come on! If my daughter has a Bachelor's degree in physiotherapy and bills for it through the system, but also privately, she examines people, she prescribes, what is the problem?'

TT: She has professional standing.

PM: Exactly. Anyway it's not a battle I'm going to win.

TT: When you were back in Vancouver, you were doing private work, you're in the hospital, you're teaching, are you doing all of these at the same time?

PM: Let me just correct that. It's almost impossible to make a living as a medical geneticist in private practice, because there are no billing codes. So you can bill as a GP for extensive counselling or as a paediatrician for extensive counselling, but there's no fee for service for medical genetics in Canada. As a paediatrician and medical geneticist I was recruited into a pathology group where I was a pathologist. The Department bills on behalf of me and the hospital tops it up. I never had a private office on my own, it was always in an institutional setting in a hospital setting, and I was teaching, had a big teaching load at Queen's and then I came back to Victoria and there was no Medical School, and the only teaching I would do was these dog and pony show things in biology about three or four times a year, but not much, to the medical students who came over for their paediatric rotation. But now beginning in September we're going to have two slots funded for paediatric residency, and that means a big teaching commitment, and we don't have the resources to do that. So as I'm winding down they would like me to gear up to teaching.

TT: That's a very sensible use of retired people's time and experience.

PM: Across the board what we do is just completely misunderstood. And other people will get into trouble because, 'Ah, genetics is easy, I'll start a Cardio-genetics Clinic,' you know, and then run foul of how complicated it is to deal with, a patient is one thing, but it's the rest of the family. And they're not used to doing that.

TT: Could you say something about your research when you got back to Vancouver?

PM: Well, my story here began in about 1976, living in Vancouver, participating in the Western Society for Paediatric Research meetings in Carmel, California, because the birth defects focus of attention at that meeting was in Carmel every year. So after these sessions we'd meet at Clint Eastwood's bar called the 'Hog's Breath' for an after-session beer or two. And as I was leaving to fly home, I noticed there was a *TIME* magazine, two-years-old, lying on the desk, I thought, 'Nobody's going to miss this. I'll read it on the plane.' So I got on the plane, had my dinner, went through it, and here was this half page story of this 40-year-old woman, who had recently buried her brother to the 'family disease' that she decided that she was going to do something about it. So she wrote to the National Genetics Foundation asking for assistance and they sent a neurologist, Roger Rosenberg, and Bill Nyhan, a medical geneticist, to interview her, which resulted in a family reunion of some 120 of her family members in Oakland, California, in a park where they had this family-room-come-clinic. And they were now part of what was called the 'International Joseph Disease Foundation'. I'm interested in neuro-genetics, so I'll tear this out and take it back, and I stuck it in my basket and under "J" for "Joseph", and forget about it. Then about two years later my Department Head, who was a PhD, asked me to see this young woman because it involved a physical examination, which he wasn't able to do. This is a 22-year-old young woman, she's been married, she has a two-year-old son, and she's in for genetic counselling with her father. And I wondered, you know, why is she coming in now, if she was worried two years ago? Well, it turns out in the interval her father had come down with the 'family disease' and she said, 'Well, this goes back for ten generations.' I said 'So what do they call it?' and she said 'Joseph's disease.' I went over and plucked out "J" for "Joseph" and thought, 'Oh that's autosomal dominant, I can tell you what's going on,' 'Thanks,' end of the story. But I thought I'd just see if the people in the Foundation knew this family in Canada. 'Oh yes, we know this family, the extended families are large Portuguese families, and how would you like to be on our Medical Advisory Board?' Like on one patient! 'Okay, I'll be on your

Medical Advisory Board.' So that's fine, I never saw another patient. Another year went by and I got a phone call from the Foundation, 'We're having a meeting in Lisbon and we want you to come and participate in the meeting, talk about your research.' 'I don't do research in this area at all, I can't go to Lisbon and take your money for that. The next thing I know I get a call from Roger Rosenberg, the neurologist, who is now the President of the American Academy of Neurology. We chatted a bit and he convinced me that I really should come as a medical geneticist, because there aren't too many involved, and just sit and listen and make notes, and at the end of the three days, wrap up seminar. So I said, 'Sure, I can do that,' and off I went. Well, before I left I went to another meeting, and on the train I was reading the issue of the *American Journal of Medical Genetics*, when they were publishing the first article on RFLPs. And I read this and I said, 'Isn't that interesting?' and just filed it away. Got to Lisbon and said, after the three days, 'You've got 200 three-generation families perfect for linkage analysis, I think you should seriously go after doing this gene.' And they thought it was a great idea, and we wrote it up, and that was the end of the story.

TT: How did that connection, that interest, develop?

PM: About a year later I got a call from the Foundation saying, 'We want you to map the gene.' And I said, 'Look, I don't have the lab, I'm a clinician. I can't possibly do this.' Fine. So then at this annual meeting of our Canadian College of Medical Geneticists, I was on a committee to look at manpower requirements across Canada, interviewing all the programme heads, and one of the programme heads in Kingston, Ontario, was recruiting. But she was the only person in Canada doing linkage analysis with RFLPs. In fact, she was one of the only few basic scientists in the whole country who actually was doing gene mapping with red cell enzymes, and serum proteins. Well, one thing led to another, and I came home one day and said, 'Muriel, there's an opportunity for me in Queens,' and we had four young kids, and off we went to learn linkage analysis. That's fine. The nice thing about it was I could drive down from Kingston Ontario through upstate New York to the outskirts of Boston to New Bedford, Massachusetts, where these large collections of Portuguese families who had come to the States in the fifties, because of the opening of the immigration requirements opportunity, and that was you know a great opportunity.

I'm getting ahead of myself. At that Lisbon meeting we realised that the Eastern seaboard was collecting families, and their patriarch was Machado, and our patriarch was Antone Joseph. And they were cousins. So suddenly all these pedigrees clicked, okay? And that's what made me say, 'You know, we should do this.' It turns out to be a founder mutation in the Azorean population, and mass migration to the States had occurred. So going to New England was an obvious thing to do. So we could leave on Friday afternoon with a graduate student, drive down, have dinner, next day in clinic with the local neurologist, collect pedigrees and DNA samples, and bring them home to Queens. And that went swimmingly well for a while, but the politics of that early period of time in DNA mapping put the clinicians and the basic scientists on opposite sides of the equation. The basic scientists said, 'This is DNA, this is our knowledge. Now, we'll share it with you, but we're running the show.' Well, they didn't realise that's not how it works. And so one thing led to another, and there was a friction/fraction/dissolution, along with all my samples disappeared.

So I went through the process: Division Head, Department Head, Dean's Office, Vice-President of Research, and got absolutely nowhere with them; that was a great disappointment to me. So I had to start all over again. So away we went again, and this taught me a lesson about the legal aspects of these things, because although we had consent from a lawyer's point of view, possession is nine tenths of the law. And they were reluctant to initiate anything that would bring anything down on the University from there. Now, I would have gone to the Dean and stopped there and gone to a lawyer, and for $200 I would have had a legal letter which would have changed things. But things happen for a reason. So we started all over again, and at one of these meetings in New England I met a fellow who was working with the group in Boston on Huntington's Disease and he said, 'Well, there's this fellow, Guy Rouleau, who is a neurologist doing a PhD with us, and you should go and talk to him.'

So I did, and he was going to go back to Montreal so we began a collaboration. So all the samples were dropped off in Boston then and he went to Montreal, and he started this Institute for this group in Montreal, and away it went. And we had young people from Portugal and Brazil coming to his lab to learn this new-fangled thing of genetic analysis and he grew a great, big programme, which was great. Eventually the gene was mapped, although we didn't do it, the Japanese did it by searching through for just repeats. They found a repeat and then a disease – bing, bang, boom – solved. We published all our data which confirmed that.

TT: How did that work develop?

PM: There was an opportunity to go back home to Victoria this time because the lab was without a Director and there was nobody there, and this is perfect for me because I wanted to build something. And so off we went. I would commute to Vancouver for clinics and I persuaded the molecular lab there to set up testing for SCA3, as it was called then, and that included SCA1 and eventually SCA2. My colleagues who were involved in all of this were initially Jorge Sequeiros who was training with Victor McKusick and his team in Baltimore, at Hopkins, and he would come to these clinics and that's how we got to know one another, and we collaborated on a number of issues. And we involved some other people. One of them was Marie Boutté, who was a medical anthropologist and she had done some nursing in Brazil, and was fluent in Portuguese. So she came to see what we were doing in these clinics, and one thing led to another, and she decided to do her PhD in anthropology, on stigma about genetic disease. This was the first large-scale study of what it means to be from 'the family' of the afflicted. It was really seminal work that she did.

Jorge Sequeiros goes to Porto to start his Institute and five years later, 10 years later, I guess, we had a series of five yearly workshops on Machado Joseph disease. And at that meeting was a young PhD-candidate who had come from Cuba to do her genetic counselling PhD in Porto. And we were chatting and she said, 'You know, we have this meeting in Cuba on ataxia, you should come.' And I said, 'What do I need to do?' She said, 'You need to submit an abstract.' And this is where providence comes into the telling of these stories. I came home from that meeting and the first patient I saw on Monday morning has SCA2. Well, what sign do you need to go to Cuba? So off I went and we presented, and that was fine, and I thought it would be in and out, goodbye. One of the students approached me and started e-mailing, and one thing led to another, and now 10 years later and 20 visits to Cuba, we've been very much involved in helping them set up pre-symptomatic and diagnostic testing for hereditary ataxias. And the latest thing that should be on that list of good things was a young MD there who wanted to do her PhD, and so she selected this large cohort of Cuban families, the paediatric cases. And she just recently published successfully her PhD Thesis on paediatric onset Friedreich's ataxia. And so our efforts were winding down, just nicely winding down when the lab tells me, 'We went through this and we found nine families who have SCA3.' So this thing keeps going on and on and on and on. So when I give this talk to the students I say, you know, 'Early on in your career, get a disease and stick with

it, and see the world.' And here I am at 75, enthusiastic about working part-time, and I was in Cuba in November again, so I would really encourage young people, there's a wonderful career path outside of the lab.

TT: Were there any notable disappointments in your career, Patrick?

PM: When I was commuting between Vancouver and Victoria once every three months to provide some clinical supervision there. And the Department Head, new Department Head, didn't want to have anything to do with any other programme in the province, and so it was either I stop doing that, or leave. And so one day I got this idea in my mind, 'Jeez, I'm going to have to leave Vancouver. That's heresy, nobody leaves Vancouver.' And that led to the snowball effect of recruiting in Kingston, and it just fell into place, effortlessly fell into place. And when those things fall into place like that, I mean you're on the right road, so I just go with the flow. So the two people that really, three people that really I had issues with were the Department Head and then my biology colleagues, who thought DNA was their thing. And this is in the very early days and eventually things fell apart for them. So those are two big setbacks or disappointments, both of which I've been able to get around.

TT: Is there anything particularly special about Canada in terms of medical genetics, because of immigration or because of the longstanding families. I'm thinking here of Jane Green's work up in Newfoundland of very old families, quite isolated families.

PM: Jane Green was my lab partner in UBC Zoology.

TT: Was she really?

PM: We're old friends. She went off and married a marine biologist from UBC and he went to St John's and she had her family. Meanwhile I went to Medical School, one thing or another happened, I caught up with Jane many years later. She was in Newfoundland, it's a fascinating, part of the colorectal cancer story.

TT: We know her from our Witness Seminar on cancer genetics, which focused on polyposis.

PM: And her contribution has been recognised. She won the Founders Award for the Canadian College of Medical Geneticists just recently at our insistence. The National Research Council, or the CIHR, Canadian Institutes of Health Research, gave her a one year stipend to travel back home just go give seminars at these outreach hospitals. But you probably don't know that story very much. She

has her children and they're out the door, she has a bit of an empty nest during the day, what am I going to do, sort of thing. So she wanders around the hospital and she sees this sign about rounds this week, and an ophthalmologist's giving a talk on some aspect of some form of retinitis pigmentosa, hereditary thing, so she went and listened and said, 'Oh, that's pretty interesting,' introduced herself to him, and Pryse-Phillips was his name, and they started to work together. And he had the responsibility for making sure that the blind individuals who were getting Canadian National Institute for the Blind pensions, were actually getting the money. So they had a boat that pulled into all these little outposts, you know. Jane went along with him and started collecting family histories and one thing led to another and her pedigrees and her pedigrees and pedigrees. And then, while she's there in these remote places, there's something it's not an eye thing, it's a cancer thing. Caboom! Just at the right time when we, we being the collective, wanted to map the genes for breast and colon cancers, she had these large well-developed pedigrees. So she rocketed up through that, but she's such a quiet, unassuming person – not the kind of person that goes to meetings and makes a big name. Dragged up to the podium sometimes.

TT: She was lovely. She brought us a copy of her PhD.

PM: She's a great friend of mine. And then my mentor, Clarke Fraser, when he retired from McGill, went and took over the programme at St John's, and encouraged her to get her PhD. Which was great. Just, just wonderful. When Clarke died, I asked his wife if she had a copy of it, because I would love to have a copy of Jane's Thesis, just as sentimental value.

TT: Now coming back to the idea of professionalization of medical genetics, there are a number of factors associated with professionalization like accreditation, recognition, societies, and journals. What about societies? Here you are, we are talking at a European Society meeting. I hadn't expected to find a Canadian here.

PM: Oh, there's a secret to that. For 25 years I've been going to the American Society meetings and they're in interesting places like Philadelphia. But four times in Philadelphia is enough already. I was bemoaning this to somebody one day about, 'Oh, not in Philadelphia again.' Wherever it was. And they said, 'Well, you know, you should look into the European Society meetings.' So I looked this up and gee, they're going to have this meeting in Prague. Yes! So

off I went to Prague. And next year off we went to Amsterdam. It's a smaller meeting, it has these neat, much more interpersonal mixers. At the last count the American Society was 7,500 participants. So I much prefer these meetings.

TT: Tell me about the American Society for Human Genetics.

PM: It spun off from the American Eugenics Society and I think it was 1950 that they changed the name. And I was just thinking about this, you know, every year they have several awards. There's the Allan award, which is the most prestigious and the winner's picture and their talk is published in the journal, but I don't think they're ever recorded a video recording of the presentation. Too bad. And I thought the same about the Canadian College of Medical Genetics Founder Award, there's lots of pictures and things, but I don't think the remarks are recorded. So Jane and I are going to change that.

TT: What do you consider your major professional society?

PM: The College of Medical Geneticists. The Royal College hasn't really sponsored anything particularly along that way, because we're a small number of people, you know. There's 100 Royal College people – we're sort of lost. The Canadian College meetings are well attended and they are well supported through donors and have really good science. Every second year they meet conjointly with the Canadian Association of Genetic Counsellors, so they have a big dual meeting, which is a proper way to do it.

TT: How big is their membership? The genetic counsellors?

PM: I should know off the top of my head, I'm going to say probably 150.

TT: And what about publications, Patrick? What main journals are we talking about, *JAMA*?

PM: I think most of my colleagues in clinical genetics try and get into the journal *Clinical Genetics* or the *American Journal of Medical Genetics*. Lab stuff goes into the high-end stuff like *Cell* and *Nature Genetics*. But those are the main clinically-oriented journals that we participate in. I haven't had any trouble getting published in the *Canadian Medical Association Journal*, because it's got a broad readership, particularly for someone with an interest in genetics. In fact Alasdair Hunter, my cohort from Ottawa, has published a series called *How to…* for physicians, for family doctors. A lot of Canadians will go to the American Society meetings, because it's the most prestigious, and particularly

for the training programmes you want to get your abstract into that. The Society for the Inborn Errors of Metabolism has probably six or 10 Canadians who participate in that.

TT: You really are a very small group, aren't you?

PM: Yes, but we have clinics in St John's, in Halifax, Quebec City, Montreal, Chicoutimi, Winnipeg, Edmonton, Calgary, Vancouver and Victoria. We cover the whole country in that sense, but there are long distances between. But that's how we try and maximise our outreach abilities and outreach is talking to someone about how the advent of telemedicine. It started because we used to have, for 14 years, the Hereditary Cancer Programme, and we went out of our way to educate the family doctors on the island about what constitutes a referral for hereditary cancer. We had educational pieces for them, and my genetic counsellor would come up to these outreach activities with me, pretty much exclusively to do the hereditary cancer piece. There were some autosomal, recessive things once in a while. Mine was all hands on, because these people had to be examined. And then, in their wisdom, the Cancer Agency decided 'Cancer control is our thing and we're going to move it all to Vancouver.' So they moved everything to Vancouver and now the new manager says, 'No, that wasn't a good idea, we'll move back.'

So with the advent of telehealth, I had done something for one of the IT people, I don't know what it was, but she seemed to think she owed me a favour and the favour came in the form of, 'We've got this extra telehealth suite we need to site somewhere. Would you like it?' yes I would, bring it on. So we have a conference room, a small conference room, and it has a big screen and the health authority, because it's such a remote population, has orchestrated 232 telehealth sites, and booking is child's play and you get up the index and hit the button, and boom, you're ready to go. We do over 200 a year. And what's really interesting is to see the aboriginal community buy into this. Five per cent of the population is aboriginal, there's a large population of aboriginal communities on the island, and for all kinds of reasons, political and historical reasons, and they've really not gotten the healthcare they deserve. They've tried to generate their own health authorities within each reserve and things like that, but it struggles. For example one family lives seven hours away from Victoria; that involves six hours by car and one hour by boat to get to the mainland. And so they think nothing of sitting down in their local health clinic, and there's telehealth and us. It started primarily around the breast cancer stuff, because you don't have to see anybody, but it's more now to pre-symptomatic testing

for Huntington's. The initial assessments, the first couple of sessions, can easily be done by telehealth. Now physicians order up lab tests every day of the week and the bioethicists are not breathing down their necks about all the things that might go wrong. There's a formal article in *Nature* some 10 or 15 years ago talking about the ELSE, Ethical Legal and Social Issues component, the five percent of the Centre's budget. Somebody's done an economic analysis in the States that a minimally invasive ethics review costs $300,000. So you start counting the number of people and their hourly rate, okay, so a simple little thing costs $300,000.

TT: It's very interesting you talking about the aboriginals, because you know the Wellcome Trust, and the Burroughs Wellcome Company, all originated from Henry Wellcome. The very first thing he started supporting and the first book he ever supported publishing, was Mr Duncan who was the vicar in Metlakatla, up north of Vancouver Island.

PM: Let me say this on the aboriginals, they are getting involved. We're getting them to participate more and more and they're just so interesting. You have a young couple with a congenital malformation. We now learn from our ethicist, an anthropologist, at the University, the importance of bringing the elders to the meeting. Fine, that's great. So we bring the elders in and talk to them first and say, 'This is what we're talking about.' And this is a young lady who has a baby with spina bifida, prenatally detected by a maternal serum screen. And it's a real push among the aboriginal communities to have lots of babies. So things like marriage is not necessarily a requirement, so there's a real push to have the next generation explode. So she's going to have a termination of pregnancy, that's fine. She goes back to her remote part of the island and a week later the public health nurse calls me up. She says, 'I want to congratulate you guys on what a wonderful job you do, but there's a little sidebar here that you should be aware of. The local word out here is that we're trying to address this teenage pregnancy issue by providing Depo-Provera, and the word is out that Depo-Provera causes spina bifida.'

TT: Unexpected consequence you have to deal with.

PM: If you want to do research in Canada with federal money you have to jump through so many hoops now to get approvals and things. Now there's an interesting story for some of this and that takes me back to my early days in Vancouver where they recruited a population geneticist from New Zealand, and he had been working in the high planes of the Amazon with Jim Neo, a physician,

looking at the Yanomami Indian community, which was so isolated from the rest of the planet, so their DNA would be pristine. They were comparing that to the bloods they got from Hiroshima survivors to see the impact of genetic mutations. They came to UBC and among the aboriginal community there's this chronic problem of cold-induced arthritis, and arthralgias, and they decided to map the gene for this. They had great cooperation with rheumatologists and with the public health officers and with the native communities and rounded up a whole bunch of these families, and got all this DNA stuff. They then decamped to Utah because there were much bigger resources in the human genome group in Utah, and took all their samples. Then publications began to appear on the origins of the aboriginal community of British Columbia based on mitochondrial DNA. Now, the community hadn't approved that at all. They were in to find out why they got this terribly arthritis gene. So shortly after arriving on Vancouver Island, I got a call by one of the medical officers of health, telling me about this problem and could I help move this ahead? So I said, 'I don't know much about it, but I'll certainly try.' I called the rheumatologist. He just tore a strip off of me and slammed the phone down. He was so angry. I let the thing cool off a bit and I phoned him back and said, 'Wait, I'm innocent here. I had nothing to do with this.' So he listened and talked to me about the problem, he'd done all this work and the pedigrees and the DNA had disappeared, and he was just left holding the bag. Well, justice comes in the form of a pub. That medical officer of health is in a pub in London on BBC2 news, interviewing the new Professor of Biological Anthropology at Oxford, who is our chap from British Columbia. Gotcha! So they tracked him down and it made it into *Nature* about this idea of doing research with samples without consent.

TT: What date is this?

PM: Oh, this is four or five years ago. So it's just, with this modern communication, you don't want to go too far into the public domain. Somebody will catch you.

TT: What do you think have been the major changes over your career?

PM: Well, thinking about the major changes over the last 40 years in my career, I arrived home in Vancouver in 1973 just after the first successful amniocentesis results were coming out. And so we started, it was a very long involvement with women who were at risk by virtue of age. As much as we tried to divest ourselves of this and give it to the obstetricians to do, the counselling fell upon us for advanced maternal age. But, eventually, that morphed into other things.

This is before we had what is now standard practice in the biochemistry lab; the ability to study various inherited diseases, lysosomal storage diseases, Tay-Sachs disease, those kinds of things. Now it's a routine matter. I witnessed the birth of genetic testing for Tay-Sachs disease in Montreal. We brought it back to British Columbia and screened the Jewish community with their assistance. Then it snowballed into more and more sophisticated cytogenetic techniques, more and more sophisticated biochemical genetic techniques, and then about 1985/86, this business of DNA for fragile X came about, in Kingston for some reason. I don't know the history there, but there was no end of families with fragile X, and I remember Stephanie Sherman, who is now in Honolulu, and Sherman's paradox about fragile X. She came to Kingston to review the files of my colleague there, Michael Partington, who had about 38 families. We were having lunch one day, and I chatted her up and I said, 'Have you ever seen a patient with fragile X?' And she hadn't. There she is, a PhD, basic science researcher, working at the cutting edge of fragile X who had never been in the same room as someone with fragile X in them. Well, as serendipity had it, I was seeing a family that afternoon, so Stephanie came with me and that was sort of a little thing for me with other PhDs who were so welded to the lab, who never got out and saw the patients. And I have witnessed the most profound change in their behaviour. So I'll give one example; in Montreal we did a project on this other syndrome, and there was a young PhD-candidate who was going to work on Rett syndrome. And she came and spent the day with me at the children's hospital; I'm not sure why I had a clinic there when I was travelling. And two weeks later, two months later I visited her lab and pictures all over the wall of these kids. You know she really hadn't understood what this was about, and did she get motivated then. So I insisted that anybody doing a PhD on a human disease got to spend some time with the family, at least one time. So Stephanie started that.

Then molecular genetics just became more and more. We were doing linkage analysis for Huntington's disease and this was in the mid-1980s. Michael Hayden had started this big institution in Vancouver and he had 17 sites across the country that were sending samples and linkage analysis and that became much more precise with actual gene testing. That then set up a really interesting dynamic. He had done such good work with his team in the whole concept of pre-symptomatic testing and guidelines and things you should follow, that he and I were approached by the BC [British Columbia] Cancer Agency then to do the same kind of protocol for testing for *BRCA1* and, eventually, *BRCA2*. So they really essentially took the Huntington's protocol and made it into *BRCA1*,

and away we went. So we had a real growth in pre-symptomatic testing for these cancer diseases. I witnessed the time when the potato blight theory was rampant for spina bifida; I heard something about that yesterday. Well, it wasn't the potatoes, it was the ink in the paper that the potato chips were wrapped in thing, and eventually the trials and tribulations that led to folic acid.

TT: Could you say something more about the spina bifida work, and some of your other work?

PM: I watched some of the interesting politics of that. As a group we petitioned Health Canada to support the introduction of folic acid into the prenatal thing, and that went on and on and on and on, back and forth, back and forth. Well, some little old lady might be pinching pennies and take prenatal vitamins to save money, as they are cheaper, and there's folic acid in her vitamin, and that suppresses the fact that she's got B_{12} deficiency and she'll get this terribly anaemia, and she'll get neuropathy. Well, supplement the pill with both. Finally, the Spina Bifida and Hydrocephalus Association of Canada called this, 'Enough already. Ladies, take folic acid.' Then in 1999 the American powers that be legislated that folic acid be mandatorily added to flours, cereals, food grains and things like that, but not in Canada. Oh no, we couldn't do that. And then one day, just like that, overnight there was a law passed and that was because of free trade. Prime Minister Mulroney had negotiated a free trade alliance with the United States, and we were sending massive amounts of wheat products into the States. And they said, 'Wait a minute! No folic acid, no trade.' That was fun to watch happen.

Then, with the decline in congenital malformations, came an increasing awareness of families' concerns about the genetics of behavioural issues, the autism, autism spectrum disorder type family, started to come to the genetics clinic. For one primary reason, that was for diagnosis, because with the diagnosis the school board would provide you with an aid. So they flooded in at the beginning just to get in the programme, and then of course with the advent of some of these newer genetic techniques, particularly the deployment of microarray testing, and all the different findings we were coming across. There's a wonderful website in this country called "Unique". I don't know if you know about it but if you just Google "Unique", there's a "Unique" chromosomal website. If you go on there and click the right button, up comes a listing of all these different chromosomal deletions and all the syndromology, and these

wonderful seven, eight page reviews for parents. And this is written by parents for parents, but it's vetted by medical authorities. This is a wonderful source, you can put that out.

I've actually had much more success using microarrays with adults, which is problematic because I work in a children's hospital, so I get 'this is not an adult hospital, it's a children's hospital', but we'll sneak them around. Everybody is right now juggling until the Government decides they are going to fund microarrays. So I snuck a few things in. Primarily in my neuro-genetics thing, which is probably 75% of what I do now. And finding some really interesting things, that takes me back to the ataxia story. After seeing many patients with ataxia, my reputation is 'I'm an ataxia guy.' I was consulted by a physician, who's now retired, moved to Victoria concerned about his family history, not so much for himself, but for his daughter who is in her forties and has schizophrenia. And he wants to know if they need to make provisions for her. And that taught me a second or third thing, I've lost track of how many: the neurologists take a neurological family history, medical geneticists take a genetic family history. So when you take a genetic family history you learn all kinds of things about these other non-neurological phenotypes, and this was not a family history typical of schizophrenia, and it was not a family history for typical ataxia, so let's do an array. Bingo! He has a deletion on chromosome 3, he has spinocerebellar ataxia type 15, probably the first person in Canada to be diagnosed as SCA15.

TT: And are you doing exome sequencing?

PM: Now we're on the verge of having access to exome sequencing – and still in British Columbia it's considered a research priority – but there are ways that you can persuade the provincial insurance people to allow us to send a sample to one of the American labs for exome sequencing. And we're making all kinds of diagnoses now, which takes me into the future, which I'll talk about in a minute. But the most recent thing, to bring the spina bifida, the prenatal diagnosis to its origins, I was just looking at television last night about this country's decision to have a pilot study of non-invasive prenatal diagnosis. So that's been available to us for a year now, a year and a half in Canada. You have to pay for it, it's about $800 which is roughly €400 and £400, but the population that's asking for that are primarily couples who have gone through a great deal of effort to become pregnant, because of infertility issues. They spend $20,000 becoming pregnant, they're 40 years of age, they're at risk for chromosomal abnormality, the last thing they want to do is an invasive amniocentesis, and so they're happy to pay that kind of money.

The people in Vancouver who run the provincial prenatal screening programme have signaled that they're going to persuade the Government to swap out ultrasound and maternal serum screening and all of that, in favour of non-invasive prenatal diagnosis, because then we won't be doing amnios, we won't have the lab culture costs, so we're in that kind of transition.

TT: And what would you like to see happen in the future?

PM: Well, the future's here. It very much is here. Here's an interesting story of two young women that I knew in their pre-teen years with some terrible neurological disorder that none of us could figure out. I did all the biochemical genetics I could do at the time. They became young adults, they exited the paediatric system, and they didn't come back. These two girls have a mother and a father. This mother has a cousin and she's married. And they have a child who is three. And dad thinks that she has what they have. He approaches the medical genetics people and they say, 'She's got something, but the only way to answer that is to do exome sequencing.' So he gets on the blower, he gets hold of GeneDX, 5,000 Canadian dollars, bang! Diagnosis. And it's treatable. It's an inborn error of vitamin B2 metabolism, which is treatable. So the three-year-old, is now on treatment and improving. We're about to start treating the older two. Similar stories are now appearing frequently in the *New Yorker* magazine about families who have done the same. Or they see a geneticist who calls them up three or four years later saying, 'I've got this experimental thing called exome sequencing. Do you want to participate?' Bang! Diagnosis.

So much so that the last American Society of Medical Genetics, meeting was in March in Utah, there was a whole half day on exome sequencing for newborns. So that's the future and that is coming. And then finally getting back to my interest in neuro-genetics from these repeat diseases, because any autosomal dominant disorder that has a neuro-genetic phenotype, is likely to be a repeat. We've heard about Huntington's, we've heard about fragile X, we've heard about Kennedy's disease, but there are several others. In Portugal there is a second disease called 'Portuguese amyloidosis', which is a point mutation rather than expansion. It misfolds the protein and accumulates in the liver, but also in the peripheral nerves, and it causes just a devastating peripheral neuropathy, a sensory neuropathy, so you're not aware that you've injured yourself and you get these terrible leg ulcers. And then you have to have a liver transplant. Well, this time last year back-to-back articles in the *New England Journal of Medicine* talked about the safety and efficacy of RNA interference to knock down that mutant allele.

Why that's so exciting is because it takes you off into the Alzheimer amyloid story, but also if you look at big pharma, they have done everything in their power to make a new statin for hypercholesterolaemia and they've bent the molecule seven days to Sunday and they can't, the patent's off. So they're looking for some other way to block that enzyme and they've very much heavily invested in RNA interference. So you're going to see Huntington's fall; clinical trials are underway now in North America using RNA interference. And when it goes a whole bunch of other diseases will go. And hopefully, I'll live long enough to see some of the things happen. But on a more sobering note, I was at a meeting a couple of weeks ago in Banff about these children with these lysosomal storage diseases. And there are 14 children in Canada with this one disease and they're all on enzyme replacement and as they get older they need more enzyme by weight, and some of these children are consuming $600,000 a year, that's £300,000 a year, for one patient. They're covered with some kind of orphan disease regulation, but how long can that last?

So I'm a bit concerned about the future, with health economists saying this is not a good use of money, etc. etc. I can see why somebody would make that argument. So I see that as a future problem. But on the other hand, being an Irishman with my optimism and all that, more and more people are going outside the medical system and spending money. I mean $5,000 is not a lot of money to get a treatable diagnosis on your child. Canadians spend a billion dollars a year outside of the country for personalized medical care. It can be anything from a knee replacement to a magnetic resonance imaging (MRI) scan to whatever. And the politicians are very frightened by that so we're seeing the slow, steady rise of two-tier medicine in Canada, where you can get an MRI 10 days from now for €400. That's not a lot of money. It's cheaper to get an MRI than fly to Toronto, for example. People fly to Toronto all the time, and don't think much about it. So if you've got some terrible thing and need MRI, that's what I see. So I see these pushing and pulling.

TT: That's all been most interesting, thank you so much Patrick.

Figure 7: Ms Kay Neale

Ms Kay Neale MSc SRN (b. 1946) qualified as a nurse at the Royal Free Hospital in 1967. 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, initially based in Colindale but moved to 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, at St Mark's; a post funded by the ICRF. She gained a Master's degree in 1985 in survey research methods and helped with the computerisation 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 localisation of the *APC* (adenomatous polyposis coli gene) and *MYH* (*MUTYH*-associated polyposis gene) genes. Latterly, she was the Manager of the Department of Inherited Intestinal Cancer Syndromes within the London North West Healthcare NHS Trust. She was a Founder Member of the Leeds Castle Polyposis Group (1985) that evolved into the International Society for Gastrointestinal Hereditary Tumours (2005), and remains the Honorary Administrative Secretary.

7 Neale, Kay*

Kay Neale: Before we start, can I just clarify why you've asked me because I personally can't understand why you would want to interview me. In your email, you said that you wanted to ask me about why am I doing my job, and my achievements; that sort of thing. Now, really, I'm quite a low level person in all of this, so a lot of my achievements, I think some have been achieved through me, because if I wasn't there to implement it, it wouldn't have happened but they wouldn't have happened with me alone, if you see what I mean. So I'd quite like to make sure that other people do get credit.

Tilli Tansey: This whole project is called "Makers of Modern Biomedicine", which includes the Witness Seminars like the one you contributed to, and we're doing lots of supplementary interviews with people who came to these meetings. The point of these, it's kind of like a Witness Seminar, getting behind the papers, behind what you read in papers, that sort of thing. You're real people, even if, as you say, you're only one cog in the whole thing.

KN: In the whole wheel, yes. Exactly, I can see that. The professors have all the great ideas but if somebody's not there to do the groundwork it doesn't happen.

TT: Sometimes it's not just the professors having great ideas. We're trying to get as many different voices as possible who've contributed. Thinking of your career and your contributions, particularly to the Polyposis Register; that's something I really want to know about.

KN: Well I made some notes because one of your questions is about my 'achievements?', but I haven't achieved anything. And I had to think really hard: what would I say is my main achievement? And, of course, once you start thinking about it you do, you know, I did come out with things and then I showed it to a friend of mine who worked with me in the Polyposis Registry for 10 years, and she said 'But Kay', she said 'What about all the lives you've

* Edited passages from the interview conducted by Professor Tilli Tansey, 18 May 2016, in the School of History, Queen Mary University of London. For more details, see 'Related resources' at the end of this volume.

saved?' I said 'Well I haven't saved any lives.' She said 'Well, if you didn't trace them, they would've got very sick, you know,' and so she kind of gave me some more thoughts.

TT: We all know science and medicine is not just all the Nobel Laureates, and all the Fellows of the Royal Society.

KN: Well, Dr Bussey – the man that I worked with for so long – he taught me an awful lot about polyposis, and how he started the Registry and how it was run. I never felt that his story was properly told, and it was nice to be able to give him some credit in the Witness Seminar and the blog piece you did. Because people do get lost over time, and so it's to record their contributions. Polyposis, well would it be where it is now without him doing what he did, which stimulated other people's interest?

TT: And it provided continuity because you have a long series of records that informs so much, and has been such a valuable resource. I just want to start with where you come from: did you, as a child, want to go into nursing? Did you want to go into a caring profession?

KN: No, not really, I don't think I was the sort of person that really had goals. My parents both left school early and went out to work. I was brought up with the view that if you work hard and you're honest, that's really all you need. I wasn't brought up with the idea that I should go to university because I don't think the money was there to send me to university. My older sister went to nursing and I think I probably felt quite suffocated at home, and so it was a wonderful opportunity to get away from Leamington Spa, where I was born. I went to school in Warwick; it was a new school and it was one of the post-war bulge years, so there were a lot of us, and the school was finding its feet, and I decided to leave. I became a cadet nurse, went to college one day a week, where I got some O Levels, and then went to the Royal Free Hospital as a student nurse.

TT: What is a cadet nurse?

KN: It's when you're young; I was 16 to 17 and I did bed making and bed baths and washed the bandages. I was responsible for keeping the linen cupboards tidy, I enjoyed that. It was in an eye hospital; we weren't allowed to work in sort of a mainstream general nursing. And I was quite frustrated, because they wouldn't allow me to do the things the student nurses and the staff nurses did, because I was very capable and very careful.

TT: So you went to the Royal Free; had your sister been to the Royal Free?

KN: My sister had been to the Royal Free so I went to the Royal Free. I lived in nurses' accommodation. I had some good friends and I enjoyed caring for people. When I qualified I became a staff nurse on the gynae ward, which I didn't enjoy so much. I then went to do six months midwifery, which I didn't enjoy. I enjoyed delivering babies but I didn't enjoy being so much with the women who were very hormonal. I always enjoyed surgical nursing much more than the psychological side of things: treat them, get them well, send them home happy, rather than long-term things where people need a lot of psychological support – this was in the Whittington hospital in Highgate.

From there, I became a private nurse. I wasn't sure what I wanted to do and it would give me an opportunity to experience different things. I joined an agency and various hospitals or private people would contact the agency and they'd send the person they thought was suitable. I went sometimes to people's home to look after elderly or sick people. One of the places I enjoyed going to most was King Edward VII's hospital, just off Marylebone Road. I liked being there, it was a good atmosphere and good care. My job there was mainly what we called 'specialing', which is being with people after surgery so the ward nurses could get on with the general duties, and my job was to sit with one person and do whatever was necessary after surgery. Of course, in those days it was before intensive care units.

TT: It could be traumatic in lots of ways, could be quite demanding?

KN: It could be quite demanding but you knew your job so you got on with it. Doing that sort of thing for a short period of time is ok but it does become boring.

TT: You're a student midwife, you're doing some private nursing, and then what?

KN: I became a District Nurse full-time with Islington Borough Council and then the idea of having nurses attached to a GP group practice came in, and I was attached to Dr Rosen's practice in Balls Pond Road. We had a close liaison; they knew how much to trust me or how much to take my word for things so it relieved them. And I also started up a clinic – I think this happens everywhere now, that doctor surgeries have nurses who run their clinics in the practice, and I did hundreds of ear syringings, and I did minor dressings. I would hold a clinic one or two nights a week.

TT: One or two nights?

KN: Yes, it would be in the evening. I would do my daytime work and then have an evening clinic for people after work to come and have their dressings changed or their ears syringed. I was always eager to help, and I think that was what my parents gave me, the understanding that you get on and do your job, and I never felt that I had to work 9:00 to 17:00 and clock off; I would just carry on until I was finished.

TT: But you didn't stay in that for very long?

KN: No, I became ill and I found that the physical side of nursing was too much, but at the same time I met someone I thought I was going to marry. I didn't in fact marry him, but neither of us had much money; I started as a barmaid in the evenings to save some money to get married. It was there that I met a man that ran a driving school and he said to me 'It's ridiculous, why are you working in a pub, why don't you become a driving instructor, you'll earn lots more money.' I thought that was a wonderful idea, and I learned how to instruct, passed my test, and then I worked with them for a while: evenings and every other weekend because district nursing was every other Saturday. And then I left district nursing and worked at the Italian Hospital as a private nurse. I think I was looking for something that I was interested in, and I decided to start looking for another part-time job to go alongside the driving instructing, which I did enjoy.

From the Italian Hospital, I must have seen the advertisement from Eve Bendall. Now Eve Bendall was a wonderful woman: she was a nurse and she was doing a PhD, and she was interested in finding out whether nurses who are good at exams are not necessarily the nurses who do the good work on the wards. She employed three of us part-time, and we would go to a hospital and we would be given a ward and certain nurses to watch. We had clipboards and we had to watch for certain actions, simple things such as 'Does she look at and shake down the thermometer before she puts it into the patient's mouth?' And she then gave the nurses the written test and a psychological profile, and at the end of the day she proved that actually the good nurses are not so good at writing down what they do. It's a practical profession really, but I have to say now that I work with nurses that are very well qualified and very specialised. I'm impressed at their knowledge and their professionalism; I think nursing has changed enormously.

TT: Did you get a flavour, or an interest, in research from that experience?

KN: Well it was a short-term job. I was carrying on the driving instruction. Because I needed to earn a full-time salary. Then, I think, I saw an advertisement for a research nurse working with Dr Michael Hill at the Public Health Laboratory Service, Colindale, at a laboratory called the Bacterial Metabolism Research Laboratory (BMRL), and for some reason they had to move out. He was offered laboratory facilities at Porton Down, and a lot of the staff went with him. He collaborated with St Mark's Hospital.

TT: What did he do?

KN: He was a biochemist and bacteriologist, he was interested in what goes on inside the gut, and one of the things he discovered was that patients with polyposis don't degrade their bile. My job was collecting stool samples in clinic, because in those days, and again it's different now, every patient who came to clinic had a sigmoidoscopy, with a stainless steel rigid sigmoidoscope. So once the doctor had finished examining the rectum I would be standing waiting with my little pot that had a spoon on the lid, and I would manage to catch a little bit of poo, and then the samples would be labelled and put into a freezer. And I would also collect the basic information about the patient, and what was wrong with them, and over time I was continuing to update the information – so he was looking at patients with colitis; patients who had had cancer previously; patients with polyposis. If a patient with colitis developed cancer, which some of the long-term colitics did, that was of great interest because he could then match it up to his laboratory findings. So it was quite a basic job but I found that I really enjoyed collecting the data. He allowed me to develop my own record system and labelling system, and every Friday afternoon I would drive to Porton Down with my specimens and talk to the guys in the lab, deliver my stuff, and he would take me for a meal in a local pub, and then I would drive home. We got on very well, he got on well with everybody; he was really amiable.

TT: Can you pick out what it was you enjoyed about it, because it seems very different from when you were doing your private nursing?

KN: I enjoyed patient involvement, because I had to meet the patients in the clinic, I would talk to the patients who were waiting to be seen, and a lot of St Mark's patients are regulars: the patients with colitis, with polyposis, you see the same people coming back over and over again. Crohn's disease patients come back regularly. So over the years I got to know a lot of them. But in particular I got to know Dr Bussey who ran the Polyposis Registry, who was

a great teacher and loved explaining his work. In those days he wasn't really involved in the clinics in the way that we as the Registry team became involved in the clinics later, but I wasn't working with him – I was only at St Mark's doing a different job, I was only collecting samples from different polyposis patients so I would talk to them. He had explained to me the importance of screening for the children, and I would be talking to patients and asking them about their children, and I would advise them to bring their children to clinic. So it was in the days before contracts, before you had to get a GP referral. In many ways for the patients with polyposis, it made life easier because it's very difficult for parents to suggest to a 14-year-old – that's the age we started – to come to clinic to have their bottom examined. The Registry staff chose 14, because they thought it was an age at which children would obey their parents, and the idea of the medical staff was to be very welcoming to the children, and although they would have a sigmoidoscopy, if they agreed, it would be very limited so it would prove to them that it didn't hurt – it might be a bit embarrassing, but it was worth it if it was going to save your life. So I understood all that before I worked in the Registry. Because of my involvement, I would leave little notes on Dr Bussey's desk, you know 'Saw Mr So and So in clinic today, he's promised to bring his children next time'; that kind of thing. The Registry team got to know me, and the doctor who was in charge of the Registry at the time was Dr Basil Morson, he was the consultant pathologist, and he had apparently said to Dr Bussey that at some point Dr Bussey would go under a bus, because he was beginning to get older, and that he really ought to find somebody to work with him. He worked at the time with a lady called Dr Sheila Ritchie, who was amazing, and taught me a huge amount about what I eventually got to learn about polyposis, but she was a volunteer, she worked free of charge, she just had her petrol costs refunded to her. And I think in Dr Morson's mind, they needed somebody permanently salaried to know where everything was. He used to say 'I think it's all in Dr Bussey's head,' well, of course, it wasn't, it was all documented meticulously on a card system, no computers at that time. So I was offered that job.

TT: The job was to be the boss's apprentice, so ideally you were going to take over?

KN: An assistant. Well not really: at that point they didn't say to me that I would take over. I think I've missed out the fact that when I was working with Michael Hill I was also working with Ian Todd, and I'd given up the driving instruction. With Ian Todd, that job involved designing a questionnaire, which I could take

to people's homes to interview them about what it was like living with a stoma. It was huge because it covered not only questions about living with a stoma but how do you cope in your normal life. We had a section for housewives, for people who were working, people who were sick and disabled, and for students, so it was quite a thick book. Every time we made alterations, I typed it all up on a little portable typewriter, and I would have to retype however many pages came after the addition. The aim was to interview 100 people with a colostomy, and 100 people with an ileostomy so I had to do 200 questionnaires. Of course, there were boxes of these things because they were so big, so I was getting help from all over the place; then I went out and interviewed people at home. That was a really, really fascinating job.

TT: How was this work being funded?

KN: Cancer Research Campaign who paid my salary was also funding Mike Hill. The Ian Todd work was funded by voluntary contributions from stoma care companies, appliance companies.

TT: So then you become what I call Dr Bussey's apprentice?

KN: Yes, when I was doing the stoma care I got introduced to Richard Barron who was involved in a new masters/diploma course at City University called Survey Research Methods. And he advised me to do the course as a diploma student, but I came top of the first exam which was Questionnaire Design, which I knew very well how to do! A request went forward for me to transfer to the master's course, which was approved, and so that's how I got onto the degree course. I got that in 1985 after I'd started working with the Registry, so when I started working in the Registry, they agreed to give me one day a week to go to college.

TT: When you started working with Dr Bussey, what exactly were you doing?

KN: I knew Dr Bussey, I knew Sheila Ritchie, when I started working with them I had a desk, face to face with Dr Ritchie and she kept saying 'I don't know why you're here, Kay.' So it wasn't a very happy start, but she really taught me the systems. Dr Bussey was already fairly elderly. He taught me a lot about polyposis; I would spend the working day with Dr Ritchie and the mealtimes we would have the three of us together, and Dr Bussey would talk about polyposis and polyposis patients, and stories about patients. And sometimes we would feel 'Gosh, can't we talk about something else,' but when Dr Bussey was no longer there, I realised how valuable it was, because it is the personal stories that

imprint the knowledge on your brain. If somebody just lectures you on facts it's hard to retain them, but having the personal stories about the patients, we would see the patients in clinics and he would tell us the whole family history. And it became imprinted. I was really helping Dr Ritchie with the paperwork.

TT: So these were all the record cards?

KN: Dr Bussey kept the cards; Dr Ritchie kept the family files. There had been a trial called the ascorbic acid trial. There was an American doctor, Professor, called Jerry DeCosse, who developed a theory that vitamin C would reduce the size of the polyps or make the polyps go away, the adenomas. All of this research was in adenomatous polyposis, not the other syndromes. He was convincing enough that they agreed to do a trial. St Mark's always was able to produce bigger numbers of patients for trials than any of the American centres because of the NHS. Patients would come to St Mark's and they could continue to come to St Mark's, because they got very special care and it was free. Whereas in America patients would tend to go to the cheapest doctor and therefore they didn't have the same call on patients that we had. So it was agreed that Professor DeCosse would come every three months to St Mark's, to examine a group of patients. So the patients were enrolled by Dr Bussey and Dr Ritchie and the idea was that they would all come during one week because the consultant's clinics were Monday morning, Monday afternoon, Wednesday morning, Thursday morning and Friday afternoon. So they would come on the same day that they would always come for their consultant, but they would come to a different location in the hospital for their examination. And Sheila Ritchie, a very clever lady, she realised that this was a really good system, having all the polyposis patients that were coming come during one week, because they met each other, and they chatted, and it became sort of a self-help group for them, and they would bring their children. It gave her the idea that she should put into place what became known as "polyposis weeks". So when the ascorbic acid trial finished, she and I would go into clinics during the polyposis weeks and we would then retrieve the information out of the patient notes as to how many polyps were seen and whether the patients had had any other illnesses, and what about other family members, whether there were any new babies, and what children were coming of age and needed to come into clinic next time. So that was our job and then we would come back to the Registry, and would write it all up by hand into the family files. So the record of each patient was stored in their own family file.

TT: And were you constructing pedigrees at the same time?

KN: Dr Bussey constructed the pedigrees by hand, yes. We would take the family history and draw it out as a rough diagram, and he would then draw the cards – tiny little writing. This was how I learned my job.

TT: When was this?

KN: I joined the Registry in 1984, and in 1985 St Mark's celebrated its sesquicentennial, doctors from all over the world came to a big meeting at the Barbican Centre. Ian Todd, he might even have been Sir Ian then, was the senior surgeon. He had a patient, a young girl, very pretty girl, a nurse with a very big desmoid tumour. Desmoid tumours are myofibroblasts – it's like fibrous tissue that grows, particularly in polyposis patients, in the abdomen. Maybe in the abdominal wall but very often they're intra-abdominal, rooted in the mesentery, so they're very, very difficult to remove without removing the small bowel, or some of the small bowel. And, at that time, doctors or surgeons were warned that if you did cut into them or biopsy them it tended to stimulate the growth, and the patients would look pregnant. The tumours were very painful, because they were pressing on the gut but within the tumour itself they would describe it like a burning pain. And Ian Todd was absolutely distraught that he couldn't help this girl. And these tumours were very rare; I mean polyposis is rare, or adenomatous polyposis, familial adenomatous polyposis (FAP), as it hadn't yet been named. It was about to be named – we called it adenomatous polyposis coli in those days. FAP is rare; the number of people getting a desmoid tumour is about 10% of those people, and only about 10% of those are the big ones, so very, very rare. Ian Todd decided that he would hold a polyposis meeting just after the 150th anniversary of St Mark's meeting because all the people around the world who had knowledge and specialised in polyposis would be at the Barbican meeting. With Sir Walter Bodmer from what became CRUK, they arranged to have a meeting at Leeds Castle, in Kent, it was quite limited, because there's only space for about 30 people to stay overnight at Leeds Castle. I was not invited, because I was very much the baby; I'd only been there a year, and Sheila Ritchie said to Ian Todd 'If you expect Kay to understand, really become involved in polyposis, she has to come to this important meeting.' By being at that meeting I met all the important people and I began to understand, through feedback from Sheila Ritchie and by seeing what happened at that meeting, I understood how knowledgeable the St Mark's team were compared to some of the people around the world who were so-called experts, and really didn't understand a lot about what the diseases were. Basil Morson, the St Mark's Consultant Pathologist, was at the meeting and there was a slide put

up by a leading professor and he said 'this is an adenoma', and Basil Morson banged on the table and said 'Mr Chairman, that is not an adenoma,' and he said 'Oh, I'm so sorry, my pathologist must have got muddled up,' and put up his next slide, 'This is an adenoma.' 'Mr Chairman, that is not an adenoma.' To somebody like me who's learning, it was an eye-opener that you have to be very careful about who you believe.

At that meeting, *APC* renamed FAP, because it's not only the colon that's affected. Dr Bussey was there, of course; all the important people were there. At that meeting, it was suggested that nobody else knew how to treat desmoid tumours, and it was decided that Sheila Ritchie and I would do a piece of research whereby we sent questionnaires to any hospital where we knew there was a registry, to collect information about how many patients they had in the different groups, like with desmoid tumours, upper gastrointestinal disease, and other cancers. When we got back we designed a series of questionnaires and we sent them out to the different hospitals, ready for the next meeting in Washington in 1987. Again, it was a limited group of people who were invited. The idea was to just have the experts invited; it wasn't meant to be a meeting to teach people, which is what it evolved into ultimately.

TT: Did this group have a name?

KN: So it became known as the Leeds Castle Polyposis Group (LCPG). It continues in a way. At the beginning it was mainly surgeons because it was mainly a surgical disease but by the early 1990s the gene that caused FAP had been discovered so a lot more geneticists began to be interested, and we were very seriously accused of being exclusive, and we realised that we had to open the meeting to anybody to come. And we encouraged people who had started new registers to come. We were only looking at that time at FAP. In the meantime, Lynch syndrome, hereditary non-polyposis colorectal cancer (HNPCC) had come onto the map, and another group started up, including Henry Lynch himself, called the International Collaborative Group on HNPCC. They were holding their meetings every year and the LCPG were holding their meetings every two years. We in the Polyposis Registry didn't go to the Lynch HNPCC meetings because at St Mark's we have two separate departments, because we have so many of these patients and they are managed in a completely different way, so we have a Family Cancer Clinic. So the people from the Family Cancer Clinic would go to the HNPCC meetings and we would go to the LCPG meetings. Gradually they merged and by 2005, when Professor John Burn held

the joint meeting, we formally evolved as InSiGHT, the International Society for Gastrointestinal Hereditary Tumours. I think as a society it does need to become more active, we do very little apart from our biennial meetings.

TT: Do patients get involved?

KN: Not at the moment, there's a suggestion to have a patients' session at the next meeting in Florence next year, in 2017, but how far they've got with that I don't know. I'm the Honorary Secretary, so I do the minutes and the agenda, I keep the membership database, send out the invoices, receive the money, manage the bank account, that sort of thing. I enjoy doing the organisational side, it's good.

TT: Can we go back a little, Kay, to when you are charged at the Leeds Castle meeting with doing the questionnaire, and you and Dr Ritchie write to other registries. How many other registries were there, and how did you find them?

KN: Dr Morson and Sir Ian knew people from around the world and we always had a good exchange programme, so there would always be somebody from a hospital somewhere around the world working to learn how St Mark's did the pathology. We only involved the people we knew, and hopefully now with our website, and the internet, more and more people will become involved. It does surprise me now when I see a paper written about a polyposis syndrome, and I see that they're not Members of InSiGHT: why would they not want to be? Maybe they don't know about it.

TT: Thinking back to 1987, it was a very different world then?

KN: It was a very different world but you know the people who were really interested would have been in touch, even after Dr Bussey died in 1993, people would come and talk to me and Sheila Ritchie, and the person I was working with, Judith Landgrebe, and they would say to us: 'We've learned more today than we've ever heard.' By 1993 I'd been working there for nearly 10 years, and I'd learned from Dr Bussey and Dr Ritchie, and from all the surgeons because we regularly attended the clinics, and from the patients because you learn a lot from your patients.

TT: Did Dr Bussey teach groups of students?

KN: He taught the post-grads. We run regular post-graduate courses at St Mark's, and as a young man he was in charge of the museum, of all the specimens, because he was an expert colorectal pathologist. Dr Bussey could draw you the

most wonderful diagrams, and he did draw all the diagrams for the cancers and any of the polyposis patients who got cancer, he would draw the lymphatic spread as well as he would take photos – he was the hospital photographer; he had a very interesting life.

TT: I was interested in whether his expertise was throughout the hospital, or whether he had a wider impact?

KN: He would lecture abroad if he was invited, he did become at the time one of only three honorary members of the American Society of Colorectal Surgeons. He taught people from all over; yes, all the pathologists that came to learn from Dr Morson would get a teaching session with Dr Bussey, and any Registrar or Clinical Research Fellow who wanted to do some research with cancer or polyposis.

TT: It sounds as if you had joined quite an exciting hub.

KN: When I first started at St Mark's with Michael Hill, I remember talking to him and I said 'Well I'll probably stay for a couple of years, I normally stay in a job for about two years,' thinking to myself by then I'll be bored. It was the first hospital that I'd worked in where I met doctors who seemed they had a genuine interest in finding out why people were ill, and why people weren't getting better. I had huge respect for them, and I enjoyed working with them, I enjoy doing a job that's worth doing, and I don't like wasting time, and at St Mark's I felt that I could contribute to things that were worthwhile.

TT: After Dr Bussey died you became the Registrar, the Manager?

KN: When I first joined the Registry nobody had any titles, and Dr Morson was the Head of Research, and the Registry existed and we just kind of worked together. Obviously I was the baby, and Dr Ritchie by this time was doing most of the hard work, and Dr Bussey was keeping his records from the information we gave him. Dr Morson realised that he was going to retire, and he said 'I've got to protect the Registry.' It had always been part of the wider Research Department. So he said, 'You need to become a formal Hospital Department and you need to have a Director,' and it was agreed that Mr James Thomson would be our director, and he said 'We must have headed paper, and we must have our names on it,' and so it was agreed and I think we designed it with the St Mark's lion and the Polyposis Registry, and our names went at the bottom.

We had to have titles, and Dr Ritchie said 'We register births, marriages and deaths, so I'll be the Registrar and Kay can be the Assistant Registrar,' which was a terrible title because people immediately thought that I was a doctor.

TT: Could you just say a little bit about your funding?

KN: It shifts enormously throughout the time. Once I became funded to work in the Registry, which was 1984, formally, in the Registry, I was funded by the ICRF, which then became CRUK. They continued to fund me until after St Mark's moved from City Rd to Northwick Park in 1995. Then at some point the CRUK decided they wouldn't have research workers within hospitals, and the research staff moved to other centres. I stayed in the Registry, and my contract was moved to Imperial College, but the funding was still from CRUK. Then, Imperial College decided to make me redundant, and that's a few years back, and so I took one month off, had a lovely month at home, and St Mark's in the meantime were negotiating to fund me through the NHS, so I went back to work funded by the NHS.

TT: Doing the same job?

KN: Doing exactly the same job, yes. I have a contract with the London Northwest Hospitals Trust and my title is "Manager of the Department of Inherited Intestinal Cancer Syndromes".

TT: How has your job changed over the years? It's now computerised?

KN: When I first worked with Sheila Ritchie, we would go to clinic during the polyposis weeks and would busily write down what the doctors had written in the notes onto our clip pads and we could come back to the office and write it all in the family files. When I started working with Judith, we decided that we would collect the notes from the clinic, bring them to the office and write directly from the notes. It was still the same job, talking to the patients, getting the family histories. The most important part of the job really for me was taking the family histories, and teaching the patients about their conditions, encouraging them to attend, ringing people up when they didn't attend. Cancer prevention has always been the main aim of the Registry, and Dr Dukes when he started the Registry said: 'Care of a polyposis patient means care of the whole family.' The collecting of data for research was very important but you could only do the research if you had the patients, so the patient care was vital. When we moved to Northwick Park things did change. The computer came in the late 1980s with Sheila Ritchie, and she helped to design what data should

be collected. But the truth of the matter is, Dr Bussey could find the answer quicker using his cards than we could because the computer kind of clicked over one patient at a time, very, very slowly, and we used to have little competitions, who could find things out first. He always used to beat us. But when we moved to Northwick Park we set about finding a company to give us a new computer system and a man to design a database for us. So the big change from those early days to now is the fact that we now have far more clinical responsibility from the days in the beginning where we weren't even allowed to sign our own letters. From that first NHS-funded nurse that helped me with family histories, we've now got two nurse practitioners; the nurse endoscopist; a paediatric nurse practitioner specialising in polyposis, and a nurse specialist taking the family histories. And we've got two administrators helping me. The database has changed because it doesn't just collect research, information, it keeps records of when people attended, when people are due to attend – we're forever running off lists, chasing people up, tracing people. When a baby is born we can make a note to say 'This baby is due to be examined in 12 years' time,' so each year we can pull up the people who are due that year, so it's changed in that way but we still keep the research data.

TT: Have you done retrospective digitisation for all your records?

KN: No. That's something we did talk about at one point. I think it is something that probably should be done because the paper records are quite vulnerable. So much research now is laboratory-based, and what the researchers want is information about the patients from whom they've got blood or tissue, and so the old information I don't think is used nearly as much as it used to be. So there's something that goes on that's much more, we need to learn much more about the way that the cells are working.

TT: In terms of achievements, could you reflect a little on that?

KN: I think the achievement really is that the Polyposis Registry, started by Dr Bussey in 1924, and almost stopped by the surgeons in the 1950s when they started to be able to take out the colon of patients with FAP, and they said 'Right, well, we've cured it.' The first colectomy with ileorectal anastomosis was 1948, and by 1958 Dr Dukes said 'You know, it's the perfect model of a disease that people can be saved from because you diagnose it in the pre-cancerous stage, and you treat it.' Dr Bussey carried on keeping the information on all the patients, and all of that formed a basis which I've continued to build on. I think the fact that I stayed there so long meant that there is continuation, people don't

stay in the same job so long any more. It has been a continual worry to me, I expected to retire when I was 65, and this year I'll be 70. I now have a team that I do believe is capable to run the Registry without me.

TT: What do you think the main contribution has been of the Polyposis Registry?

KN: Saving people from getting cancer, without a doubt. The average age of colorectal cancer in a person who carries a mutation in *APC*, which causes FAP, is 39. And by just doing a colectomy with ileorectal anastomosis we extend their life by 30 years. Without the Register, and the Registry, a lot of people wouldn't get traced in the first place. We spend hours and hours and hours trying to get hold of people, and now that we have access to the national database of patients registered with GPs we've started to write to the GPs when we can't actually get hold of the people themselves. Sheila Ritchie and I, of course, would try to get hold of people through other family members, and that carried on until fairly recently; that we would have to rely on family members, ask continually, 'Well, can you try to get your brother's address, tell him again that he needs to come' – you don't really know that they are telling their relatives. Some people are frightened that because they've got an inherited condition themselves, that if they tell their brothers and sisters that they're also at risk of the same condition then they're responsible for it, and parents don't want to tell their children that they might have inherited something from them. So if parents are refusing to bring the children for screening, we can write to the GP and we can write to the GPs particularly when the child becomes an adult, and say 'This person is at risk,' and then there has to come an end to our responsibility for chasing people, but it's a lot easier now that we've got the access to the GPs.

TT: Have you seen a change in patients' responses to you over your time, particularly with the Polyposis Register? Have there been changes in patients' expectations when they come into a clinical encounter: the information they have, their clinical expectations; I wonder if you've seen any shifts and changes?

KN: There have always been people who would do anything to help because they know their children and other relatives are at risk, so with regard to research projects they're only too keen to take part because they know they're going to help future generations. With regard to attending hospital, there have always been people who are poor attenders. There's been a shift in the way the hospitals deal with patients: if a patient fails to attend an endoscopy appointment, they are not sent another one, they're not sent a follow-up appointment. For patients

with a lifelong condition, and they're at risk of malignancy, it's not just that they might be frightened of what the examination shows so they back out at the last minute but when it's lifelong, there are going to be times when they forget, and I feel it's a bit mean to only give them one chance. But, of course, the NHS is suffering, it's hugely in debt and each endoscopy appointment, if it's missed, the hospital loses the money. So going back to the days when I worked with Sheila Ritchie, we could say 'Just bring your child in if you want to,' we're now at the stage where every single appointment is paid for and has to be funded by somebody; it's a different system. It's a good system in some ways, but it doesn't accommodate ordinary people with all the difficulties that one has in life. We had a system in the Department whereby we'd say 'If they missed one appointment, we will send them another,' but now we're not allowed to send them another endoscopy appointment, we have to send them a clinic appointment. If they miss that second appointment we send them a third clinic appointment with a letter saying: 'If you miss this one we're not sending any more, you need to get a new referral letter.' So we try our best but you can't go on and on and on. But it happened just recently that I was saying 'Well, you know, he's never missed, he's missed three now and we can't just keep sending him appointments,' and then discovered that he was in hospital very ill with something else. So people have good reasons to miss their appointments, and if you're very ill you're not thinking about the hospital appointment somewhere else that you ought to cancel.

The people themselves, yes I think people have more expectations. When I first started working at City Road, when I was collecting samples of faeces, although patients got very good care, the doctors really didn't expect to have long discussions with them, and the patients didn't expect to have long discussions. Now patients want long discussions, about what's wrong, what's likely to happen, and then sometimes people expect to come back and have the same discussion all over again. We'd say that is their right, and that's why the Registry, with the nursing staff, can accommodate quite a lot of that. Doctors working on their own don't have the time to accommodate long discussions. People are sick, people need to be seen, people want to be seen, and people want to talk about what's wrong with them. And that is different.

TT: Have you ever got very close to some of these patients, some of these families, because you were talking about Dr Bussey who obviously knew them all. What about your personal interactions with the people?

KN: I haven't worked in the clinic now for quite a long time but in the early days I knew the families very, very well. I remember Dr Bussey saying to me, 'Oh, I knew him when he was in his pushchair,' and I thought 'Gosh, I'll never be like that'. I came out of the hospital one day to go home and there was a lady standing there, 'Hello gal!' she'd say, 'Hello gal!' And she'd got this teenager with her, and she said 'This is Kay, you need to remember Kay, because if you're ever in trouble you just ring up and you ask for Kay.' I knew her very well, because I'd met her on lots of occasions, but I had no inkling that that was how she saw me. For her, I was a port of call, someone to call if she was in trouble, and that for her to pass that information on to her boys, that it was important for her to make sure that they also knew that this was the person to go to if they needed help, and if she wasn't around.

TT: How did that make you feel?

KN: It felt great, it felt great. It is nice, but then on the other side of it there are people that I knew very well who died young as a result of their disease, and that's very upsetting. Some of the most upsetting work I did was the stoma-care research actually, when I was interviewing people at home, because the interviews would take a couple of hours. I was in their own home, they'd make me tea or coffee, they would often give me a tour of the house. They would say 'Nobody's ever talked to us about it,' or 'Nobody's ever been interested.' They were incredibly grateful. But the people who had colostomies, of course they'd all had cancer, and I remember driving along one day and just feeling guilty because I smiled at something, because it was just, it was so depressing, and I hadn't thought about it being depressing actually. I was just doing my job, getting on with it, day by day. Of course I wasn't doing it with anybody, it was just me, and it's only since looking back on it I think how awful that is. Because it's wrong that you should do a job that makes you that depressed that you actually feel guilty about being happy.

TT: Actually going and talking to people, was that a therapeutic intervention?

KN: Therapeutic for them, yes. But with the people with polyposis, there are some absolutely tragic stories because there are some people who die young but then, on the other hand, there are the families, there's one particular family that comes to mind, where they inherited from one of the parents. There were four children, three of them that inherited the polyposis, the one that didn't get polyposis died young from a heart condition. And so there's always that question about prenatal testing, not that we would give any advice that you

should or shouldn't have it, we just tell people it's available, if they want. If they're interested in prenatal testing we always refer them to the geneticists, because we've never been trained to deal with that kind of counselling. We're trained to talk about polyposis, the meaning of polyposis. But prenatal testing, I do sometimes think to myself 'Well, polyposis can be awful, but choosing a foetus that hasn't got it, doesn't actually guarantee a healthy child' – and the thought that someone who's not perfect is in some way not valuable.

TT: I was just thinking about stopping there, Kay. Thank you so much for your time.

Figure 8: Professor Marcus Pembrey

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

8 Pembrey, Marcus*

Tilli Tansey: How and why did you become a clinical geneticist Marcus?

Marcus Pembrey: Well, as a medical student I didn't want to go straight from second MB into the wards and I persuaded eventually somebody to let me do a BSc where there was some genetics, because I'd always been sort of vaguely interested in genetics. And at the same time I discovered that I had β-thalassaemia trait, which is a bit unusual for an apparently endogenous English family and we were a big family. So I did a little research as a medical student on β-thalassaemia, and I got into that type of genetics. At that time one did a secondment as a clinical student and I went to Great Ormond Street Hospital to see how they did genetics there, with Cedric Carter, and we had Paul Polani who would do the occasional ward round, which were absolutely inspiring.

So, I suppose, after all those things, I ended up qualified and wondering whether to do paediatrics or clinical genetics. But there wasn't really much on the clinical genetics side then; there wasn't really a discipline. John Fraser Roberts had just come over from Great Ormond Street to Guy's Hospital, so I knew there were people doing what I regarded as clinical genetics. Anyway, it was actually quite straightforward: when I was a houseman I saw an advert for a job, SHO job in Liverpool with Cyril Clarke as one of those people doing clinical genetics. So I contacted Cyril Clarke because I had read his book and he said, 'No, no, don't come to that, don't apply for that job. Meet me at the College.' So I met him in the College (the Royal College of Physicians) and he said, 'Yes, oh well that's great, you want to become a medical geneticist,' he didn't use the words "clinical geneticist", and then he said, 'Get back in contact when you've got the Membership,' which since I'd only just qualified, was some time away.

But in fact, when I did get the Membership, in fact he rang me up. I got the news on a Saturday morning and by Saturday evening he rang me up and said, 'Come to Liverpool.' Because of the β-thalassaemia interest I linked up with Professor David Weatherall who was there, because I had this idea that if I switched on

* Edited passages from the interview conducted by Professor Tilli Tansey, 5 February 2016, in the School of History, Queen Mary University of London. For more details, see 'Related resources' at the end of this volume.

foetal haemoglobin – it wasn't my idea, I'd heard Professor Phaedon Fessas say it. But I was enamoured by the idea of switching on foetal haemoglobin and curing sickle cell disease and thalassaemia.

TT: Over your career, what do you think have been some of your most notable achievements?

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

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

TT: You also got involved with, associated with, ALSPAC right at the very beginning?

MP: Yes, and that's the other thing that I might call 'timely impact'; helping Jean Golding set up the ALSPAC study. When we first started in 1988, planning it and so on, well, Jean started planning before that, but I joined in 1988, and we were the first to build in from day one, genetics and cell lines. We were applying for cell lines but we didn't get those for another, I don't know, 10 years or so, but none the less we did eventually get the cell lines. The idea was to have living genomes. We had living cells in our cell lines, which we could use eventually, and that, I think, is gradually just beginning to show that you can use them for studies. But the other thing is that at the time there was a general feeling that case controls, often in adults, were by far the most efficient and we had Biobank and all those things, but I never bought that and nor did Jean. We always needed to have a developmental perspective, from conception onwards really. It has gradually come back into recognition that that is the approach. Epigenetics operates in terms of foetal plasticity and development and that, I think, has been the big change, a change in the right direction over my career, that we've gone from studying the 1958 cohort, but then it went into case studies. GWA studies are a good example of something which has had a lot of hype and is going to help a bit but only a bit, it's not the whole story at all.

TT: And what about your own personal research Marcus?

MP: In terms of my own research, when I went to Great Ormond Street in 1979, I decided to concentrate on non-Mendelian inheritance; that is monogenic but non-Mendelian. It was already quite clear that eventually we were going to get sorted with Mendelian disorders with gene mapping. For example, as I mentioned, we had the first link probe for haemophilia in 1984, and that approach was going to carry on, clearly. So I concentrated on non-Mendelian inheritance. The first was fragile X, which has a very strange inheritance, and I was the first to propose a premutation explaining the bizarre inheritance of fragile X in 1985.

Then, very quickly after that we were trying to work out the inheritance of Angelman syndrome, very soon after the fragile X side of things. Angelman was a syndrome that had not really been recognised in the States, people weren't quite sure what it was, whereas at Great Ormond Street we were very clear with the neurophysiology and everything else, of this as being a discreet syndrome with lack of speech and some learning difficulties and a jerky gait. But the inheritance

was very odd. Paul Polani thought it was a chromosomal thing. Anyway, to cut a long story short, we worked out the inheritance and it was due to a deletion on chromosome 15. But blow me down – it was the identical deletion to the Prader-Willi syndrome, a completely different syndrome. It was identical down the microscope, chromosome deletion, a deletion on chromosome 15.

So we had found this deletion on chromosome 15, but the problem was it was the identical deletion on chromosome 15 that we knew was the cause of Prader-Willi syndrome, an entirely different syndrome. We didn't know what to think of that. And Pat Jacobs, this would be around 1989, Pat Jacobs was established as the cytogeneticist in Salisbury and she had done a big survey of these minor deletions around, in chromosome 15, and the one that we thought was associated with Angelman's syndrome that overlapped with Prader-Willi, she said, 'Oh we've got one of those. It's part of normal variation.' Indeed, we looked at her survey and she said, 'Well, we've got a child as extreme as the syndrome that you're talking of.' So we went and saw the child, and it had Angelman's syndrome, so that really clinched it. So then how could you explain this? To cut a long story short, we soon worked out, together with the people working on Prader-Willi, that if the deletion was on the maternal chromosome the patient would have Angelman's syndrome; if the deletion was on the paternal chromosome they would have Prader-Willi syndrome. So that was the discovery of imprinting involving Angelman syndrome: genomic imprinting. Then we went into the diagnostics of it in the lab, in the DNA lab, and found that a methylation signal was the thing that you could use for telling whether a person was affected with this condition or not. That got me very much into epigenetics and that led on, to a speculation I raised in 1994, published in 1996, that perhaps imprinted genes might mediate transgenerational responses. By that I mean, exposures to the environment, experiences of the parent or the grandparent might actually change the setting of the imprinted genes and lead to consequences in subsequent generations.

TT: Is there anything that you felt went particularly wrong in your career?

MP: Things that went wrong? Misjudgements and so on in my career? Yes, I think there was an episode and it arose when I was in Liverpool doing my thesis on foetal haemoglobin; that would have been in, I was there from 1969 till 1971. Cyril Clarke was really adamant that at my stage I should definitely go back and do general medicine or paediatrics, or a general medical job and get accredited in medicine, and then do genetics. And a job came up at St Thomas'

Hospital and I went there as a Lecturer in General Medicine and it was dire, partly because St Thomas' Hospital hadn't moved into the current century, as it were, in terms of attitude towards all sorts of things.

One always gets good experience and I got a lot of medical experience, that's true, in the time I was there, but when David Weatherall contacted me and said, 'We're going to do this project in eastern Saudi Arabia to see if foetal haemoglobin is protecting against sickle cell disease there,' I jumped at the chance to leave. And that was end of 1971, something like that, and then I established a link with the Arabian American Oil Company, went out there and did a lot of research on this benign sickle cell disease in the Eastern Province. And although a lot of people said, 'Come on a minute, you're going to Saudi Arabia when you should be going to the States,' you know, to Victor McKusick's lab, various centres like that. Well, I was escaping from St Thomas' Hospital, and it really was very valuable in all sorts of ways. I was completely running my own research; nobody was telling me what to do. I was deciding how to do it. David Weatherall never came over; he didn't like flying at that time. We sorted it out and I learnt quite a bit of epidemiology too. And people were very helpful there. So that I think that stood me in good stead, as good a stead as going to the States, I suspect.

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

TT: What would you consider to have been the major changes over, say, the past thirty years or so, especially in diagnosis?

MP: The most important changes since I qualified in medicine? I qualified in 1966. At that time we basically had chromosome analysis really and beyond that there was relatively little we could do in terms of diagnosing various syndromes and so on. We relied heavily on the very good work that John Fraser Roberts at Great Ormond Street, and then Cedric Carter afterwards, had done, gathering these empirical risk factors. That's all we had. But once the DNA analysis came in, we made fantastic progress and really what we've done has gone right through to pre-implantation genetic diagnosis. We've had *in vitro* fertilization (IVF) and all the success of that and so on, and amniocentesis, and that is amazing.

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

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

TT: Do you have any particular hopes, or expectations, for the future, for the next thirty years or so?

MP: Right, the future, 30 to 40 years [laughs]. Ten years perhaps but anyway, the first thing is a sort of caution really. I sincerely hope that the way clinical genetics works is preserved, and that a key aspect of that is we keep family-based notes. I think we're one of the few disciplines that have family-based notes as opposed to individual notes, and I fear that people will eventually say, 'Well, it's personalised medicine now, you don't need to keep these family notes.' And that would be a disaster not only for the research but for the service. So that's one thing I hope for.

What I think is going to happen is the monogenic diseases are really going to be sorted – the therapies for monogenic diseases are going to improve. We will have many treatments because gene editing's going to make it possible, and where you can do transplants to combine transplants: bone marrow transplants, stem cell transplants – with gene editing that's already happened, with leukaemia for example. I think we're going to accept gene editing even in the pre-implantation embryo in the next 30 years, in that time period. From the point of view of the

common diseases and personalised medicine, now even in that timescale I'm doubtful it's going to be as big a player as people think. Obviously with cancer, where you're actually looking, is at the tumour that's being genotyped to help with the treatments, and there will be a little bit, I think with cancer it's going to be important and will deliver very well.

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

Certain things, imprinted genes, as I predicted in 1996, are going to be big players in this, and out of the chaos will come a certain canalised developmental trajectory, which works fine. But it's going to be different for each sibling, even different for some twins. And we may be able to screen children when they're born and know whether they're particularly at risk of something or other in terms of public health interventions, but there's a lot of research to do. But we will be able to do it. So personalised medicine, I think it's going to quietly disappear as the broad answer to everything. It's going to be very important in cancers in terms of getting the cancer, of getting the tumour, assessed. But I think we've been missing a trick up to now, that's my view.

TT: Thank you so much Marcus.

Related resources

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Names in **bold** refer to interviewees

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