

THE DEVELOPMENT OF BRAIN BANKS IN THE UK c.1970–c.2010

The transcript of a Witness Seminar held by the History of Modern Biomedicine Research Group, Queen Mary University of London, on 12 November 2013

Edited by C Overy and E M Tansey

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WHAT IS A WITNESS SEMINAR?

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

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

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

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

¹ See pages 113–18 for a full list of Witness Seminars held, details of the published volumes and other related publications.

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

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

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

² See our group’s website at www.histmodbiomed.org

ACKNOWLEDGEMENTS

The topic of ‘the development of brain banks in the UK’ came about as a result of a discussion with Professor Paul Francis at the British Neuroscience Association meeting in April 2013 and we are very grateful to him for his help in the planning of this meeting. We thank Professor Hugh Perry for his excellent chairing of the occasion and Professor James Ironside for writing the introduction to the volume. Our gratitude also goes to Dr Joanna Jenkinson for providing material for the Appendices; the Wellcome Library, London, for permission to use photographs from the meeting; and the MRC for permission to reproduce Figure 19.

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

Tilli Tansey

Caroline Overy

School of History, Queen Mary University of London

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ABBREVIATIONS

ARUK	Alzheimer’s Research UK
BDR	Brains for Dementia Research
BSE	Bovine spongiform encephalopathy
CC75C	Cambridge City over-75s Cohort Study
CFAS	Cognitive Function and Ageing Studies
CJD	Creutzfeldt-Jakob disease
CNS	Central nervous system
HTA	Human Tissue Authority
IP	Intellectual property
MRC	Medical Research Council
MRCPath	Membership of the Royal College of Pathologists
MS	Multiple sclerosis
NHS	National Health Service
NHSBT	NHS Blood and Transplant
NIH	National Institutes of Health
OPTIMA	Oxford Project to Investigate Memory and Ageing
PD	Parkinson’s disease
PM	Post mortem
PR	Public relations
UKCRC	UK Clinical Research Collaboration

INTRODUCTION

A personal account

It is a great privilege for me to be invited to introduce this Witness Seminar on Brain Banking in the UK. My background in this field started in 1980 when, after graduating in medicine in the University of Dundee and completing my pre-registration posts in medicine and surgery, I started my postgraduate specialization in histopathology. I have always been more interested in mechanisms of disease rather than treatment; this speciality allowed me to begin study of the tissue-based changes occurring in disease both for diagnosis and research.

After gaining the knowledge required to pass the first part of the examination for Membership of the Royal College of Pathologists (MRCPath), I was given some time to develop a research interest. I was fortunate at the time to be able to work with Dr John Anderson, who was interested in neuropathology in the elderly, in particular the changes occurring in the brain in Alzheimer's disease and in normal ageing. He and his research assistant, Dr Beth Hubbard, used a collection of brains donated for research to work on precise volumetric methods to measure the severity of cerebral atrophy in Alzheimer's disease and normal ageing, combined with detailed quantitative studies of the histological abnormalities of the brain. This work interested me greatly, and I decided to specialize in neuropathology.

In 1983 I obtained a training post in neuropathology in Sheffield with Dr (now Professor) Walter Timperley, who gave me an invaluable broad experience of all aspects of neuropathology, particularly in the detailed examination of brains for diagnosis and research. He had a well-established interest in forensic neuropathology and in vascular disorders of the brain, both based on the examination of a large series of brains. Although there was no formal Brain Bank in Sheffield at that time, there was a rich archive of material available for study. I was encouraged to use this to begin my career in research, which gave me an opportunity to establish an interest in neuro-oncology.

I was able to continue this interest in 1986 in my next position as Lecturer and then (having passed the final MRCPath examination in Neuropathology) Senior Lecturer in the University of Leeds, the same year that the first case of bovine spongiform encephalopathy (BSE) was identified in the UK.¹ The subsequent epizootic of BSE and its emergence in domestic cats and other species focussed my attention on the rare spongiform encephalopathies in

¹ Wells *et al.* (1987).

humans. I encountered cases of sporadic Creutzfeldt-Jakob disease (CJD) and the very rare Gerstmann-Straussler-Scheinker syndrome in Leeds, and I later became aware of a plan to establish a national surveillance project for CJD and related disorders in the UK, to establish whether any changes in this disease attributable to BSE might occur.

This project was to be led by Dr (now Professor) Robert Will, a Neurologist in Edinburgh, who had previously worked on a surveillance project of CJD in Oxford. Unexpectedly, a Consultant Neuropathologist post became available in Edinburgh in 1990, and I was delighted to be appointed to this post to work with Robert Will and my neuropathology colleague Dr (now Professor) Jeanne Bell. Jeanne had already established a Brain Bank in Edinburgh funded by the Medical Research Council (MRC) to study the effects of HIV/AIDS on the brain and other organs. I was very happy to support Jeanne in this work and she became an internationally recognised expert in this field. She felt that a similar approach would be essential for the CJD Surveillance project, but this would require the co-operation of Neuropathologists across the UK, not just in Edinburgh. Jeanne received funding from the Department of Health in 1991 to set up a Neuropathology Laboratory to support the CJD Surveillance project, including the establishment of a Brain Bank for CJD. In view of the national importance of this work we managed to obtain the support of colleagues in UK Neuropathology, but I have to say that inevitably some colleagues took more persuasion than others!

Over the next few years the CJD brain bank grew and was widely used, proving invaluable in 1996 when we reported the first cases of a new disease now known as variant CJD, which represents the result of BSE infection in humans.² The recognition of this disorder is a tribute to the surveillance mechanisms for CJD in the UK, and to our colleagues in Neuropathology who supported our work. Without the CJD Brain Bank and the availability of CJD brains in Oxford from the earlier surveillance project in the 1980s, variant CJD could not have been identified at such an early stage.

This work and the many other successes resulting from brain banking activities across the UK were thrown into jeopardy by the Alder Hey scandal in 1999 and the findings of the Redfern Report in 2001 on the retention of organs at autopsy without the consent of relatives.³ This report led to the Human Tissue

² Will *et al.* (1996).

³ See pages 24–31 *passim* and note 45.

Act 2004, which created a new body, the Human Tissue Authority (HTA), to regulate the retention, storage and use of human tissue in a wide range of settings, including post mortem examinations and research.⁴

My conviction that human organs and tissues were essential for medical research, particularly for neurological disorders, led me to apply to be a Professional Member of the HTA. In April 2005, I joined my fellow pathologists Professor James Underwood (whom I knew well from my time in Sheffield) and Professor El-Nasir Lalani (whom I knew from my time in Leeds) as Members of the HTA Board under the Chairmanship of Baroness Helene Haywood. Over the next four years, my work with the HTA helped create the regulatory framework for the use of human tissues in medical research, after much engagement and debate with the research community. This regulatory framework is still evolving and hopefully will continue give both the public and researchers confidence to allow this essential work to proceed.

During the early years of the twenty-first century, the requirement for brain banking to support medical research in the UK was becoming more apparent and it was also becoming clear that the needs of key researchers, particularly for control brain samples, were not always being met. Professor Jeanne Bell tackled this particular problem with characteristic imagination and vigour, and secured MRC funding in 2005 for the Sudden Death Brain Bank in Edinburgh, aimed at collecting the control samples required by researchers.⁵ In 2006, the MRC held a Workshop to review brain banking activities and needs across the UK, after which a Steering Committee formulated recommendations to improve these activities in a Report in 2008 to the UK Clinical Research Collaboration 'Towards a National Framework for Brain Banking in the UK'.⁶ This report proposed that brain banking in the UK should be organised into a network, with a central co-ordination centre run by a Director.

After much consultation and discussions with colleagues, I applied for the Director's post and was appointed in 2009, establishing the co-ordinating centre for the MRC UK Brain Bank Network in Edinburgh. Over the next four years, I worked first with Dr Catherine Moody and then Dr Joanna Jenkinson in the MRC to establish the Network, set up an operational and regulatory framework and formulate a

⁴ The Human Tissue Authority, www.hta.gov.uk (visited 19 January 2015).

⁵ See page 41 and Appendix 2.

⁶ UKCRC Brain Bank Strategy Advisory Committee (2008). See the discussion on pages 56–58.

plan of work that addressed the issues raised in the 2008 Report.⁷ It was a great pleasure to work with Catherine, Joanna and my neuropathology colleagues in the UK Brain Banks to make the Network a reality, during which I was greatly assisted by Mr Chris Tindall as the Database Manager and Mrs Sheila Clarke as my PA for the Network. By the end of my appointment in 2013, the Network was a well-established functional entity, the need for brain banking in the twenty-first century had been well recognised,⁸ the MRC had renewed the funding of the four UK MRC Brain Banks for another five years, and an online database of over 9,000 brain tissue samples available across the UK was opened to researchers, who have made good use of this new resource.⁹ One of my final tasks as Director was to co-chair the MRC Brain Donation Workshop,¹⁰ which identified future priorities for the Network. Professor Seth Love will very capably take forward the actions from this Workshop as the new Director of the MRC UK Brain Bank Network.

As I have described above, much of my career in neuropathology has been spent in various matters directly concerning brain banking, so I was very disappointed not to be able to attend this Witness Seminar. The transcript has made fascinating reading and I am sure will be both interesting and informative to a much wider readership.

Professor James W Ironside

Professor of Clinical Neuropathology

University of Edinburgh



Figure A

⁷ UKCRC Brain Bank Strategy Advisory Committee (2008).

⁸ Samarasekera *et al.* (2013).

⁹ See page 57.

¹⁰ MRC Brain Donation Workshop, www.mrc.ac.uk/documents/pdf/mrc-brain-donation-workshop/ (visited 19 January 2015).

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Participants*

Professor Carol Brayne
Professor Margaret Esiri
Professor Paul Francis
Dr Djordje Gveric
Dr Joanna Jenkinson
Professor Peter Lantos
Professor Seth Love

Professor David Mann
Dr Catherine Moody
Ms Brenda Nally
Professor Hugh Perry (Chair)
Professor Gavin Reynolds
Ms Karen Shaw
Professor Tilli Tansey

Apologies include: Dr Rob Buckle, Professor David Dexter, Professor Stephen Gentleman, Professor William (Bill) Gibb, Professor Paul Harrison, Dr Gillian Hayes, Professor James Ironside, Professor Andrew Lees, Professor David Neary, Professor Elaine Perry, Professor Robert Perry, Professor Roy Weller

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



Figure 1: Professor Tilli Tansey

Professor Tilli Tansey: Good afternoon ladies and gentlemen. May I begin by welcoming you to the Wellcome Trust and thanking you all very much for coming to this Witness Seminar on the history of brain banks. The purpose of these meetings is to try to get behind the published stories to learn what really happened, not just the formal scientific literature or Research Council funding report. But who were the drivers? Who were the people who really moved things ahead? Why and when? Did some ideas not come to fruition? So we want you to tell us what happened in your own careers. We want to hear the authentic voices of brain banking in the UK in the past 40 or so years, and perhaps even to go a little behind that to what happened before the brain banks started (Table 1).

This Witness Seminar came about as a result of the British Neuroscience Association meeting in April this year that was held at the Barbican.¹ I'm sure several of you were there. I met Paul Francis there and talked with him about his work. I'd been interested in brain banks as a casual academic interest since leaving the lab myself, having worked on MS and Parkinson's disease when I

¹ The Festival of Neuroscience, the British Neuroscience Association's biennial conference, took place at the Barbican in April 2013. Alongside the scientific programme was the public programme 'Wonder: Art and Science on the Brain'. The event attracted nearly 2,000 delegates and over 5,000 members of the public. See the BNA website at www.bna.org.uk/BNA2013-festival-of-neuroscience.html (visited 5 August 2014).

<p>Sharing brain samples/tissues before brain banks</p> <p>Early brain banks (c.1990) Started by? Funded by? Where? Purpose? Public perception of brain banking and changes with time</p> <p>Further development of brain banks Started by? Funded by? Where? Purpose? Technological changes, e.g. fixation, staining, storing etc. Getting the brain faster?</p> <p>Networks and collaborations Communication technologies National International</p> <p>Implications and ethics Storage, maintenance, usage Recruitment of donors The increasing importance of linking brains in banks to clinical information during life Disposal of unused material?</p> <p>Future of brain banks</p>
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Table 1: Outline programme for 'The Development of Brain Banks in the UK c.1970 – c.2010' Witness Seminar

was a practising scientist. As an historian it seemed to me that this was an issue that we really should try to look at, to capture the reminiscences of those of you who were there at the very beginning, and to look at how this field has changed in the past 40 or 50 years.² A key part of any Witness Seminar is finding a suitable chairman/moderator, and I'm delighted that Hugh Perry, Professor of Experimental Neuropathology from Southampton, has agreed to chair this meeting. I know you will all know him. We're very pleased, Hugh, that you've agreed to do this and I will hand the meeting over to you.

² See Appendix 1 for a timeline of brain banking from 1950.



Figure 2: Professor Hugh Perry

Professor Hugh Perry: Thank you very much. I can only echo what Tilli has said – I hope that everyone will feel that this is a conversation to get behind the usual things that people say at meetings, an opportunity to say what you think is important, what you think is not important and shouldn't be given the time of day. To discuss those things that you might not otherwise say in a meeting. Maybe we could just briefly go around the room and make sure that we do all know each other. I'm a mouse biologist, my brain bank is full of very small brains, mostly olfactory, but I have had the opportunity to get very close to brain banking, so that's where I come from.

Professor Peter Lantos: I'm Professor Emeritus of Neuropathology, retired happily. I worked at the Institute of Psychiatry – Maudsley Hospital for well over two decades. This later became the King's Clinical Neuroscience Centre (Department). For most of this time I was also actively taking part in brain banking issues and I have not given this up even after retirement since I'm one of the trustees of Alzheimer's Research UK which, as you know, considerably supports brain banking in this country.³

³ The dementia research charity, Alzheimer's Research UK (the Alzheimer's Research Trust until 2011), specializes in research into the causes, prevention, treatment, and cure of dementia. See the website at www.alzheimersresearchuk.org (visited 3 November 2014).

Ms Brenda Nally: I'm the outreach coordinator for the Brain Bank for Autism and Related Developmental Research at Oxford, which is a very new area of brain banking; it's only just over four years old and I think there are some quite distinctive issues around the work we do.⁴

Professor Margaret Esiri: I'm a neuropathologist who describes herself as semi-retired. I'm still in Oxford where I've carried out most of my career and I've been interested in dementia and inflammatory diseases of the nervous system. More latterly, with Brenda, I've started the UK Brain Bank for Autism.

Professor Paul Francis: I'm currently at King's College London. I direct Brains for Dementia Research, which is an Alzheimer Society's and Alzheimer's Research UK network of UK brain banks.⁵ As my day job, I like to describe myself as a consumer of human brains. I do a lot of research on human brains, and have done since 1982, focused on dementia research.

Dr Joanna Jenkinson: I'm a Neurosciences Programme Manager at the Medical Research Council (MRC) and, until a couple of weeks ago, I looked after brain banking, having taken over from Catherine Moody.

Dr Catherine Moody: I'm also a Neurosciences Programme Manager at the MRC, Jo's predecessor from 2006 to 2010. The MRC set up a UK network of brain banks in 2009.⁶ I currently look after neurodegenerative diseases.

⁴ The Brain Bank for Autism & Related Developmental Research is part of the Thomas Willis Oxford Brain Collection at the University of Oxford. Funded by the Charity Autistica, it was set up in 2008 to research the causes of autism and the way in which the autistic brain develops and functions. See their website at www.brainbankforautism.org.uk/index.php (visited 6 August 2014).

⁵ Brains for Dementia Research is an initiative set up in 2007 to create a network of brain banks to promote brain donations to provide tissue for research into the causes and treatment of dementia. Funded by the Alzheimer's Society and Alzheimer's Research UK, it is based in six centres – London, Oxford, Newcastle, Bristol, Manchester, and Cardiff. See www.brainsfordementiaresearch.org.uk/ (visited 6 August 2014).

⁶ Dr Joanna Jenkinson wrote: 'The MRC set up the UK Brain Banks Network in 2009, an independent and co-ordinated national network of existing UK brain tissue resources, to manage the provision of brain tissue. It aims to provide operational efficiency for the benefit of donors, researchers, and future patients. Member banks have signed up to common standards for brain tissue banking, including donation, access and availability, protocols and procedures – to make it easier to find out about brain banking and to donate brain tissue. A further aim is to speed up the collection of tissue that is currently in short supply for research, including tissue from individuals unaffected by disorders of the central nervous system, as this is critical for use as a baseline for comparative studies.' Note on document sent to Mr Adam Wilkinson, 13 November 2013. See also the MRC website at www.mrc.ac.uk/research/facilities/brain-banks/about/ (visited 6 August 2014).



Figure 3: Participants at the Witness Seminar

Professor David Mann: I'm a kind of neuropathologist at Manchester. I say a kind of neuropathologist because I've never been formally trained in neuropathology in my entire life. I'm a kind of self-taught scientist come neuropathologist. I started on this game in the late seventies so I'm nearly retired: not quite semi, not quite fully, but on the way. I work on degenerations, Alzheimer's, frontotemporal dementia, motor neuron disease, Parkinson's, that kind of thing.

Ms Karen Shaw: I'm the nurse specialist at the Queen Square Brain Bank, a brain bank mainly involved with movement disorders.⁷ I've been there for about 13 years and I've been asking people and talking to people about donating their brain for research, probably for about 16 years.

Professor Gavin Reynolds: I started my involvement with post mortem tissues in Vienna in the late 1970s and spent a couple of years running the Cambridge Brain Bank in the early 1980s⁸ and carried on collecting brains in Nottingham for five years and subsequently have been using them up. My main interest has been in schizophrenia and other psychiatric disorders, but I've done a little work on Huntington's and Alzheimer's too.

⁷ The Queen Square Brain Bank for neurological disorders was established in 1984 and specializes in Parkinsonian movement disorders. See www.ucl.ac.uk/ion/departments/molecular/themes/neurodegeneration/brainbank (visited 2 June 2014).

⁸ The Cambridge Brain Bank was established in 1975 for research into neurodegenerative disorders. See their website at www.cuh.org.uk/research-and-development/for-public/cambridge-brain-bank (visited 2 June 2014). For information on the history of the Cambridge Brain Bank see Parry and Gere (2006); also Department of Health (2003), Chapter 26.

Professor Carol Brayne: I'm a public health physician from Cambridge and I became involved in brain banking as an epidemiologist around 1984 with the Cambridge Brain Bank and Claude Wischik,⁹ and working on brain donation from populations. I've been involved in brain banking ever since and particularly in the Cambridge City over-75s Cohort and the MRC Cognitive Function and Ageing study brain donation programmes.¹⁰

Dr Djordje Gveric: I'm currently manager of the Multiple Sclerosis and Parkinson's Brain Bank at Imperial College.¹¹ I started some 20 years ago with the then MS tissue bank at the Institute of Neurology.

Perry: Thank you everybody. My interface with brain banking actually first came about because of meeting Margaret Esiri, which touched on two ends of brain banking, one historical and one where we hope to be now. In the historical bit we had done some experiments in rodents and had seen what had appeared to be inflammatory disease leading to injury to axons in the brain. Being a rather pragmatic sort of person, I wanted to know whether this could possibly be true of human brains. One of the things we immediately recognized was that if you're somebody who has worked with experimental rodents most of your science career, getting to grips with the human brain is a completely different business and you really do need to work with somebody who knows their way around. I think this is often not appreciated by people outside the field. I got together with Margaret to ask whether we could look for axon injury in the brains of people with multiple sclerosis. Margaret said yes, of course we could, but we would have to get the material from different

⁹ Professor Claude Wischik holds the Chair in Mental Health at the University of Aberdeen. His research focuses on the molecular neuropathology of Alzheimer's disease.

¹⁰ The Cambridge City over-75s Cohort Study (CC75C) started in 1985 as a long-term study of over 2,600 men and women aged 75 and above. This has investigated, among other topics, the prevalence, incidence, and risk factors for cognitive decline and dementia; patterns of cognitive change; neuropsychology, depression; and the brain donor programme. See the study website at www.cc75c.group.cam.ac.uk (visited 2 June 2014). The MRC Cognitive Function and Ageing Studies (CFAS) are longitudinal studies in several centres across the UK, which look at ageing and health and cognitive function in older people. A brain donation programme is managed in each location and has had more than 500 donations. See the website at www.cfas.ac.uk (visited 2 June 2014), and, for a discussion of the neuropathology from the donated brains, see Wharton *et al.* (2011); see also Neuropathology Group of the Medical Research Council Cognitive Function and Ageing Study (MRC CFAS) (2001); Xuereb *et al.* (2000).

¹¹ The Multiple Sclerosis and Parkinson's Tissue Bank, based at Imperial College London, is a national tissue bank that collects tissue from individuals with MS, Parkinson's, and other neurological conditions.

places and some was in the Radcliffe Infirmary and some was also from a place I had never heard of – the Corsellis Collection at Runwell in Essex.¹² I wondered: ‘How on earth do all these brains end up in a place called Runwell in Essex?’ I’m sure Margaret will enlighten us in a little while. We published what I think is still a very interesting paper; I like to think of it as sort of a landmark paper.¹³ I’m not going to go into all the details but it was about axon injury in multiple sclerosis and it was really a great way to start working together on human neuropathology. But at the same time I was in a new department for me, the Department of Pharmacology, in Oxford, and I got talking to Margaret again and discovered that the OPTIMA project (Oxford Project to Investigate Memory and Ageing) was really just beginning to gather pace in the early 1990s. This was trying to do something that we are talking a lot about right now, which is: how do we map clinical phenotype onto neuropathology?¹⁴ Remarkably, when we did the first study together, when we talked about axon injury in multiple sclerosis, we didn’t really think about the fact that these brains might have come from people with lots of different types of MS; we just wanted enough MS lesions so we could get to grips with what we thought was going on. I think this was an interesting separation between the two approaches: one was the collection of brains where the phenotype, the clinical phenotype, didn’t seem to be important, and maybe Margaret will correct me on this; and then at the same time this new approach of OPTIMA. The MRC Cognitive Function and Ageing Study (CFAS) of course started in the same year, 1988, so it was an idea that mapping clinical symptoms and pathology had to be brought closer together rather than ‘this was a clinical disease’. Maybe, Margaret, you would comment on the Corsellis collection?

Esiri: Peter may know actually more about the Corsellis collection.

¹² Professor John (Nick) Corsellis (1915–1994), a consultant neuropathologist, set up a brain collection at Runwell Hospital in Essex in the 1950s. It is now the largest brain collection in Europe with over 6,000 specimens, a large number of which came from people who suffered from psychiatric and neurodegenerative illnesses. The collection is now managed by West London Mental Health NHS Trust. For a brief history see Department of Health (2003), Chapter 33. See also pages 10 and 15 and further biographical details of Nick Corsellis on page 92.

¹³ Ferguson *et al.* (1997).

¹⁴ The OPTIMA project was set up in 1988 to study the causes of dementia, especially Alzheimer’s disease. It also aimed to investigate changes that occur in the ageing brain, ways of diagnosing Alzheimer’s disease and other dementias, and how onset might be prevented or delayed. See www.medsci.ox.ac.uk/optima (visited 23 September 2014).

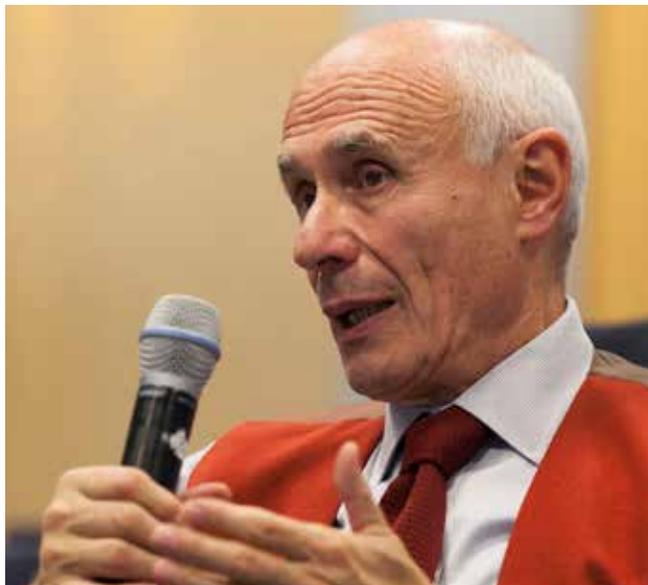


Figure 4: Professor Peter Lantos

Lantos: I would like to make a point at the beginning, which may be pertinent to later discussion, that there is a difference between collecting brains and brain banking. Collecting brains for diagnostic purposes goes back a very long time, you can argue to the beginning of medical research. If one has brains for one's own interest, preserving material for one's own research, and research with immediate collaborators, that is collecting brains. On the other hand, brain banking is something completely different: preserving tissues with specific aims and distributing tissues to the scientific community without necessarily the locals being involved, but they usually are. So I'm not sure whether the Corsellis collection started as a brain bank or whether Nick Corsellis, who was interested in certain neurodegenerative processes, including dementia, had a fantastic collection of brains, which he was generous enough to distribute to other people as well.¹⁵ But, for instance at the Middlesex Hospital, which exists no more, we had a brain collection but it was not a brain bank. We kept brains that were of some interest to us and our immediate collaborators. So brain banking is somewhat different.

Esiri: Yes, I agree it's somewhat different. I think there is a definite link between the two – they're not totally different activities – and I think brain banking

¹⁵ See note 12.

has the form that it has now developed into because of the way in which our understanding of disease has developed. So in Oxford in the seventeenth century we had Thomas Willis, a physician who saw people with strokes and things like that and realised that what was wrong with them was that something was wrong with their brains. But that was just a sort of gross beginning of understanding neuropathology.

Lantos: There was Leonardo before, so you can argue that it goes back further. And there were Egyptian surgeons who interfered with the brain so it is very difficult to draw a line that distinguishes interest in the brain, from collecting brains and brain banking.

Esiri: Brain banking involves studying the disease and then moving on. But I think over our professional lifetimes what has happened is that we've gone on from being able to link pathology in the brain with a clinical symptomatology in some detail. We've done that but the techniques that have been developed have allowed much, much more than just looking down the microscope and seeing what the features are that characterize a particular disease on a microscopic level. The thing for me that really turned me to brain banking was a paper that was published by David Bowen, a biochemist at Queen Square, in the mid-1970s in



Figure: 5 Professor Margaret Esiri

Brain.¹⁶ He showed that you could detect differences in the activity of enzymes in the brain in post mortem material and show that in a particular condition there were differences in these enzymes from controls. Paul will know a lot more about this than I do, but it just amazed me that you could actually take post mortem brain tissue and find that there was still meaningful enzyme activity there. So I thought to myself: ‘Well, it doesn’t make sense to be always putting every brain we receive into formalin if some of this tissue could be studied by a biochemist like David Bowen, who may be able to find out more about these diseases.’ So that’s really what started me off on brain banking, and two or three years afterwards, a gerontologist in Oxford became interested in Alzheimer’s disease and wanted to study it with me. As a neuropathologist you need tame clinicians who are interested in the same condition as you are because you can’t get direct access to the tissue – it only comes through the process of being looked after and having a clinician. Gordon Wilcock was this clinician, at the time he was a senior registrar but he soon enough became a consultant and he had beds in the Radcliffe Infirmary where he had everybody tested to see whether they had dementia or not.¹⁷ When they died he asked their relatives if we could study their brains, so we got very quickly a very, very good series of cases that were, or were not, demented on the gerontology wards. That was a huge boost to our opportunity to study this aspect of things.

Perry: So was this the first time brains were not just put in formalin and people started taking frozen samples? Is this the beginning of freezing brains?

Esiri: Well, it was in Oxford. I don’t know whether it may have been done earlier in other places.

Reynolds: Yes, I think it was at much the same time that Ted Bird in Cambridge had done it.¹⁸ I think maybe I should also make the point that almost all brain

¹⁶ Bowen *et al.* (1977a and b). David Bowen (1940–2011) joined the department of Neurochemistry at the Institute of Neurology, Queen Square in 1970. His research focused on the neurochemical basis of Alzheimer’s disease. See page 91 for further biographical details.

¹⁷ Dr Gordon Wilcock was Consultant Physician to the Departments of Geriatric and General Medicine from 1976 to 1984 and Clinical Lecturer in Geriatric and General Medicine at the University of Oxford from 1978 to 1984, when he was appointed Professor of Care of the Elderly at the University of Bristol. See, for example, Wilcock and Esiri (1982).

¹⁸ Dr Ted (Edward) Bird was an MRC Clinical Scientist in the MRC Neurochemical Pharmacology Unit, headed by Dr Leslie Iversen, and an Honorary Consultant in the Department of Neurosurgery and Neurology at Addenbrooke’s Hospital, Cambridge. His research focused on the neurochemical factors of Huntington’s disease. He moved to the USA in 1978 and set up the the Harvard Brain Tissue Resource Center (HBTRC).



Figure 6: Professor Gavin Reynolds

banks came out of personal collections and I think that is what happened with Ted Bird. He was interested in understanding Huntington's disease and set up what was essentially a nationwide collection scheme in order to generate as many Huntington's brains as he could get hold of. That probably was the first time that Huntington's brains were investigated in a chemical manner rather than in a classic neuropathological manner, and it was very successful in understanding the neurotransmitter pathology of the disorder. It was from that nationwide collection that enabled the Cambridge Brain Bank to develop nationwide collecting of schizophrenia samples and also Alzheimer samples.

Brayne: I was just going to add to that, the sequence of Bird and Iversen and then Wischik, in terms of taking that protocol, which was half frozen, half fixed.¹⁹ Bronwyn Parry, in a previous Wellcome award, has documented that

¹⁹ Bird and Iversen (1974); Lai *et al.* (1995).



Figure 7: Professor Carol Brayne

history in her papers in collaboration with CFAS.²⁰ She did a detailed embedded social science Wellcome-funded project, which led eventually to the Mind Over Matter exhibition.²¹

Lantos: Establishing seniority of brain banks, one of the oldest in London was probably at the Maudsley Hospital. The credit should go to Professor Alfred Meyer, who was Professor of Neuropathology and started collecting brains with psychiatric diseases and later on with Creutzfeldt-Jakob disease (CJD), which at the time was of very little interest to the general public.²² In a way it was a personal collection but it later gradually became a brain bank in the sense that the material was distributed quite widely, including the National Institutes of

²⁰ Parry and Gere (2006).

²¹ Bronwyn Parry is Professor in Social Science, Health & Medicine at King's College London. The Mind Over Matter exhibition, held at Shoreditch Town Hall, London, in October 2011, featured the identities and photographs of brain donors. See www.mindovermatterproject.co.uk/about.html (visited 9 June 2014), and further comments by Professor Carol Brayne on page 28.

²² Alfred Meyer (1895–1990) left Germany in 1933 and worked at the laboratories at the Maudsley Hospital. He was appointed Professor of Neuropathology at the Institute of Psychiatry and the Bethlem Royal and Maudsley Hospitals in 1949. See Anon (1991).

Health (NIH) in Bethesda, and this work, which later was crowned with a Nobel Prize, used some of the material provided by the Maudsley Hospital.²³ So that's one of the very old brain banks. The other that Margaret mentioned is the Runwell collection started by Nick Corsellis, I think, in the early 1950s. He got involved in dementias, particularly Alzheimer's disease and also in dementia pugilistica or boxer's dementia.²⁴ This brain collection was extremely useful and many other people benefited from it. But if I go back just for a minute to the Maudsley, I should have mentioned another very interesting, quite unique, part of that collection – brains of patients who had a lobotomy. What's happened to those brains now, which is of great historical interest, I don't know, but we could find out. So that collection goes back really to the early 1940s.

Mann: I suppose my interest and experience of brain banking came through an entirely different route. I got into it essentially as a fairly raw PhD student and postdoctoral work in the sense that I graduated in zoology of all things for my sins and did a PhD in a pathology department, which just happened to be a project that related to some element of nervous system anatomy. It was a question that some people who are old like me might even remember. There were a few papers about polyploidy in the nervous system that my supervisor, Peter Yates, thought was an interesting thing for a PhD student to look at,²⁵ and this project was designated to me.²⁶ But, in fact, after about 12 months it turned out to be a complete load of nonsense and I was stuck in the middle of a PhD looking for something to do.

Perry: Not the first, I suspect.

Mann: So I turned my attention to this rather dark and gloomy room in the pathology department at Manchester University, which had all these jars and buckets with pickled brains in them, and thought: 'Well, there must be something

²³ In 1966 Elizabeth Beck, a neuroscientist at the Maudsley Hospital, provided the American virologist Carleton Gajdusek and his colleagues at the NIH with a sample of a brain biopsy of a patient with CJD; this was used to inoculate a chimpanzee that later developed a prion disease. In 1976 Gajdusek was jointly awarded (with Baruch S. Blumberg) the Nobel Prize for his work on kuru and CJD, showing that prion diseases were transmissible infections.

²⁴ See Corsellis, Bruton and Freeman-Browne (1973); Corsellis (1989).

²⁵ Peter Yates (1921–2001) was Professor of Neuropathology at the University of Manchester Medical School and Consultant Neuropathologist at the Manchester Royal Infirmary. See Herman and Lapham (1968, 1969); Lapham (1968).

²⁶ Mann and Yates (1973a and b).



Figure 8: Professor David Mann

interesting here to work on.’ So I rummaged through the catalogues and came across some really weird and wonderful disorders with names I’d never heard of, including something called Alzheimer’s disease. I thought: ‘Hm, this sounds interesting. I’ll have a look at a few glass slides of this.’ And looking at those I was confronted with these wonderful structures, which we still don’t understand even now, called plaques and tangles. I thought: ‘Good grief, what on earth is going on here?’ and that stimulated the interest. So I rummaged through the collection and saw what else there was, and there were some odd things like motor neuron disease and Parkinson’s, and I thought: ‘Right, we could do something with these for the PhD’, and that’s really how the Manchester Brain Bank originated, from sifting out material that pathologists had kept essentially for teaching.²⁷ They did do research on these things – they used them for diagnosis and teaching obviously – but they kept them there as products of the pathological museum. And that turned into a research exercise.

²⁷ Mann (1972).

Perry: Who was paying for these collections? We know when anybody collects anything it costs an enormous amount of money. But, of course, it wasn't that long ago that quite a lot of research didn't cost that much money.

Mann: Departmental budgets, I guess, or some nebulous income from the Health Service or from the university which supported diagnosis.

Lantos: In Manchester again we talk about using, or collecting, brains for diagnosing purposes, which was obviously part of the departmental budget, but it was a different matter when we were actually advertising to obtain more brains well beyond the interest of the host institution, and that is brain banking. So even if the difference is reflected in funding, the same way as certain other parts of the body have been kept for a while for research, some brains had been kept as part of the routine diagnostic service. The funding of this was obviously part of the department or institute or the hospital's budget, but once we started to have brains from other sources and from other parts of the country, funding became very important and it was necessary to obtain outside funding. When I was at the Middlesex Hospital, we looked at the brains – no one paid for those because it was our diagnostic service to do so. At the Institute of Psychiatry when I started a brain bank with David Marsden, then we obtained the help of the Medical Research Council for a very long time. In fact the MRC, I think, still funds the same brain bank.²⁸

Mann: Just going back to what Margaret said, I think the impetus for me to collect brains locally within Manchester, working with local clinicians to recruit cases of Alzheimer's disease particularly, again came through working with David Bowen and the cholinergic story, and not specifically at that time to do the initial studies on post mortem material.²⁹ Then we were more interested, with Paul and David, in the product of that enzyme activity in terms of acetylcholine synthesis rather than assessing the cholinergic enzymic capability of the brain

²⁸ The MRC London Neurodegenerative Diseases Brain Bank was set up in the Department of Neuropathology, Institute of Psychiatry, King's College London, in 1988 and is funded by the Medical Research Council. (Charles) David Marsden (1948–1998) held the chair in Neurology at the Institute of Psychiatry and was a consultant at the Maudsley and King's College Hospitals from 1972 to 1987 when he was appointed to the chair of Clinical Neurology at the Institute of Neurology, Queen Square, a post that he held until 1995 when he became Dean. His research focused on neurological disorders affecting movement, especially Parkinson's disease. See Quinn (2006).

²⁹ See pages 11–12.

in Alzheimer's in particular.³⁰ To be able to get brains, and to measure the rate and degree of acetylcholine synthesis, was a completely different kettle of fish to simply collecting post mortem brains and measuring relatively robust markers, such as choline acetyltransferase activity. But there are lots of stories there, and I'm sure Paul will regale you with them at some point in the afternoon. If he doesn't, I will, and this will link in with the items further down the list in terms of post mortem delays and such like, and the experiences we had in connection with that study.

Perry: So it's obviously an interesting transition from collections to bank. One of the things I'm intrigued to know about is how did it feel to be a neuropathologist? That may sound like a slightly odd question but we know that in medicine there are hierarchies, people are seen as the top of the tree and other people less so: I would say, for example, our friends in psychiatry clearly feel that this is an area that is withering because young people don't want to be psychiatrists any more. I think that recruitment into neuropathology is also a bit of a problem. How did it feel to be a neuropathologist at a time when it was not a discipline, but had all these techniques to hand? We can start with our more emeritus colleagues – it's more how you think people perceived you rather than whether you were happy. Was pathology, neuropathology, seen as a premiere discipline?

Esiri: I think neuropathology in Oxford was quite fortunate because there was a lot of money put into the medical school by Lord Nuffield who made cars.³¹ One of the departments was the Nuffield Department of Surgery and the first Professor of Surgery that was funded by that source was Hugh Cairns, who was an absolutely outstanding neurosurgeon who understood completely the importance of neuropathology.³² So the first neuropathologist in Oxford was brought in by him to help him and his colleagues, other neurosurgeons, because they need to know what sort of a tumour something is before they can provide advice about how to manage it. So our main bread and butter work was diagnosing tumours.

³⁰ See for example, Neary *et al.* (1986).

³¹ William Richard Morris, Viscount Nuffield (1877–1963) was a motor manufacturer and philanthropist. He set up the Nuffield Foundation in 1943 to provide medical and social welfare and, from the 1950s, educational grants.

³² Sir Hugh Cairns (1896–1952) was appointed as the first Nuffield Professor of Surgery in Oxford in 1937. See Jefferson (1959).

Perry: Do you think you were highly regarded?

Esiri: No, I don't think we were highly regarded. We were definitely back room boys and girls. But it was a very comfortable back room. We had very nice colleagues and it worked.

Lantos: I think it depends on the actual place one is, or has been, working. There was a difference in the perception of neuropathology by others at the Middlesex Hospital and in the Institute of Psychiatry. The Middlesex Hospital where I started in 1968 as a Wellcome Research Fellow from Hungary for one year, with a generous stipend of £1,200 per annum, was expanding research into neurological diseases. This was made possible because one of the senior consultants was given an endowment of £1 million, which in 1968 was quite a lot of money. We called this later the 'Biscuit Money', since the donation was by Garfield Weston of Fortnum & Mason and other enterprises.³³ That later became the Institute of Neurological Sciences, which exists now. So there was a perception that we need neuropathologists, and my senior colleague, Dr Helen Grant, was on the diagnostic side and I was working on a PhD.³⁴ Our work was appreciated by the clinicians: it was not glamorous but was well thought of. At the Institute of Psychiatry it was different because there are the biological psychiatrists who think that we need brains and there are the social psychiatrists who think: 'Well, what are they for?' So at the time there was this division but obviously early on I found collaboration with biological psychiatrists, mainly with neuropsychiatrists and also old age psychiatrists. This turned into a very fruitful collaboration and these colleagues appreciated neuropathology, so I can't complain.

Perry: Gavin and Paul, neuropathology – is it still in this back room or are you more front room?

Reynolds: I'm not a neuropathologist. I trained as a chemist in fact, a biochemist, and then a pharmacologist. I think that I, with David and Paul, probably share the view that we did our best to work closely with neuropathologists and

³³ Williard Garfield Weston (1898–1978) was a Canadian businessman and philanthropist. He moved to the UK in 1932 and established Associated British Foods in 1935 and in 1958 set up the Garfield Weston Foundation, a grant-making trust that supports organizations and activities in the arts, education, youth, health, community, environment, religion, and welfare across the UK.

³⁴ Dr Helen Grant (1922–2012) was a consultant neuropathologist at the Middlesex Hospital and later at the Charing Cross Hospital. During the 1980s and 1990s she was one of the first scientists to warn of the dangers of BSE crossing from animals to humans; she also warned of the danger of brain damage caused by boxing. See Lantos (2012).



Figure 9: Professor Paul Francis

other general pathologists, but we were often seen, I think, as sort of eccentric scavengers. In Cambridge I, or my technician, used to go downstairs to the mortuary and negotiate over brains. This was, of course, in the days when this sort of thing was rather more possible. We could discuss the opportunity that we might be able to provide some pathological feedback in exchange for having these brains that we could then bank and formally provide for those who in the future wished to withdraw. But it was very much a sort of negotiated process, wasn't it?

Francis: Yes. I came from a background working on chicken brain so, like Hugh, I had an even bigger journey when I came to human brain. When I moved to Queen Square in 1982 to work with David Bowen,³⁵ I very quickly worked out that there were helpful neuropathologists and there were probably those who were less likely to be useful to the sort of things we were doing. The Department of Neurochemistry at Queen Square was, I think, set up in 1970, and Alan Davison was the chair.³⁶ He brought together people who were

³⁵ See note 16.

³⁶ Alan Davison (1925–1993) was Professor of Neurochemistry and Chair of the Department of Neurochemistry at the Institute of Neurology, Queen Square, from 1971 until his retirement in 1990.

interested in studying chemistry of the brain, multiple sclerosis, Alzheimer's disease, and other forms of dementia. David Bowen was there, Louise Cuzner was particularly focusing, with Alan Davison, on MS.³⁷ I think the first studies had perhaps happened in the late 1960s. There's a name that comes back to me and I wonder if Peter or Margaret know this, Korey, who I think may have done some of the early chemical studies on the brain.³⁸ So the idea that you could use frozen tissue and do chemistry was something and then perhaps going back to Arvid Carlsson and looking at the monoamines.³⁹ I think that would be the time of things. The Department of Neurochemistry at Queen Square was then set up to try and take this forward. Of course, one of the imperatives was that, in addition to studying animal models, you could actually have human tissue to study – frozen human tissue that would be suitable. As Margaret says, I think in terms of Alzheimer's disease the key studies were in the mid-1970s – Newcastle, London, and Edinburgh would be the main ones – actually looking at enzyme activity in the brain. Now, what you needed was a neuropathologist who wasn't going to slip the whole of the brain into formalin. You needed someone who was amenable to actually not do that, and fortunately there were people. Nick Corsellis was, I think, the supplier for David's studies – I checked with Margaret on this – and he was the supplier of material for the 1976/77 papers that David did.⁴⁰ I don't know who supplied Peter Davis from Edinburgh;⁴¹ Newcastle had its own sort of brain collection at the time. But obviously there were people who were prepared to listen to you, people like Gavin and David.

³⁷ Louise Cuzner is Emeritus Professor of Neurochemistry at the Institute of Neurology.

³⁸ Saul Korey (1918–1963) was Professor of Neurology at the Albert Einstein College of Medicine of Yeshiva University from 1955, where he was a pioneer in the field of neurochemistry and Alzheimer's disease. See Scheinberg (1964).

³⁹ Professor Arvid Carlsson (b. 1923) is a Swedish pharmacologist best known for his research on the neurotransmitter dopamine. He was jointly awarded (with Paul Greengard and Eric Kandel) the Nobel Prize in Physiology or Medicine in 2000 'for their discoveries concerning signal transduction in the nervous system'. See www.nobelprize.org/nobel_prizes/medicine/laureates/2000/carlsson-autobio.html (visited 9 June 2014).

⁴⁰ Bowen *et al.* (1976; 1977a and b).

⁴¹ Dr Peter Davis joined the Medical Research Council's Brain Metabolism Unit in Edinburgh in 1974 where his research focused on Alzheimer's disease. In 1977 he moved to Albert Einstein College of Medicine, New York, as Professor of Pathology and Neuroscience, and in 2006 was appointed Director of the Litwin-Zucker Research Center for the Study of Alzheimer's disease at the Feinstein Institute for Medical Research.

I think around the same time, as a slight tangent to this, when I first came to work with David Mann, we'd done a lot of work on post mortem brain but we wanted to be sure how representative this was. So we had colleagues in Manchester who were undertaking neurosurgical biopsies of people with dementia for diagnostic purposes, and we said: 'Please can we have some of that tissue to do some chemistry?' because, of course, from a living person the amounts taken were tiny but we only needed a small amount. And you know biopsies were done; they were done in the USA as well for a short time. I remember a paper that David did comparing people who had had a biopsy in life with follow-up neuropathology looking at the changes.⁴² We also were able to access neurosurgical samples from Queen Square so we were in the right place at the right time and we had something which resembled control material for the neurosurgical biopsies of people with dementia. So I think all of this came together and it was probably a slow burn but eventually we had a large collection of people in strategic areas. Margaret Esiri and David Mann particularly were most helpful in helping us to get the sort of tissue we needed to do these studies: a variety of tissue, relatively standardized tissue that could be used and applied to a particular question. I think that's where I came in. I pick up Peter's point about collections versus brain banking, that brain banking was really probably mostly driven by the need for chemical analysis of the brain rather than neuropathological analysis of the brain which could be done on collections. People would say: 'Well, this case is a bit different to that case, which is a bit different to that case, which is a bit different to that case.' There was a big distinction at the time in Alzheimer's research between presenile dementia and late-onset Alzheimer's disease. People thought they were different diseases but eventually chemistry and the pathology showed that actually they were very, very similar. So I think the whole field was dragged along and brain banks were probably often driven by people like us asking for frozen tissue – you didn't need one case, you needed ten cases maybe.

Perry: That's potentially very interesting because, of course, the demands now of modern techniques are also for fresher, better preserved, frozen tissues for study of the transcriptome, proteome, lipidome, and so forth. Again, there's a slightly different pressure but it's interesting that chemistry was driving it rather than simply detection of pathology.

⁴² Professor David Mann added: '...looking at the same plaque and tangle pathology and comparing the amounts of them at the two time points (Mann *et al.* (1988)).' Email to Ms Caroline Overy, 14 October 2014.

Mann: I'll follow up from Paul. Having done the biopsy work myself, I think one of the really important issues that came out of it was that, not only was the basic enzyme responsible for making acetylcholine defective in Alzheimer's disease, but also what was there was incapable of making the right levels of acetylcholine. We wanted really to follow this up in a large number of cases, and getting cell biopsies and the right amount of material from cell biopsy was really not easy to achieve. So we looked and said: 'How can we use post mortem material to answer that question?' In Manchester we set up a system whereby we obtained pre-mortem consent to brain recovery with the relatives fully involved when the whole situation was explained to them. They gave their agreement that we could obtain the brain tissues as soon as the patient died, so we weren't hidebound by this 'green form' paraphernalia that so besets us nowadays.⁴³ And the net effect of that was that I would make journeys across Manchester at 2 o'clock in the morning to Prestwich Hospital, a big psychiatric hospital at the time, where many of the patients were resident. There, I would meet the local mortician and we would extract the contents of the head from these individuals who had kindly agreed to donate the tissues for research, and I would hot foot, literally, across Manchester back to the University of Manchester laboratories, where we would dissect the brain and put it into these wonderful containers that David and Paul had devised, which contained preservative fluids.⁴⁴ The next day the brain would find its way, courtesy of British Rail, down to Queen Square, and Paul will love to tell the tale that I would ring him up at some unearthly time in the day or night and say in my best Yorkshire voice: 'Hello Paul. There's a brain on a train for you.' [Laughter] And really, as Paul says, it was the chemistry that drove the need not only to collect brains, but to collect brains of better quality than those you could simply get hold of from pathological archives, where everything had just been stuck willy-nilly into preservative. It was a rather surreal experience carrying really warm brains across a city at 2 o'clock in the morning.

Lantos: Just to redress the balance between biochemistry and other investigations, I think the key was really the short post mortem delay and the collection of the material soon after the patient died, not only for biochemistry but for other

⁴³ The 'green form' is the Registrar's Certificate for Burial or Cremation. See comments by Joanna Jenkinson on page 51.

⁴⁴ Professor Paul Francis wrote: 'These were large plastic "cool-boxes" such as you would use for a picnic and inside there were "hors d'oeuvres" trays with lids into which dissected slices of brains were put. Each sample was in physiological buffer.' Email to Ms Caroline Overy, 5 November 2014.

investigations as well, since one driving force was the development of various investigative techniques. One example is electron microscopy because we shouldn't forget that the first major discoveries of modern Alzheimer's research were achieved by morphology; it was electron microscopy which established that the neurofibrillary tangle is composed of paired helical filaments. Again, it was electron microscopy that revealed that subacute sclerosing panencephalitis (SSPE) is caused by a virus. So it's not only biochemistry that was a driving force to have good quality tissues for examination but also other techniques. So in the 1970s, or even much earlier, we experienced an era in which brain research expanded enormously, and within a couple of decades we learned more about the function, structure of the brain, and its diseases than during the previous centuries. That really was the force to have the tissues for as wide-ranging investigations as possible. In addition to traditional formalin fixation for histology, different methods of tissue preservation were necessary for neurochemistry, later immunohistochemistry, electron microscopy, and it goes on to molecular biology and genetics. So the driving force for brain banking is not only neuropathology, although it is the keystone in this whole edifice, but also the expanding investigations, the technology which has developed so enormously and so rapidly.

Perry: I'm very interested in that, so there are the drivers for more brain tissue. I'm also interested in what you thought the public thought about the work and we'll come to this again later when we think of our newer brain banking activities. I'm interested in that period of the 1970s and 1980s. What did the person in the street think about people studying brains? Was this really something that was acceptable or not?

Mann: I think actually it was not in the public perception until the Alder Hey story broke and then the stuff really did hit the fan at that time.⁴⁵ That really did impact upon brain collections and brain donations. I think, by and large, people had an understanding of why it was necessary to collect brains and were happy to participate in that process, but with the Alder Hey scandal, the whole notion of pathologists became people who kept things in cellars and dark rooms. We were tarnished badly by the whole business.

⁴⁵ The Alder Hey story broke in 1999 with the report that a large number of hearts, organs, and fetuses had been retained without consent at the Alder Hey Children's Hospital in Liverpool. The subsequent investigation and publication of the Redfern Inquiry in 2001 led to recommendations for an independent commission to oversee cataloguing and return of 105,000 organs retained by hospitals in England, new laws on informed consent, and a review of the Coroner's System (*The Royal Liverpool Children's Inquiry Report* (2001)).

Perry: Since you were there at the time before Alder Hey, before that came to the press, was it benign? Was it simply not in people's consciousness or did they think it was okay, or satisfactory? What was the general feeling?

Esiri: I think it was to do with the fact that people held medical professionals in high regard, and if a post mortem was requested by a clinician who had looked after somebody in life, the relatives were very inclined to say 'yes'. If that clinician said: 'This is going to help us to understand this disease' the relatives hardly ever said 'no'. That held really until, as David says, the time when the Alder Hey problems arose. I think before that, because the imaging had been progressing so fast, clinicians had less of a need for post mortem examinations because they knew more about what was going on in the brain, certainly on the diagnostic side, though perhaps it wasn't so much the brain banking side that this applied to, but certainly the neurologists had better ideas of what was going on because of CT scanning. They became less likely to ask for post mortems, so that the post mortem rate for diagnostic purposes fell off dramatically all over the world because of CT scans and the fact that the neurologists were no longer in the dark.

Perry: There are two interesting sides to this story: one is people's perception and that of the press. What did you think? When Alder Hey broke, as a pathologist, what did you think? 'This is an outrage? This has been waiting to happen?'

Esiri: I felt very, very undermined by it. I felt the media portrayed it in the wrong way. I felt we were the victims of a system that involved particularly coroners' post mortems, which had nothing to do with the hospital system, where we had what we called medical interest post mortems and that often contributed to the brain banking as well. That was completely different to the coroner system where the problem was, I think, that the coroners never really explicitly said what you should do with an organ after you'd examined it for their purposes, which was to find the cause of death. So departments ended up with a lot of organs that they'd taken from coroners' cases and they didn't know what to do with those organs afterwards. I don't know exactly what was going on in Liverpool, but my understanding was that these organs were retained because the pathologists felt that there was something valuable to be gained from studying them, but they needed funding to be able to do those studies, which should have been provided by Liverpool University and that funding hadn't been forthcoming so those organs had just been sitting around waiting to be studied.

Perry: The impact on you was one of betrayal in some sense?

Esiri: Yes, absolutely. There was nothing that one could do about it. I remember going to somebody who had quite a lot to do with television productions and saying: ‘How can we change this understanding? It’s completely misleading; the media coverage has been completely misleading.’ He said: ‘Well, the only way that you could do it would be if you could have a patient who had a disease, had been part of a film while they were alive, and then you told the audience why it was valuable to look at the brain’, and this would have to come into a television programme or something.⁴⁶ It was impossible.

Perry: It’s a bit hard to plan among your colleagues.

Reynolds: In Cambridge we were picking up many of the brains through coroners’ cases, particularly psychiatric cases where there were no clear next of kin. The coroners were often very positive about this; they saw that they were responsible for these cases; they were in lieu of next of kin and they actively supported the collection of psychiatric cases. In particular I think that the Depression Brain Bank or collection in London that was run by Roger Horton, had a very close link with the local coroners who were extremely supportive of their collection scheme.⁴⁷

Perry: How did it affect you personally when all this happened? I think this is one of the interesting aspects because we can read about what the newspapers thought all the time but we never hear the voice of the people who were actually affected as a consequence of what happened in the newspapers. What was your feeling?

Reynolds: Fortunately I was not directly brain banking when Alder Hey broke.

Perry: But you were using human tissues?

Reynolds: I became very, very nervous about using human tissues and there was in fact some work we’d done with a paediatric pathologist where we had some paediatric brain tissues. That had provided us with some very interesting information regarding brain development. I have not published that really

⁴⁶ See comments by Professor Carol Brayne on page 28.

⁴⁷ Roger Horton was appointed Lecturer in the Department of Pharmacology at St George’s Hospital Medical School in 1979, rising to Professor of Neuropharmacology in 1998 and Vice-principal from 2000 to 2007. He collected brain samples for research on suicide and depression from 1984 until the mid-1990s.

because I felt very nervous and I wasn't absolutely sure where exactly the permissions had come from for those brains because they were collected by somebody else so I couldn't check.

Perry: But you felt the public pressure was enough to make you hesitant about carrying on this work?

Reynolds: Absolutely, yes.

Perry: So it was pretty unpleasant.

Reynolds: It is worrying. And yet, as Margaret says, where we have been able to inform and educate the public in general or patient groups and carer groups, we've had enormous support for brain collection. In Cambridge we had a prospective Huntington's disease brain collection scheme that was initiated in the early 1980s. That was a slow process but it had a lot of support from the Huntington's disease charity, and the same is true for other disorders, Parkinson's disease in particular of course.

Brayne: I was just going to mention the prospective agreement by individuals during life. We started the Cambridge City over-75s Cohort Programme, which was a population study with participants who prospectively gave their intention to donate tissue, in Cambridge in about 1987/88, and then in CFAS a little later.⁴⁸ We had that programme running during the Alder Hey media blitz as it were, and we experienced mostly positive responses to the brain donation programme within both studies and didn't really see much of a blip, because we had established a relationship of trust with our respondents. So that I think there were streams within society where people did feel that things were okay; I think we only lost one or two brains because of Alder Hey.

Perry: That is a very interesting issue. As long as you have the right communication, information, and relationship with the people who are going to be your donors, or prospective donors, then you can preserve the trust. Whereas the sort of thing Margaret was saying, if you're just on the receiving end, it must be more uncertain.

Brayne: Finding things out afterwards is a problem. The reason why we introduced the declaration of intent to donate brain tissue at post mortem to the prospective population with the liaison nurse was because people in our team began to feel uncomfortable about the fact that we were following people.

⁴⁸ See note 10.

We were following our respondents and we wanted their brains and they didn't know that we wanted their brains. That was how the programme of going to people to talk carefully beforehand emerged for our population-based studies.⁴⁹ Before that we had lists in mortuaries and it was on spec. If they happened to come through to a post mortem, if the physicians were asking for a post mortem, we might get the brain as part of that post mortem process because it was covered by the rather broad consent forms at the time, for the purposes of research, but it was a very small section. So we had that in place in a major way; we did a lot of activity to try and capture people who came through the hospital system and the mortuary, but people weren't coming through that way and our team felt uncomfortable. So we then went to the Ethics Committee and they said: 'We've never handled anything like this before' and we had to create the process in the late 1980s. Just to say, the Wellcome-funded Mind Over Matter project, many years later of course, did exactly what Margaret would have loved at the time, which was to interview our brain donors who have now given their brain tissue. So we now have the images and the voices of our brain donors and their reflections on their lives, and we have their brains as well.⁵⁰

Lantos: Going back to Alder Hey, that was a very regrettable incident and it became more so because it was heavily politicized. We didn't have any problems with brain donations because we had an obviously dedicated cohort of patients and their relatives. But against that there has been always a problem with post mortems in this country – what they are for. If I may, I wish to say something on a more general note. The British public rightly expects the delivery of cure and therapies of all diseases but at the same time objects to post mortems, protests against animal experiments, and is suspicious of genetic work. This attitude doesn't bode very well for medical research. When I started to work in this country, I was surprised that one had to ask permission for a post mortem because in the country where I was trained, Hungary, one had to ask permission *not* to have post mortems because all the patients who died in university hospitals and clinics came for post mortem. The relatives were informed that post mortem is part of medical learning and training. At the time, of course, we did not use the term medical audit. So the post mortem rate at the time was around 90 per cent and when I came here I was amazed to find that it was, even in the early 1970s, around 20 per cent. So that is the background to why it is quite often difficult to obtain tissues from various diseases.

⁴⁹ See Barnes *et al.* (2005).

⁵⁰ See page 14, note 21 and page 26.

Mann: One aspect of the Alder Hey event impacted upon the number of donations. We had a small blip, but that quickly recovered, as Margaret and Carol said, through trust with the people that you're working with. I think the most savage aspect that hit us was the Isaacs Enquiry.⁵¹ This related to the brain of a patient in Manchester by the name of Isaacs whose spouse wanted to recover the tissues that had been obtained through the coroner's system for appropriate funeral arrangements, and the brain could not be found. This created a huge scandal both locally and nationally, and we were descended upon by the rottweilers of the Department of Health – very officious people who went through everything that we did with an absolute fine-tooth comb several times. At the end of it we were able to assure them, firstly that we had had no part in the retrieval of this particular brain but also, in a sense it was a bit of a double-edged sword, they could see really that how we did things was in their words 'exemplary', so actually it paradoxically came out in our favour. But it wasn't a very pleasant experience getting the Men from the Ministry down on you, who had no real conception of what brain banking was about and what brain research was about and the need for post mortems. They were just looking at it from the element of 'here's a scandal and how deep does it go?'

Perry: Seth Love has just joined us.⁵² We're talking about Alder Hey and its impacts: whether individuals involved in pathology personally felt threatened or betrayed, as Margaret described, or anxious or whatever.

Professor Seth Love: I had an interesting experience in that I have responsibility for two brain banks or two brain archives. In the NHS Department of Neuropathology in Bristol we have an archive of brains we have retained over many years and have come through a range of sources, hospital autopsies, coroners' autopsies, a few medicolegal brains; and then a brain bank that is the South West Dementia Brain Bank. From the contrast in relation to what happened to the two collections I think you can learn something. We have never had any problem at all in relation to the South West Dementia Brain Bank; we've had an increasing number of donations year on year irrespective of events like Alder Hey and the Isaacs brain retention. I think the people who donate brains often initiate the donation process. They have a very clear

⁵¹ The Isaacs Enquiry investigated the events and procedures following the death of Mr Cyril Isaacs in 1987, and the removal and retention of his organs after the post mortem at Prestwich Hospital mortuary. The report was published in 2003; see Department of Health (2003).

⁵² Professor Seth Love became the Director of the MRC-funded UK Brain Banks Network in 2013, succeeding Professor James Ironside.



Figure 10: Professor Seth Love

understanding of the purpose of the donation and the sorts of good to which the tissue may be put and they have a one-to-one relation with the brain bank in terms of discussions, transferring paperwork, and recording all of that sort of information.

In contrast, the situation relating to the retention of brains in the hospital archive was much more problematic. I had several interviews with families who hadn't been aware that tissue had been retained, although they'd signed consent forms at the time. What happens at Frenchay Hospital is that most of the brains don't derive from autopsies that we ourselves do. A general pathologist in Taunton or Yeovil or Gloucester will do an autopsy and will want the brain examined. He will send it to us and we will examine the brain and send out a report. We aren't primarily responsible for obtaining the consent and for having the related discussion with the families. We're often also not directly the people who liaise with the coroners or with the Crown Prosecution Service. So we have a situation where there are lots of different authorities involved in communicating, in obtaining permission, and in keeping documentary records of consent. And there are several different legal authorities involved in the brain retention process, particularly when a criminal prosecution is involved. Finally, there's often much less understanding amongst the next of kin as to why

this is all happening; they don't want an autopsy but the coroner has insisted on it, they are not clear why the brain is being kept or why it's being sent elsewhere for specialist examination. It's under those circumstances that you get problems. What we need is something more brain bank-like where there's direct communication between the family and the neuropathology service, and a single point of responsibility for advising on all aspects of the process.

Perry: I'll come back to the good bits that I think came out of Alder Hey but personally what did you feel when the press and public almost took to the streets about this? Did you feel threatened? Did you think it was worrying?

Love: I didn't feel threatened. I felt hurt sometimes because you have been doing the very best that you can: (i) for the families in terms of trying to diagnose things, particularly if there are genetic implications; (ii) for the coroner; (iii) for your pathology colleagues. You haven't had any responsibility for the things that have gone wrong and yet you feel you're being blamed. So I felt hurt, not threatened.

Perry: So tarred with the same brush?

Love: Tarred with the same brush, yes.

Perry: Brenda, you deal with children, or potential donors of younger ages. Do you think Alder Hey still leaves a trace behind?

Nally: I'm not sure that neuropathology of autism, which is really very new in the UK – it's been developed just in the last five years – has much resonance for families with people with autism and people themselves who have autism, with what happened at Alder Hey and Bristol.⁵³ I think it's not been such an issue for them. I think that they have doubted the value of this area of research partly because of very different perceptions of autism and attitudes to autism from the whole range of other diseases, which are under investigation through brain banking and neuropathology. I think that's because people who experience autism as a lifelong experience don't feel that they have a disease that ideally would be eradicated or where causes could be identified and lead to some form of cure; they have suspicions about this whole area of research because they feel it undervalues the people who have autism as an intrinsic part of themselves. That's a very strong body of opinion, which particularly people on the wide

⁵³ The Alder Hey scandal was immediately preceded by a scandal at Bristol Royal Infirmary when the story broke that the hearts and other organs of 170 children had been retained without consent. See Bristol Royal Infirmary Inquiry (2000).



Figure 11: Ms Brenda Nally

autism spectrum who are of high intelligence have developed and have used to influence the much wider autism community in the UK and other parts of the world. So it's a very different set of issues from the other issues we are discussing.

Perry: You've just taken us into a really interesting territory. We were talking about dementias and diagnosis of diseases that people are pretty clear that they don't want. They don't want Alzheimer's disease or Parkinson's disease, they don't want motor neuron disease. Some aspects of some mental disorders are different; I have a colleague who has bipolar disorder and he tells me 'the good bits are great; the really good bits are absolutely fantastic; just a pity about the really bad bits'. But the trouble is that all the drugs he takes gets rid of both, and he doesn't really like that so he tries to sort of titrate himself into some hinterland that doesn't do him a lot of good. Is this true of other psychiatric diseases, that brain banking is here perceived as an intrusion in some sense, rather than something valuable? Do you think this is what you've just said about autism – do you think it's something bigger than autism?

Nally: I think it is perceived as threatening by those people who experience autism and members of their families who emphasize the strengths associated with autism: the ability to focus very clearly, to think very logically, to develop

special interests and special intellectual understanding and expertise because of the way that their brain works. I think they feel that investigation of that, leading to interventions to change, is a threat.

Francis: It's interesting picking up on that. One of the big problems with brain banks is that we have a lot of people who have dementia in them, and we have very few people who don't have dementia. This is a misconception that we've tried to correct in the sense that we're saying to people: 'Actually, if you don't have dementia, from our perspective in Brains for Dementia Research (BDR) you will be making a valuable contribution to research, because we want to know what it is in your brain that means that you haven't developed dementia by the time you die and we will, of course, use that as a comparator with people who do.' So we're valuing both people with dementia and people without dementia; they then understand that it doesn't really matter: both of their brains will be valuable going into the brain bank. From what you're saying about autism, and what you said about your colleague, perhaps the message is that we'd just like to understand how the autistic brain works better rather than treat it as an illness that needs correcting. Maybe that's the sort of approach that we need?

Brayne: From the ageing point of view we've clearly had that in terms of trying to get the whole population, because we want to look at the complete relationship between the non-demented older people and those who experience dementia during life. So it was about understanding the brain in its entirety, and in the older population in our case. That was quite successful in our population approaches in terms of conveying that to all of our respondents and those who took it up, because most of the people at the time that we recruited them for the brain donation programme didn't have dementia, even though many of them had developed it by the time they became brain donors. So it was largely a mixed population.

Nally: Yes, I think we found that the efforts that we've made to reach the general population have been very successful, partly because they had no idea that this area of research was under way in autism. But many people now know about post mortem brain research into dementia so I think we've found that the general public, when it becomes aware of post mortem brain research into autism, is very positive about that area of research and also about what they could contribute in terms of control tissue. I think the issues are much more with the autism community in the UK and overcoming some of the misconceptions and fears that are still very strong there.

Perry: One can understand their point of view. It does seem to me that if you value it then you might say, ‘Well, there’s nothing wrong with us; we’re fine. We just happen to have a different percept of the world and we get on with our own lives and we don’t need you to look at us.’ How do you deal with that?

Nally: Well, there are people who have autism who are extremely stressed and have very poor quality of life and whose families are in a similar position. I think that they all have a quite different attitude to the potential this research has to make a real difference to their lives and those of future generations. So it’s a difficult balance across a very wide spectrum.

Perry: Perhaps we are not dealing with their many different points of view.

Lantos: Can I ask a question about the Brain Bank for Autism? While I was still working at the Institute of Psychiatry, Tony Bailey, Consultant Child Psychiatrist, was interested in autism and we had some collaborative work.⁵⁴ At the time we had quite a few brains. Is the present Brain Bank for Autism, which you said was started five years ago, a continuation of that or is it an entirely new chapter?

Esiri: The first time I met Tony Bailey he came into my office and said: ‘I want to start an autism brain bank and it’s going to be in Oxford.’ So, just as Gordon Wilcock had recruited me to be interested in old brains, Tony Bailey recruited me to be interested in young brains. Then Tony was trying to get some money from the EU and it didn’t work and so that floundered. But in the meantime there was an effort by this newly formed charity, Autism Speaks, as it was then, Autism Speaks UK, to set up this brain bank and it was particularly driven because there was a very generous donation that the newly formed charity had to decide what to do with and that’s how the decision was made that this would be a valuable thing to do.⁵⁵

⁵⁴ Anthony Bailey has been Professor and Chair of Child and Adolescent Psychiatry in the Department of Psychiatry at the University of British Columbia since 2010. In Oxford he held the Cheryl and Reece Scott Chair of Psychiatry from 2002. His main research has focused on the neurobiological basis of autistic disorders. For his research with Peter Lantos see, for example, Bailey *et al.* (1998).

⁵⁵ Autism Speaks UK (Autistica since 2010) was established in 2004 by the philanthropist Dame Stephanie Shirley as the UK affiliate of the American charity Autism Speaks; the charity funds scientific research into the causes, diagnosis, and treatments of autism; see www.autistica.org.uk/ (visited 29 September 2014). The Brain Bank for Autism & Related Developmental Research, based at Oxford University, was set up in 2008 and is funded by Autistica. See their website at www.brainbankforautism.org.uk/index.php (visited 10 July 2014).

Nally: This work had already been under way in the USA for some time and we have worked in close partnership with the US brain bank from the outset.⁵⁶

Esiri: Yes, they were about ten years ahead of us. We work extremely closely with the US bank and they have very similar problems to the ones we have, I think it's true to say, and we're trying to solve them between us.

Lantos: We have talked a great deal about brains for dementia, particularly for Alzheimer's disease, movement disorders, and MS. What we haven't touched is the importance of brain banking in psychiatric disorders, particularly in schizophrenia. I know that it's a minefield of research from every point of view because even clinically it's not quite established what it is, one disease or more. But that's an area of brain banking that had been started at the Institute of Psychiatry and that may be something which for the future is of great importance.

Reynolds: I can address several of these points. Certainly schizophrenia brain banking was established in Cambridge as well as in London and I think a lot has come out of that actually although there has never been much support. We've never been able to generate the sort of grass roots support that Alzheimer's disease and Huntington's and so on can, and also haven't really generated MRC and Wellcome funding support. But the Americans have done rather better in terms of schizophrenia and major psychiatric disorder brain banking with the Stanley Medical Research Institute where they have had a lot of money thrown at the problem and they have in the past addressed that well.⁵⁷ The other point I wanted to make really was that, around this autism discussion, we were touching on something that back in the 1980s and 1990s was a major problem, and that was the control problem. What do we do about control subjects? It seems to me that actually this has been at least partly addressed by these prospective studies and by working closely with patient and carer groups because one can then recruit spouses as controls. That's been done, I think, in Parkinson's disease collection as well as Huntington's too. That had always been a huge problem – we never really had enough controls in the past but I think that's better addressed nowadays.

⁵⁶ The Autism Tissue Program (ATP) was established in 1998.

⁵⁷ Stanley Medical Research Institute in Chevy Chase, Maryland, was established in 1989 to research the causes and treatment of schizophrenia and bipolar disorder. The brain bank was started in 1994 and from then until 2005 over 600 brains were collected for the research. See their website at www.stanleyresearch.org/dnn/ (visited 3 September 2014). See also page 81 note 119.



Figure 12: Ms Karen Shaw, Professor Peter Lantos, and Professor Carol Brayne

Perry: Karen, can I ask you to comment? You're at the interface with potential donors. Does the negativity of Alder Hey ever reappear or do you think this era is passed? I believe you're mostly recruiting adults.

Shaw: Yes. When I first started doing this Alder Hey was a few years away. I think I started asking people in about 1996. To be honest I do not think Queen Square have really suffered as a result of that. You were saying that at Cambridge people have had a very good relationship with the Brain Bank. I've known a lot of the donors and there has been a lot of trust. I think generally people are now more aware because there are people in the media saying: 'I'm going to donate my brain', and I think over the years things have recovered.⁵⁸

Perry: At a tertiary referral centre like Queen Square, you must get people from many different cultures come through the door. Are there cultural issues that are interesting and that we ought to think about? Tell us about your experiences of that.

⁵⁸ The actress and president of the Parkinson's Disease Society, Jane Asher, and the journalists Jeremy Paxman and John Stapleton signed up to the Parkinson's Brain Donor Register in 2009. The former Home Secretary David Blunkett has pledged to donate his brain to dementia research, and the author Terry Pratchett, who was diagnosed with Alzheimer's disease in 2007, has also said he will donate his brain.

Shaw: I think I have an awareness of religious aspects and even cultural aspects. The Islamic faith is the one religion that's very hesitant about it and there are cultural aspects around that too, and the appropriate way to approach people.

Perry: Before the meeting we were saying that we don't actually know what the cultural differences are, whether there are age differences? Is there a generation that is happy to do it and another generation that feels less happy?

Shaw: Irrespective of religion?

Perry: And/or religion. There may be no interesting nuances at all; I suspect it's just 'take each person as they come'.

Shaw: I think approaching people is a very individual thing. I usually get to know people a bit. If I'm at the hospital I'm usually part of the consultation and get to know who they are.

Perry: We've talked about these diseases of movement disorders and dementia and so forth, and there are all these other psychiatric disorders but there are also paediatric disorders too. I work with two children's charities and I know that the real issue, the reason we don't understand the diseases of the nervous system, is nobody has ever looked at the brains of more than a few people with these diseases. When it comes to paediatric donation what happens? Has anyone got experience of doing it?

Nally: I think the earlier issues that we were looking at in terms of whether people have a more basic resistance to this area of research when they're affected by autism are much more influential. We found on the whole that families who have been involved in supporting research through donation have been extremely positive, and particularly families of younger people who have seen that this has been the one positive thing they often find has come out of their very traumatic experience of their younger relative's death. In the short time that the UK Brain Bank for Autism has existed we've had three young donors who have taken the initiative to discover that this area of research exists and made the decision that they want to support it through donation, and have persuaded their families that this is something that they would want to do. Those families have said that has made it very easy for them, they haven't had a dilemma as to whether this is a good thing to do or not, and how might the person have felt and what they might have wanted, because it's been very clear that it's been a positive drive from the donor him or herself. So that's been very useful learning for us to recognize

the importance of the donors themselves making that commitment and how much better it is for their families to then follow through, making sure their wishes are carried to fruition.

Mann: I think there are certainly cultural elements attached to brain donation, and you could perhaps go a little bit further beyond that and say there are class elements of brain donation. I'm sure Paul can expand more on that.

Perry: Do you mean socio-economic class?

Mann: Yes. As we've developed the Brains for Dementia Research programme, we had to set targets as to how many recruits we needed. An estimate of how many people needed to be recruited was really born out of how many brains we needed to harvest at the end of the day. The kind of balance between brains harvested and numbers recruited was really based on actuarial levels of life expectancy according to the time in life at which people would consent to donation. When we started out there was an overwhelming response to the programmes about advertisement and education among people between the ages of 50 and 70, but less so with older people, mostly from what we might call '*Guardian* readers'. The experience of the 5 years that the programme has run so far is that the numbers of brains that we've recruited have roughly been about 50 per cent or even less, 30 per cent maybe, of those we predicted we ought to have recruited through the number of people signed up to the scheme based on actuarial analysis. I guess the reason for that is that those people who sign up to these schemes, like all voluntary schemes, come from a particularly motivated background. They're often motivated to do it not only because they have a personal interest in the illness concerned, but they have an altruistic interest. One doesn't want to invoke the kind of class structure too much, but that's how it works. Middle-class *Guardian* readers are motivated to take part in these things.⁵⁹

Perry: You might say it's the scientists' fault, because we communicate to a particular stratum of society and don't bother to communicate to the others. Do you think it could be that those you describe as the '*Guardian* readers' are those who understand what's going on?

Mann: I don't think it's a case of not bothering, because as part of many brain donation schemes, in particular BDR, we have public meetings and we advertise these widely. They're open to everybody, but you know who is going to come at the end of the day.

⁵⁹ *The Guardian* is a long-established British daily newspaper which has a reputation for being liberal and left wing. See comments by Professor Paul Francis on page 39 and note 60.

Perry: That's what I mean about the communication. People come because they feel that they'll understand it and actually we don't make enough effort to talk to the people at different levels. We all know there are different levels of understanding so if we don't make that extra effort ...

Francis: It's really interesting what David says. I did an interview with Angela Clayton-Turner on Radio 4 on the *Today* programme just before 9 o'clock in the morning and I think we had 250 people contact us. And you know who listens to Radio 4 at five to nine in the morning: older, well-educated people.⁶⁰ But what's interesting, we've had more difficulty recruiting in South Wales, where there is a small group in Cardiff who would be considered 'middle class' but outside that it's a very working-class environment. Interestingly, the team there has been struggling to work out how to communicate with them but they've had a real success recently with targeting GP surgeries. I'm not quite sure how this will translate but they said they've had about 200 responses locally, so we're hoping that this will perhaps get a wider socio-economic group. But these are people that look after their health, they're concerned about their health, get all the treatments, etc. and they come into our study. So I have a question for Carol about CFAS: is that the same, do you have the same issues there? What's your actuarial analysis of your cohort?

Brayne: Because we attempt to recruit the whole population, we have the whole population there to ask about brain donation and generally it doesn't influence the uptake that much. The thing is, we have built a relationship with the people in the study and we know who they are, before we go and ask them about brain donation. So the process is very different from the cold asking people to respond to a call or to come to a public meeting. Ours is so different because we've enumerated the population to begin with.

Perry: But the point is more that you have to communicate with everybody and if you communicate with people in Manchester then guess what? People in Manchester will turn up.

⁶⁰ Angela Clayton-Turner is a retired physiotherapist who worked with dementia patients and cared for her husband with Alzheimer's for 18 years. She carries out voluntary work for the Alzheimer's Society and has been a research network volunteer since 2000. Professor Paul Francis wrote: '[This] slot on the *Today* programme resulted in a massive spike of callers in the following week and I know other centres received direct contact. Typically these people fall into a particular socio-economic group. We also had people contact us who were too young. The other point that may be being made is that death rates amongst our cohort were lower than expected, again probably because of the bias of self-referral to socio-economic class.' Email to Ms Caroline Overy, 5 November 2014.



Figure 13: Dr Djordje Gveric

Brayne: But it's Newcastle, Nottingham, and Gwynedd, and we've had brain donors across all of those, so it does cover the class spectrum but it doesn't cover ethnicity at all and I think that is a very big issue. In CFAS we don't have an ethnic minority arm. Despite many attempts to get funding for studies of dementia in ethnic minorities we were unsuccessful.

Gveric: Just to continue on this theme. We never actually attempted to collect any data regarding ethnicity specifically for MS and Parkinson's but I don't remember anyone asking for it, so that's probably the main reason we never did this. The other thing, talking about public perception of brain banking and all the problems we had, is that brain banking has never had any problems in my mind. I've been on the receiving end of public perception when one of our supporting charities decided to use celebrities and, although we've been trying over many years to approach absolutely everyone with MS and Parkinson's in this country we had really limited success, it was kind of a steady stream of donors that kept the donor scheme going. But when the celebrities appeared it was a completely different story and it suddenly opened this whole area to people who never even considered brain banking, brain donation, or any kind of tissue donation.⁶¹ It wasn't really a great thing to experience and we finally gave up on it.

⁶¹ See note 58.

Perry: Could you elaborate on why it's not been a good thing?

Gveric: It's because the perception was of brain banking being an industry, that's what came through. People were expecting us to collect their brains expediently, to speak to the brain collecting department, to someone in charge, and all sorts of things. Within a week we went from 40 to 4,000 enquiries and it was 2 of us dealing with all of this and battling with the perception of this brain bank being ready to receive all these people. It still remains a problem because we have far too many brains for our own capacity and that's why I think this kind of steady approach where you employ people who are interested, rather than just those who can make it really popular, is a much better thing to do.

Perry: Right, so celebrities are good in some instances.

Jenkinson: We were talking about control tissue a moment ago and I thought I'd mention two specific collections. In 2005 Jeanne Bell set up the Sudden Death Brain Bank and then, of course, more recently, the MRC set up the control bank in Oxford specifically to collect control tissue to help address these problems.⁶²



Figure 14: Dr Joanna Jenkinson

⁶² Jeanne Bell is Emeritus Professor of Neuropathology at the University of Edinburgh, and founder of the MRC Sudden Death Brain and Tissue Bank, which was set up in Edinburgh in 2005 to collect post mortem tissue samples and organs of individuals who had died suddenly, with either normal brains or with a CNS or psychiatric disorder. See Appendix 2 and Millar *et al.* (2007). The UK MRC control brain bank is part of the Thomas Willis Brain Collection in Oxford and was set up in 2010 to address the shortage of normal brain tissue donation to be used as comparators in research.

I think it's quite interesting that both these aim to collect from younger people. It's not the same demographic and this has been entirely possible. Actually that echoes what Carol said about having a diversity of approaches in the way that you're dealing with brain banking. So prospective cohorts are important but our experience shows that they will capture a certain demographic. I think the Mind Over Matter project showed us very clearly how successful approaches to donation can be if you give people the right information and communicate clearly.⁶³

Perry: I thought your comments chimed very well with what Djordje said. At the brain banking meeting the other week our lay member pointed out to us that if you take on lots of brains but then decide you're not going to use them, this is a real betrayal of somebody giving tissue on the understanding that this is the last gift that they can give that might be useful.⁶⁴ I think it is very difficult. I can understand how the Parkinson's disease (PD) bank now finds itself in a difficult position with very large numbers of brains and so forth. I think you're right that there are concerns that trying to turn it into an industry is not a smart thing, not that you were trying to.

Gveric: I think the main issue is not really betrayal of all those people who suddenly appeared, because they didn't really expect much, they never thought of it. They saw Jane Asher holding a brain and they said: 'That's a great thing to do. Shall we just call them and leave our brains?'⁶⁵ It's more about those people who were registered for about 10–15 years on the donor scheme and they are becoming cases that are not really interesting to researchers. We know that someone with MS who is in their 70s is not exactly the best case to look at. We had loads of discussion about this and also with management boards and never came to anything meaningful – it was just 'carry on'. But what can you do? You don't want to disappoint people, it's bad PR. I think it would be fair to go back and just explain that it's not really what we want at this point, but it's very difficult.

Shaw: In what way don't you want the 70-year-old with MS?

Gveric: It's just that people who were registered at some point and who have lived happily for about 20 years, occasionally ask: 'I'm in my seventies now or eighties; am I really useful to you as a donor?'

⁶³ See pages 14 and 28.

⁶⁴ Professor Hugh Perry wrote: 'The lay member of the Brain Bank Management Group is Archbishop Douglas Lewins.' Email to Ms Caroline Overy, 14 October 2014.

⁶⁵ See note 58.

Shaw: And do you feel able to say ‘no’?

Gveric: No, I don’t feel able to say ‘no’. You have to really judge the character over the phone and say: ‘How do you feel about it?’ and then it’s a discussion. We have quite a few of these cases.

Shaw: We have enquiries in the same way but we are able to say ‘no’ in a nice way. It’s explaining to people that actually it’s not going to be valuable for research.

Gveric: It’s more about the actual active approach, not just waiting for people to come into you, because we probably have more than 10,000 people on the donor scheme. Out of those 10,000 I’d say maybe 2,000 really shouldn’t be on the donor scheme for all sorts of reasons.

Shaw: But you could, even at the time of death, say to the relatives, ‘Actually...’

Gveric: It’s very, very difficult. It’s very difficult because then it’s the lasting gift.

Shaw: I know, and you’re disappointing them. Yes, I understand.

Esiri: I think it can be difficult to predict what people are going to be interested in so, for example, we’ve actually got quite interested in looking at Alzheimer’s changes in people who have multiple sclerosis, and then we need people who are in their seventies and eighties and we find we haven’t got very many of them.⁶⁶ The other thing is that people increasingly want large numbers of cases. We used to be studying 10 cases and 10 controls and it’s gone up to 50 cases and 50 controls. Now it’s going up to 500 cases and 500 controls, partly driven by the very large numbers of people that are needed to be studied in genetics. So I think it’s hard to predict exactly what could be valuable in future.

Francis: I completely sympathize with the approach and more recently I’ve actually started answering the telephone to people who ring up so I’ve now got practical experience of what people say when they’re on the phone. At BDR we’ve taken the approach that we want to keep a cohort of a particular size so actually now in some centres we’ve stopped recruiting and we’re telling people we’re only going to be able to take them on if people die from the cohort; we’re

⁶⁶ Professor Margaret Esiri wrote: ‘I was referring to ongoing research looking at the prevalence of Alzheimer-type pathology in brains collected from people with MS dying at different ages. For completeness we needed to include cases that had died in their 70s and 80s – cases that, for the study of MS pathology itself, are not a high priority because most of the pathology is “burnt out” by that time and for people with MS to have lived that long implies that their pathology was only mild.’ Email to Ms Caroline Overy, 15 October 2014. For the abstract describing this work, see Ridgeon *et al.* (2014).



Figure 15: Dr Joanna Jenkinson, Professor Paul Francis, and Dr Catherine Moody

going to maintain this cohort. We can say to people who ring up *ad hoc* and ask whether we'd like a brain, that for us the most valuable brains for research are those with clinical information, and that's what BDR is about. Most people, when you talk to them and say that, understand and they feel that they've done something positive by offering the brain – it's 'Yes, well I've done that, that's what my mother wanted' or whatever, and they will then accept at that point that it's not going to happen.

The other thing that we do say to them, particularly when we might decline for other reasons, is that it would be unethical for us to keep brains in our collection that are never going to be used. I take Margaret's point about what could be used and I know Seth has made a case, and Simon Lovestone⁶⁷ has made a case, that we don't need a huge number of Alzheimer brains because there are a lot already available in very end stage, but what you can do is keep those pieces that get requested more frequently. For example, with Alzheimer's disease that would be the hippocampus – everybody wants hippocampus. They don't all

⁶⁷ Simon Lovestone was Professor of Old Age Psychiatry at King's College London until 2014 when he was appointed Professor of Translational Neuroscience at the University of Oxford.

need it, as David Mann routinely tells me in the Tissue Request Committee, not everybody needs to study the hippocampus. But there are ways of dealing with this and, in my limited experience, it is better if you're honest with people; Gillian Hayes would say much more about this in her experience of dealing with people who ring up and say: 'Can you take my mother's brain?' and so on.⁶⁸ Our commitment though, if they are part of our programme, is that we will do our best to recover the brain and put it into the brain bank, mostly so that we can get some sort of neuropathological diagnosis for the family, which is often quite an important thing. But if we also say that we will then dispose of the tissue if it is not being used or it's not being requested, I think that's something that we've got to move to: that we're not going to keep these collections forever; people understand that they will have – I don't want to use the phrase in the way that it's used in a supermarket – a shelf life; these brains will be in the bank for a certain amount of time and then they will be replaced by other brains. I think that's another concept that we perhaps ought to think about and Seth, I'm sure, is going to say more about that.

Love: I was going to comment on something else. I don't think it's appropriate to have a 'one size fits all' approach to dealing with brains and I agree with you that if people have registered with brain banks and they've been on the donor register for several years it would be wrong not to accept their brains. But I don't think that the sorts of brain you've been referring to need the same level of assessment as the brains that are going to be much more in demand by researchers. I think there are compromises to be made. What I was going to pick up on relates to the comments that Djordje made about people with multiple sclerosis who want to donate brains and died many, many years after the acute illness: some chronic neurological diseases are just much more difficult to study by looking at autopsy brains than others. A lot of the psychiatric diseases are like this. For example, schizophrenia is often a disease of adolescence and these people then survive into their sixties and seventies and you have to wonder how useful it is going to be to study their brains. That isn't to say we shouldn't do post mortem research in that sort of disease but I think we have to have a slightly more imaginative and different approach from the passive one of just saying: 'If you've got the disease go on a donor register and when you eventually die we'll examine your brain.' We need to be latching on to other studies like

⁶⁸ Dr Gillian Hayes is Senior Manager at Brains for Dementia Research at King's College London. She was invited to this Witness Seminar but was unable to attend.

Biobank and various other ways to try to predict people who are at risk of diseases and who may die through other causes because otherwise I think we can expend a lot of money and not get an awful lot back.⁶⁹

Perry: The message I get from you, who are right at the front of the field, is that as long as the communication is transparent then it's clear that you can build up a degree of trust and so forth. I think the sort of problem that Djordje gets is when there is someone at the end of the telephone who doesn't know us, who says: 'I want to give my brain' and you have to think off-the-cuff: 'What am I going to say?' It's pretty clear this is not going to be an easy conversation but transparency and honesty, given what we've heard about Alder Hey and other related issues, has got to be the way forward. Maybe one of the problems is that there are still many aspects of the process of research about which people have no idea what it actually involves. I think that research to most people is somebody standing around in a white coat holding something that looks like a dagger, which is actually a pipette, stirring some bottle – lots of senior figures like myself are asked to put on a white coat and sit by a microscope for some ridiculous reason for publicity purposes.⁷⁰ This is called research and, of course, there are layers upon layers of different activities. I'm not sure in the context of brain banking, and actually many other areas of research, that we explain it well enough – what these many layers are. If we did, we might be in a position of some strength of being able to say: 'Well, we could go so far but no further'; or 'Thank you, but it can't contribute to this but it might contribute to that'; or 'We would have to assess it but you might be one of those people that we won't need'. Until we start to educate the public at every level, and I take your point, David, I think it is a problem. I think there are clear socio-economic strata. There are people who watch these dreadful hospital programmes and it seems to me they end up with a bewildering degree of trust in how some doctor will diagnose the rarest disease known to man, or discover that 24 interventions will rescue the dying child and the child walks out... I think it's so misleading and unless we're honest and communicate with the public in a transparent way we

⁶⁹ The UK Biobank, established by the Wellcome Trust, the Medical Research Council, the Department of Health, the Scottish Government, and the Northwest Regional Development Agency, was launched in Manchester in 2006 to gather biological samples and medical and lifestyle data from 500,000 people aged 40 to 69. It is a long-term research programme to create a national database to improve prevention, diagnosis, and treatment of serious illness. See the website at www.ukbiobank.ac.uk/about-biobank-uk/ (visited 8 September 2014).

⁷⁰ For a discussion on the image of the scientist see, for example, Flannery (2001).

lead ourselves into exactly this problem: that a famous figure holds a brain and that is research; somehow, by diffusion, the great neuropathologist diagnoses what's going on, just holding it in his hands. Clearly nonsense.

Gveric: I think our problem was slightly more complex than that because we were dealing with an intermediate level called charities and I was quite blessed to work for brain banks which were always supported by charities. Charities have a slightly different view of what we have, what is public perception of research and how we should go about explaining this and so forth. This was really the main issue – how do we tell these people honestly ‘This is not what we want’? Charities were not ready for that; they didn’t want us to do that. That was the main problem. The other problem, probably referring to recruiting younger people for brain banking, was the level of hope that you’re dealing with. When we tried to find these younger people with this particularly nasty form of MS who would be really good for brain banking we encountered a lot of hope among their parents because they were still hoping for this miraculous cure that would suddenly pull them out of this disease and that was it, and there was no question that we could talk about brain banking. Only when the hope disappeared could we then put this forward and tell them: ‘This is really something that we would like you to do if you are ready for it.’⁷¹ These people also seem to be very isolated, they don’t really belong to any branches of the charity or they’re not really visible, so that was another problem for us in developing all this strategy that we tried to put in place.

Perry: There are many layers. One of the things we don’t tell the public often enough is that actually most experiments fail and lots of research also fails. But because we don’t like to tell people this we paint ourselves into a corner of ‘the hope is just around the corner and a pill will be a cure to everything from obesity to smoking’, which we all know is nonsense.

What I’d like to do is now move us forward. I don’t like to use the phrase but I will – ‘post Alder Hey’. I’d like to know from the assembled company whether it had any good consequences. What were the good things that came out of this exposure of tissue pathology to a more public scrutiny? I have the feeling there are some good things that have come out of it and as a consequence of that it has

⁷¹ Dr Djordje Gveric wrote: ‘This refers to our attempts to recruit people with rapidly progressive MS and is given in the context of trying to recruit younger people onto a donor scheme. Sadly this condition usually has a very short duration and patients rapidly deteriorate. Pathologically there is an abundance of inflammatory lesions in the CNS which are of particular interest to current MS research.’ Email to Ms Caroline Overy, 23 October 2014.

changed procedures. Then I'm going to fast forward into how we think about modern banking – we're now post 'brain collections', we're now into serious brain banking – to make this a resource that really will make a difference to the lives of people living with difficult diseases. I think that would be a structure for the next little while. So, post Alder Hey – has it had good consequences?

Love: I think that standards of governance of brain banks have improved and to some extent that's due to Alder Hey or due to all of the events that occurred after Alder Hey. I think also they're much more uniform across the UK. There was an initial period when a lot of the general public were very suspicious of anything to do with tissue retention but I think that's passed now. I think as a result of some of the procedures that were put in place there is a greater level of trust now in the process and in the operation of brain banks so I think those are all good things.

Francis: It's interesting what Seth says. The general public does not understand the Human Tissue Act; they don't necessarily understand the Mental Capacity Act.⁷² Do they trust us that we're operating it correctly? I don't know. But it's at least something you can point to. The governance structure is good to some extent. There are still things that need to be addressed, which are bureaucratic rather than helpful, for example as we're having to document every slide that's used because it is human tissue – every tissue slide that goes through the process. If it's homogenate it's still human tissue but it's outside the Human Tissue Act. Now these things are a little bizarre in terms of their interpretation. If you can see cells it's human tissue, if you can't see cells it's not human tissue according to the Act. There is a sort of bedding down of the way that these various governances will work and we are in a period where we haven't reached perhaps optimal use. The other thing I would say, and this is a perennial problem, is the way that ethics committees deal with research tissue banks, as they call them. This can be very, very arbitrary. Now I know the Health Research Authority, under Jonathan Montgomery,⁷³ is going to really tackle this and try and deal with it, but all of this has come out of the processes which have gone on. Eventually we'll get to a good position but the good thing is that we can turn round to the general public

⁷² The Human Tissue Act (2004) regulates the removal, storage, use, and disposal of human tissue. See www.legislation.gov.uk/ukpga/2004/30 (visited 18 June 2014). The Mental Capacity Act (2005) is designed to protect those who lack the mental capacity to make decisions for themselves. See www.legislation.gov.uk/ukpga/2005/9/introduction (visited 18 June 2014).

⁷³ Jonathan Montgomery is Professor of Healthcare Law at UCL. He was appointed as the first Chair of the Health Research Authority in 2012 and is Chair of the Nuffield Council on Bioethics.



Figure 16: Dr Joanna Jenkinson, Professor Paul Francis, Dr Catherine Moody, Professor Margaret Esiri, Professor David Mann, Ms Brenda Nally, and Ms Karen Shaw

and say that we are properly regulated. We might not like it as being optimal, I think in two or three years, maybe I'm being too optimistic, but I think it will be better and there will be a reasonable environment that promotes research, providing nothing happens with the European Union, which I understand has a new set of regulations that might interfere with our ability to look for clinical data and I'm not competent to comment on that.

Esiri: I agree with most of what's been said about the good things. From my own perspective the bad things outweigh the good things in that the red tape has got stronger and the consent forms have become so complicated that it's just taking a sledge hammer to crack a nut for a lot of it. Shipman didn't help with the changes that came in for death certification and so on that have made it even harder to get death to post mortem removal of the brain intervals down.⁷⁴

Perry: Tell us how Shipman influenced things.

Esiri: I think it's because they've changed the rules about who can sign a death certificate. The other thing that's had an effect is the change in GP behaviour, so that they're often not there. The GP who saw the person alive last has to be the person to sign the death certificate, and there's so much change in GP rotas that it can be quite hard to get hold of the person who last saw that person alive. The consequence is that we have death to PM intervals for brain removal that are far

⁷⁴ Harold Shipman, a GP in Hyde, Greater Manchester, murdered 215 patients between 1975 and 1998. The subsequent Shipman Inquiry highlighted deficiencies in death certification and proposed reforms to the Coroner Service, death certification and registration, and the pathology service; see the report online at www.gov.uk/government/uploads/system/uploads/attachment_data/file/273227/5854.pdf (visited 8 September 2014).

too long in this country. For example, in the Netherlands they have a brain bank in which the death to PM intervals are in the region of 6 hours, and ours are all too often 48 hours.⁷⁵ So the value of the tissue is greatly reduced. I say greatly, there's still a lot you can do with it, but certainly it would be more valuable if we could bring those times down, and there seems to be no understanding of the importance of this. GPs don't give priority to signing a death certificate because they've got such a lot of living patients that they've got to look after. So they don't give priority on a Monday morning to signing a death certificate. Things like this really get in the way of providing the best service. Do any of my colleagues agree?

Lantos: I think the immediate aftermath of Alder Hey was more positive to some extent, than negative. On the positive side we reviewed all the existing procedures. This we'd done anyway from time to time since our brain bank had been funded by the MRC and they requested regular audits. Yet we went through all the procedure to tidy up anything that may have been a problem. One problem that emerged was the future of the archival collection at the Maudsley and the Institute of Psychiatry; this later became the responsibility of King's Clinical Neuroscience Centre (Department). This collection had been carefully catalogued. So that was what was on the positive side. On the negative side, and I have to agree with Margaret, the bureaucracy has become much heavier. Although the number of brains we received didn't go down at all, all the procedures actually became more complicated.

Mann: It's not only a question of getting the GPs to certify death in a reasonable period of time, but also there's the interaction with the Coroner's Service, which plays a part in the sense that Trusts, or our particular Trust and many other Trusts in the country, are not happy to allow even tissues consented for donation to be removed from the body until all elements of a potential Coroner's Enquiry have been removed. They will only do that once they have physically seen the so-called 'green form'.⁷⁶ This happened in our own Trust, not with a brain donation but another organ donation for research, where the tissues went for research, and then a Coroner's Enquiry was subsequently called and the tissues were not there for assessment as part of that enquiry. As a result of that the Trust has put this blanket policy in place, that it's not permissible even with the best of will by the mortuary staff. They're quite happy to participate and reduce post mortem times, but they're hide-bound by Trust bureaucracy.

⁷⁵ For the Netherlands Brain Bank see, for example, Ravid and Swaab (1993).

⁷⁶ See note 43.

Perry: It seems unlikely that it's going to be the prospective donor who is going to push for a shorter PM time. It just seems to be one of those things. I find it hard to imagine people doing that – 'I want my brain taken out within an hour of my death.'

Esiri: Relatives do try and do that sometimes; people do put pressure on a GP to get the death certificate signed, but they haven't got a lot of power.

Perry: The question is where does the power reside to change this? We're going to move into this new brain banking era where we don't want to do just chemistry but we want to use all these other techniques that are now available. Where does the pressure reside?

Jenkinson: We're aware that these issues existed with the green form and what we've done through the Network is work very closely with the Human Tissue Authority and the Chief Coroner to get to a position where we have an agreed set of guidance that will be available on their website for all of the banks, making it clear that the green form is not a legal requirement for donation to go ahead.⁷⁷ The NHS Trusts have all been communicated with through their chief executives by Sally Davies informing them that the green form should not be required and that they should facilitate brain donation.⁷⁸ So I think we are making as many steps forward as we can to clarify a lot of these issues with the donation process.

Perry: Who is the 'we' exerting that pressure, Jo?

Jenkinson: The UK Brain Banks Network.⁷⁹

Perry: People like Seth and Paul, is that what you're doing? You're leaning on somebody?

Love: Yes. I think we can put pressure on the coroners and, although they don't have to respond to that pressure, the Chief Coroner has responded very positively. I think it's very much more difficult to put pressure on general practitioners in any sort of systematic way to respond quickly in terms of signing death certificates. I don't know if families sometimes put pressure on individual general practitioners but I don't think you can tackle that in a systematic way across the whole country.

⁷⁷ See comments by Dr Djordje Gveric on pages 60–61 and note 96.

⁷⁸ Professor Dame Sally Davies (b. 1949) has been Chief Medical Officer for England since 2010.

⁷⁹ See note 6.

Brayne: I wonder whether it's worth talking to the Royal College of GPs about it in terms of honouring their patients' wishes and so on. I think it would need to come through some central primary care body and I guess the Royal College would be the obvious one.

Nally: There's another issue which the UK Brain Bank Network is trying to address through James Ironside, its outgoing director⁸⁰ – I think you know about this, Seth – and that is the NHSBT (National Health Service Blood and Transplant) Organ Donation scheme, which hasn't included brain donation and has been reluctant to do so, is intending to formulate a policy about that and it hasn't yet happened.

Love: I haven't been directly involved in those discussions. As far as I am aware there is a possibility of including information about brain donation on their website but that's probably as far as they'd be willing to go for the moment. Jo will correct me.

Nally: I think even that would be enormously helpful. I found, for instance, in my work in Northern Ireland that that's come to a halt because there's a presumption there that because the NHSBT's official policy at the moment is not to support brain donation, that is not an area that they would want to enter in terms of supporting post mortem research into autism.

Perry: So, if you are an organ donor for kidneys or corneas or whatever other tissues, you're not necessarily a brain donor?

Nally: No, there's no information given to you about the need for brain donation even in terms of links to the brain bank sites.

Jenkinson: I think as we continue to formulate our donation policies we need to be slightly careful because obviously brain banking has limited capacity to take these donations and we've already discussed today and many times the idea of raising expectations that we then can't fulfil. Actually I'm not sure that we would drive towards including brain donation as part of the donor registration card. Yes, it would be good if there was increased information, which is why we've been discussing with NHSBT the idea of them including information about brain donation on their website. Similarly, when we're talking to people about brain donation, perhaps predominantly those in the younger cohort, we might

⁸⁰ Professor James Ironside holds the Chair in Clinical Neuropathology at the University of Edinburgh, and was Director of the UK Brain Banks Network from 2009 to 2013.

talk to them more widely about organ donations; you've got more reciprocal discussions going on. I'm not sure that we would want to push the idea that you automatically consent to brain donation.

Perry: Is this taking us away from the older idea that you took whatever came through the door to an increased requirement for selectivity because one can do a lot with the right material.

Love: We want to encourage the assessment of people who are going to donate their brains. We want to accrue a lot of clinical information and, if possible, biochemical and radiological information. We don't want just to be contacted out of the blue after someone has died without having obtained that information, as the brain is then much less valuable for research.

Can I just point to one thing which involves a different aspect of brain banking? This is a consequence of Alder Hey that has had a very deleterious impact on Brain UK, the virtual brain bank which is also supported by the Medical Research Council. James Nicoll and David Hilton are the directors of the Brain Bank.⁸¹ This is a registry of archival material relating to collections that weren't obtained specifically for research, usually for diagnostic purposes and often coroners' autopsies, but which cover a lot of things that aren't included in the conventional brain banks. Before Alder Hey I had never heard of people wanting blocks or slides back after diagnostic assessment. I think the assumption was (and still is in Scotland) that they were part of the medical record, and they've been invaluable for quite a lot of research into entities that aren't covered by the conventional brain banks. I think that if the next of kin want the tissue that hasn't been used for diagnostic purposes to be reunited with the body for burial or cremation, it is entirely appropriate to return the tissue. What did change quite dramatically post Alder Hey, certainly in my experience in Bristol, was the expectation that not only would that unused tissue be returned, but also the blocks and glass slides would be returned for cremation and burial. We've had quite a lot of cases where, several years later, people including family members have been interested in that tissue and there's been nothing left because, in the course of very brief discussions, usually with coroners' officers, family members

⁸¹ Brain Archive Information Network (BRAIN UK) is based at Southampton University. The project has catalogued over 60,000 tissue cases from holdings of neuropathology centres in the UK, which is made available for neurological research. Professor James Nicoll, the Director of Brain UK, has held the Chair of Neuropathology at Southampton since 2001. Dr David Hilton, Consultant Neuropathologist at Derriford Hospital, Plymouth, is Deputy Director of the project. See the website at www.southampton.ac.uk/brainuk/index.page (visited 23 June 2014).

have ticked the box saying we don't want anything at all retained; everything should be returned for burial. I don't know if Margaret and David have had this experience?

Mann: I have had only one single case in my entire experience where relatives have actually requested slides, as well as the fixed residuum of a brain, for funeral arrangements. And in fact the funeral directors and crematoria hate that because cremating glass slides is an absolute nightmare, but tissue is relatively simple.

Francis: That's an interesting point. I don't think we've had any BDR cases that have actually requested material back. Going back to the business about who should we target to help facilitate brain banks, I think Jo's point is very strong, it's something we've talked about already: don't promise more than you can give; take the brains that you've got coming in; don't open the door as wide as possible. What we can do is to try to address the point about raising the quality of tissue. The relationship between post mortem delay and quality of tissue is not exact – for some things it matters a lot, for other things it matters not a jot.⁸² But one of the things we can do is engage with GPs, and I'm pleased Seth made a note about the Royal College of GPs. I think the Alzheimer's Society did have a focus group of GPs who they asked about how would they like to receive information about BDR and what would make a difference, and the results of that are available. Basically, it's about information and on the basis of that, the Alzheimer's Society target every GP surgery in the UK with information about BDR. That was probably a year ago now but the more that we can engage with GPs and persuade them that this is an important part of eventually helping patients – okay, it will be a generation further on – and the more we find out about research now, in the long term if we can improve and develop new treatments, it's actually going to reduce the load. So it's in the GP's long-term interest – if they are junior GPs, rather than people who are about to retire – that we actually do this. The other people, and this is bureaucracy, are the R&D departments and the chief executives who control mortuaries. R&D departments in hospitals or Trusts gladly sign off projects, such as Brains for Dementia Research, and from the lack of communication with other people involved, mortuaries and chief executives, you'd think they weren't on the same planet. So I think communication with these people is important, and particularly with the help of the MRC and anybody else we can muster, to really get a grip of these people and say: 'You are holding up research. You are making the quality of tissue that is coming into brain banks less good than it might be.'

⁸² See, for example, Stan *et al.* (2006).



Figure 17: Dr Djordje Gveric, Professor Seth Love, and Professor Peter Lantos

And it's important – yet again in a review that I had that came yesterday: 'Your post mortem delays are very long compared to Europe and the US.' That's a reason to reject a paper in any journal that goes to an American reviewer. Now Margaret says 48 hours;⁸³ surely we can do better than that? Some of that's about making small payments to morticians to ask: 'Will you do this?' Some of it, if the brain is coming from a bit further away, and BDR do this, is to say: 'Right, let's have same day courier rather than waiting till the next day.' You can reduce post mortem delays to 8 hours, 12 hours or something like that. There are many practical things that we can do to facilitate that but we also need something going on at the highest possible level and, Seth, this is something that I'm sure you can facilitate in your new role.⁸⁴ You are going to be all things to all men, I can see this.

Love: Expectations... [Laughter]

Francis: Catherine and Jo from the MRC have the ear of the highest level. It can happen, you know. Tanks can be driven across lawns to get this to happen. I'm not trying to be Bob Geldof in East Africa.⁸⁵

⁸³ See page 50.

⁸⁴ Professor Seth Love was appointed Director of the UK Brain Banks Network on 1 November 2013.

⁸⁵ Bob Geldof (b. 1951) is an Irish singer, songwriter, and political activist, who raised millions of pounds for famine relief in Africa, initially through his Band Aid single in 1984 and Live Aid concert in 1985.



Figure 18: Dr Catherine Moody

Moody: Seth's in charge of the Network now and I'd like to see the brain banks really rally behind him and sort these problems out. During some of these discussions I was considering, goodness me, if all these issues are unresolved why don't we in the MRC make things simpler? We could close some MRC-supported banks down and just have one bank and make it work in one location, for example, through persuasion of the local coroners and the Trust. It's slightly exasperating sitting here and hearing that the same issues are still going round and round – I would like to see a sea change in the next five years.

Perry: When were you involved, Catherine?

Moody: I was involved in setting up the UK Brain Banks Network.⁸⁶ Following a workshop organized by the MRC in October 2006, there was a UKCRC committee, chaired by Jonathan Montgomery with Jeanne Bell as deputy, that

⁸⁶ The UK Brain Banks Network includes the MRC supported brain tissue banks: Edinburgh Brain Banks; London Neurodegenerative Diseases Brain Bank; Newcastle Brain Tissue Resource; Sheffield Brain Tissue Bank; Thomas Willis Brain Collection, Oxford; Brain UK, Southampton. Also Charity/NHS partner banks: Cambridge Brain Bank; Manchester Brain Bank; Multiple Sclerosis Society and Parkinson's UK Brain Bank; Queen Square Brain Bank for Neurological Disorders; South West Dementia Brain Bank; Brains for Dementia Research Co-ordinating Centre.

looked at the potential of brain banking, because although research needs were opening up, there was a feeling that – amongst other things – tissue was available in the brain banks but it was underused.⁸⁷

A number of the funding major agencies, MRC included, got together to think in some depth about brain banking and what should be done in the UK. The UK Clinical Research Collaboration (UKCRC) committee looked at all the different angles of brain banking – and came up with the recommendation that there should be a co-ordinated UK Brain Banks Network and that, instead of banks operating just locally or for a particular disease or only for this set of patients or through a cohort, they should be connected in some way (see Figure 19).⁸⁸ The Brain Banks Network was set up by the MRC in 2009 under the Directorship of Professor James Ironside.⁸⁹ Since then actually it's gone from strength to strength and I'd also like to say one of its particular strengths is that a database was put on the web this year so prospective researchers can look in one place and see what tissue is held in each of the banks of the Network.⁹⁰ The other thing I'd like to flag up is that in the last two or three years because there's been a Network, because of the increased visibility of banks, some major genetic studies using human tissue have been possible in the dementias area, resulting in new gene discoveries made using brain material from the brain banks.⁹¹ So we really must build on this momentum and make sure that the banks are maximally used; we really must get together to sort these problems out to realise the full vision of the Network.

⁸⁷ Dr Catherine Moody and Dr Joanna Jenkinson added: 'Other issues were recognized too – for example the Human Tissue Act had yet to bed down, NHS research funding was undergoing reorganization, the coroner issues that have been mentioned and issues of compatibility and interoperability to do with the different ways that tissue was collected and preserved and information/data was not documented and made accessible. It seemed that researchers were not sufficiently aware of what brain tissue was available and that it was of high quality, and therefore work was needed to make it easier for researchers to use this valuable tissue.' Notes on draft transcript, 6 January 2014.

⁸⁸ Dr Catherine Moody added: 'This was to provide operational efficiency to maximize the potential for high quality research across the full range of CNS disorders.' Note on draft transcript, 6 January 2014.

⁸⁹ For the aims of the Brain Banks Network, see note 6.

⁹⁰ This database contains details of over 10,000 brains from all ten UK brain banks. See www.mrc.ac.uk/research/facilities/brain-banks/tissue-database/ (visited 23 June 2014).

⁹¹ For example, tissue samples from brain banks in Manchester and Newcastle have been used in the study of Lewy Body dementia in Parkinson's disease (Nalls *et al.* (2013)) and research into the presence of an altered gene in people with Alzheimer's disease used tissue from the MRC London Neurodegenerative Diseases Brain Bank and the Manchester Brain Bank from Brains for Dementia Research (Guerreiro *et al.* (2013)).

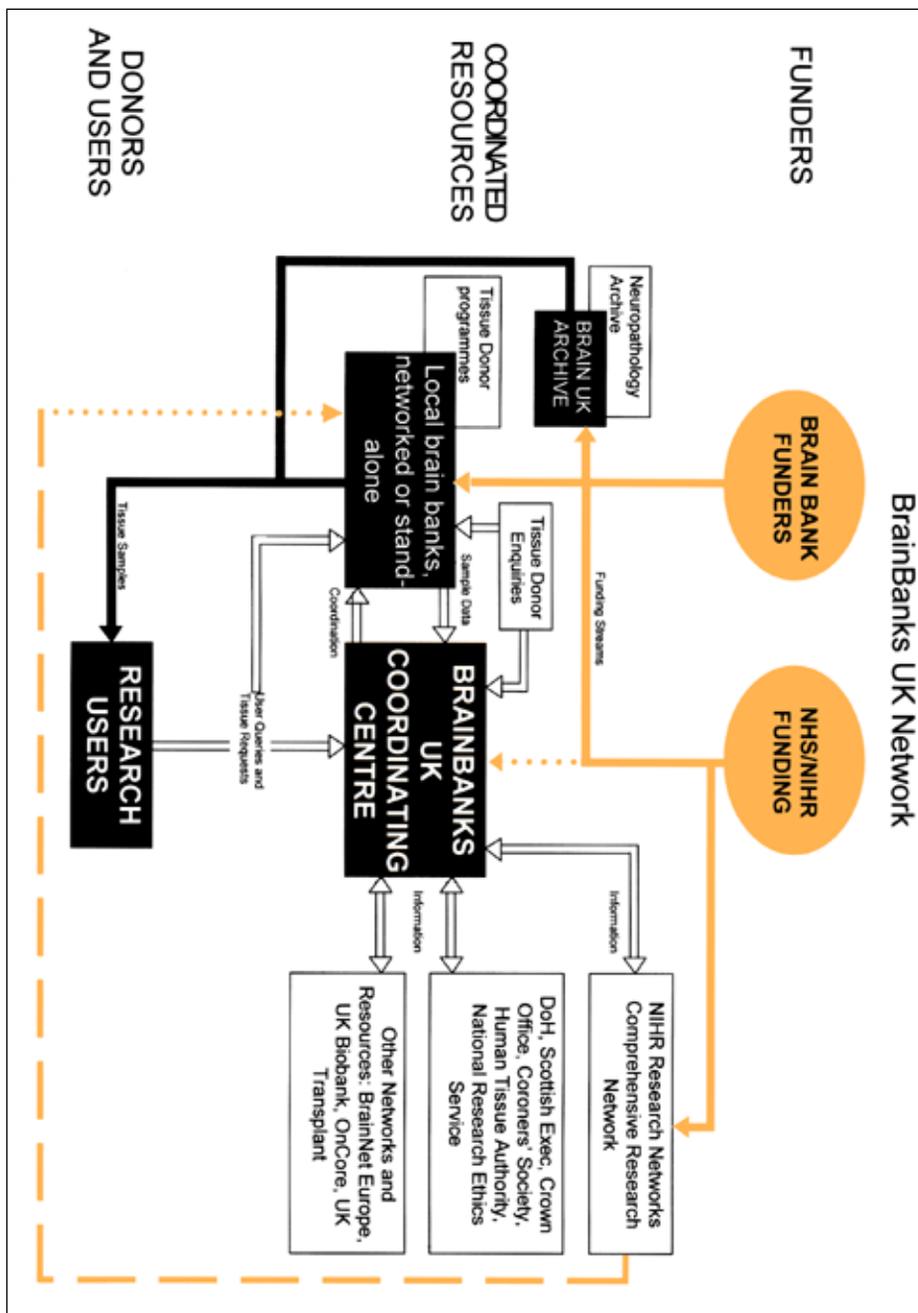


Figure 19: Diagram of the proposed Brain Banks Network. Reproduced from UKCRC Brain Bank Strategy Advisory Committee (2008), with permission from the Medical Research Council.

Perry: Perhaps people recognize that dopamine and its relationship to Parkinson's disease came out of post mortem material; acetylcholine and its role in Alzheimer's disease came out of post mortem material. I suspect there's nowhere in any of the public statements about the discovery of *Trem2* in Alzheimer's disease or recent genes in Parkinson's disease that they actually came from post mortem material.

Moody: I think that the brain banks are generally acknowledged in published papers; for example, the MRC London Neurodegenerative Diseases Brain Bank and the Manchester Brain Bank in the 2013 *New England Journal of Medicine* paper on the *Trem2* variant in Alzheimer's disease.⁹²

Perry: No, I'm sure it is in the paper but what we're talking about is in no small part public perception: when you take some post mortem tissue it goes into something called research and just disappears into the background. Margaret already described herself as a back room girl so there is an element that if brain banking is going to be perceived as being successful and contributing as an important area of research then it needs to be clearly stated that the results came from tissue taken from people.

Moody: Yes, communication to the research community and the wider public about what comes out of the brain banking is really important.

Francis: Can I add to the genetics studies? There were two genetics studies which were talking about clustering: the first discovery was on a large sample with more than 16,000 people and a small percentage were neuropathologically diagnosed;⁹³ there was a separate study with a modest sample size of 1,600 people, all neuropathologically diagnosed, who confirmed the same finding.⁹⁴ So BDR actually contributed to that study in a small way. Something I always say about BDR is that actually we confirmed something that was done in a neuropathologically confirmed group to show that clustering was a major genetic correlated disease. So I think we can do more about that and I like your point. In terms of communicating and actually getting some of these problems solved, we run a series of ethics study days where we invite

⁹² Guerreiro *et al.* (2013). Dr Catherine Moody added: 'John Hardy uses the Sudden Death Brain Bank for his research.' Email to Ms Caroline Overy, 30 October 2014. See, for example, Forabosco *et al.* (2013).

⁹³ Harold *et al.* (2009).

⁹⁴ Corneveaux *et al.* (2010).

morticians, everybody.⁹⁵ We'd love chief executives to come along so they hear about the project, so they understand about brain donation and what their role is: how you can make a difference to the process of brain donation. If you're a neuropathologist you're doing the diagnosis; if you're a mortician you can make sure that the donation occurs and you're fulfilling somebody's wishes. Occasionally we've had people come along from Trust R&D departments. Those are the sort of things that we can do and if you do it in the mortuaries that are most closely linked with the brain banks then that's one way of actually getting things to happen. That's what we try to do.

Moody: Is there something from what you do in BDR that could be done more widely amongst the other banks in the Network then?

Francis: Seth would know because he's been intimately involved.

Love: This is with respect to what? Participation in GWAS (genome-wide association studies)?

Francis: No, more generally – getting GPs or morticians to understand their importance in facilitating brain donation, making it happen more quickly is what I was thinking of. I don't know if there was something else you wanted to pick up from that?

Moody: I'm afraid I don't have any solutions for you but it does seem important to tackle this issue as a Network.

Love: This is being tackled. Quite a lot of the brain banks are involved in similar initiatives to address this. I know that locally we've been involved in initiatives with mortuaries and I know that the Parkinson's Disease and MS Tissue Bank have been involved in some initiatives in working with mortuaries. James Ironside has pushed this and I will continue to push this on a pan-network basis. I think we're all learning from each other and all doing similar things if we see that a particular approach works.

Gveric: If I can just add that the MRC fact sheet, which explained finally what's legal and what's not legal, has made a real difference to our daily lives and I can say freely that we don't really experience problems with mortuaries any more.⁹⁶

⁹⁵ For example, in May 2013, Brains for Dementia Research ran a one-day, multidisciplinary training event in Oxford, which covered the ethics of brain donation, the donor/carer perspective on donation, and the legal aspects of consent. Information supplied by Professor Paul Francis.

⁹⁶ Guidance for hospital and mortuary staff for brain and spinal cord donations was issued by the Human Tissue Authority in 2013; see <http://www.mrc.ac.uk/research/facilities/brain-banks/workshops-training-reports/brain-donation-guidance-and-faqs/> (visited 11 February 2015).



Figure 20: Professor Hugh Perry

GPs are still there and that has to be tackled on an individual level regardless of how you approach it, but the actual fact sheet really proved that the Network is working, that we can get this information across – I just need to fax this little bit of paper to the mortuaries and, regardless of the local NHS Trust rules, they will show much better understanding of what we're doing. That's really made a difference. So, yes, it's clearly working and it will take time obviously and we all need to participate and really show that kind of enthusiasm as well and share it with the MRC Network.

Perry: So, dealing with these structural issues about how to get better tissue, is critical. What I'm really keen to think about now is how to communicate to the public about why this is important. I think also that lurking around in the background of this conversation are the comments made about how people with some particular psychiatric diseases can see this as a threat. A good example, I just happened to think of, is that there are some people with deaf children, deaf people with deaf children who think that their deafness should be preserved. As we have heard, there are people with autism who feel that autism has something to offer. It suggests that we as a neuroscience community dealing with this interface with individuals and tissues are failing to convey a message that there is something

really good that can be done. One of the parallels when you think about advances in any area of medicine is, of course, oncology. Oncology has made huge advances because of the access to post mortem tissue; this led to the stratification of disease and so forth. Are we failing the brain banking community, neuroscience community, failing to portray either the good things that we do and the successes, or what is it that we're not doing that still leads to suspicion? Or is it something about the brain? Is it brain-ness and we're not communicating in the right way?

Gveric: Do we really need to work on public perception any more? I mean public memory – it has got a very small capacity. People are overwhelmed with a lot of things from recession to jobs to anything, so talking about brain banking and trying to kind of put it permanently in their memory is a lot of effort and really something we shouldn't be doing. I just want to give you an example of the latest Alzheimer's and Parkinson's diseases conference in Florence.⁹⁷ I went around looking at the posters and there were very, very few that used human tissue, or presented some kind of data on human tissue. My feeling is, using the analogy of a lunch, that research using human tissue is either starter or a dessert, very rarely a main course. So this is what we have to do: we have to work on researchers; we have to promote brain banking amongst researchers so they can use more tissue, produce better papers, better data, something that research journalists will pick up on. That's how we're going to end up in the public memory because there's something coming out of it, something valuable that people might use as a future therapy and so on. So that's the way around: work on researchers not the public.

Mann: I would echo that, Djordje. I think there is a perception, possibly amongst young researchers, that the human post mortem brain is just too difficult to work with because we can't control the course of the illness, and all the environmental and other factors that may determine the impact at said stage of the illness. We can't control these in the way we can do with cells. We can do it with mice, we can do it with chickens, we can do it with worms, we can do it with flies, we can do it with virtually everything, but man. I think there's a reluctance to actually do work with human tissues; the perception is that the problems of working with it outweigh the benefits. We can model things, do experiments that happen within weeks or months, and a PhD can be determined within a finite time as a result of that.

⁹⁷ The 11th International Congress on Alzheimer's and Parkinson's Disease was held in Florence in March 2013 and was attended by more than 3,000 delegates. Selected proceedings of this meeting were published in the journal *Neurodegenerative Diseases*. Hanin *et al.* (2014).

Perry: But doesn't this contrast with the Human Brain Project and the Human Connectome? Isn't there a desire to have human at the front of it all?⁹⁸

Mann: There is, yes, that's right. Everything is labelled 'human, human, human, human' but do we use it? And we've talked a lot about how we can increase the availability of tissues, the collection of tissues, the better storage and quality of tissues, but are we actually using them more? I'm not actually sure that that is translating through to actual usage.⁹⁹

Love: The first thing is, I don't think it's necessarily a bad thing that human tissue is the starter and dessert but not the main course. I think to some extent that's our role: we're examining human tissue because it provides the basis of a lot of disease classification, it's the starting point for the formulation of hypotheses as to what's going wrong, and then those hypotheses get tested out in the worms or the mice or the rats or in whatever system you use to manipulate the environmental and experimental variables and to reduce the problems to questions that are quite simple. And when you think you've got the answer then for the dessert you come back and ask yourself does this actually apply to human brain tissue? So you validate your findings by looking at human brain tissue. I don't think that that's necessarily a bad thing. A recent example of MRC-funded work that generated a lot of publicity came from Giovanna Mallucci, who did a fantastic piece of research showing that accumulated protein in a particular neurodegenerative disease affects the endoplasmic reticulum stress response, and that's probably one of the reasons why the cells don't function normally.¹⁰⁰ She couldn't have done that research had people not looked first at human brains and seen that there was abnormal accumulation of these rather insoluble proteins which were affecting the function of the cell, and to produce an effective therapy she'll need to go back

⁹⁸ The Human Brain Project is a European collaborative initiative, established in 2013, to use technologies in neuroscience, medicine, and computing to understand the human brain. See the website at www.humanbrainproject.eu/en_GB (visited 29 September 2014). The Human Connectome is a collaborative project between the Laboratory of Neuro Imaging at UCLA and the Martinos Center for Biomedical Imaging, Massachusetts General Hospital 'to construct a map of the complete structural and functional neural connections *in vivo* within and across individuals'; www.humanconnectomeproject.org (visited 29 September 2014).

⁹⁹ See comments by Dr Joanna Jenkinson on page 65.

¹⁰⁰ Professor Giovanna Mallucci is programme leader of the 'Mechanisms of Neurotoxicity' research programme at the MRC Toxicology Unit in Leicester. Her identification of a compound that prevents neurodegeneration in mice, and which could lead to the development of a drug to treat diseases such as Alzheimer's and Parkinson's, was widely reported in the media in October 2013. Moreno *et al.* (2013).

to human tissue to make sure that what she's identified in the prion-affected mice actually applies in human brain tissue. That's not a criticism; we don't have to do everything from start to finish by studying human brain tissue. I simply don't think we can do relevant mouse research unless we start off by looking at human brain tissue and then at the end of the day we just need to make sure that what we've observed in the mouse is real in terms of human disease.

Lantos: I happen to disagree with David. I don't think that the public is interested in fruit flies or in mice or in tissue culture; the public is interested in the human brain. Even the lay public shows great interest, since there is nothing more exciting as, for example, functional imaging, about which many reports have been published even in the popular press. Perhaps the reason for this interest is that this method is visually attractive, and ensured rapid progress in our understanding of how the normal and diseased brain works. I would not actually be so self-effacing as to say that the public is not interested in the human brain. The question of whether we are actually doing a good job in drawing the public attention to our work – that is a different issue. I personally think that actually the public finds these discoveries fascinating and not only 'Guardian readers' but also a wider variety of people.¹⁰¹

Perry: I think one important thing from all of this, the functional imaging of course, is the man in the street actually thinks the brain is coloured. I'm sure it doesn't matter.

Love: The other thing is that it's not all that surprising that so much of the research between the formulation of the hypotheses and the validation of the hypotheses is conducted in animals – more of that than there is examination of human brains. As you've said, most research hypotheses are proven wrong, most experiments don't work, so it's not surprising that an awful lot of things that are done to flies and zebra fish and mice turn out either not to work or to generate findings that aren't really relevant. I think one thing that may lead on to something to talk about later is the point that Peter made about the study of the brain being so visual. I think to some extent that's a limitation of the custodians of brain banks who have always been morphologists and neuropathologists. I don't think that brain banking should just be visual. I don't think we've done enough of the sort of biochemical and molecular genetic analysis that would maximize the value of the tissue that we have.

¹⁰¹ See page 38.

Lantos: These investigations should form the bridge between functional neuroimaging, when one actually can see what is happening at a given psychological task inside the brain, and the tissues which we have in our brain banks.

Brayne: That is incredibly difficult because by definition our brain donors do tend to live for some time after they have had a psychological experiment. Certainly you just have to set up huge cohorts with very regular testing and clearly UK Biobank is that kind of model, but you're still going to get tiny numbers where you have that proximity of the measuring and the death.

Jenkinson: I'd like to dispute the idea that we're not seeing increased use of the tissue. We've asked the MRC banks over a number of years to collect the information on how many samples they're sending out and we are seeing an increase in the number of samples they're sending out and the number of requests that they're getting. The number of new users that are coming to brain banking through the database is a really exciting development; all banks in the Network, all ten banks in the UK, have been asked to collect this information about how many samples they're sending out over 2013 and send that to the Network as part of their 2014 service support cost payments. So we are actually building up the evidence about how much this tissue is being used by researchers.¹⁰²

Perry: So David, feeling welcome?

Mann: I thought it was really important to document that we're not just setting up a network that acquires, but we're also setting up a network which utilizes, so that the rate of utilization at least matches or outweighs the rate of acquisition; that we're just not stamp collecting, because that's always the danger, isn't it – that you feel you're just collecting stamps at the end of the day?

Perry: David, since you were a pioneer of using enzyme biochemistry and biochemistry in frozen tissue, and given that the tissue collected is getting to be better quality, are we being ambitious enough about what we do with it? With all the problems of collecting these specimens, are the best analytical tools being brought to bear, are people really being ambitious enough or are they still just scratching the surface?

¹⁰² Performance criteria including the provision and use of samples is collected annually from the brain banks in the Network: '...Provision of samples – how many projects from the UK and overseas are supported by the brain banks in question and how many samples have been provided to each project? Have any new groups applied for tissue samples? What is the success rate for applications for tissue samples? Use of samples – how many papers are published as a result of the brain banking activity and how many patents are generated from this work?' See www.mrc.ac.uk/research/facilities/brain-banks/measure-of-success (visited 27 October 2014).

Mann: I'm just a simple microscope man, I don't understand genetics or worms and flies and things in test tubes. No, neuropathology has developed enormously over the years. We've moved away from an era where we poured coloured pink and blue solutions on things,¹⁰³ and a bit of alchemy involving silver,¹⁰⁴ and that was the be all and end all of neuropathology. [Laughter] But now with molecular pathology, we molecular neuropathologists deal with molecules, we don't deal with stains any more. We can define a level of pathological change using these tools that far outweighs what is possible with the test tube. We have the tools to identify a single cell on a slide, and say what that cell is and what's wrong with it.

Francis: There was a very lovely presentation at the Alzheimer's Research UK conference early this year – Konrad Talbot talking about kinase activity and showing functional studies in post mortem human brain, which I'm really impressed with. He had all sorts of studies in the publication.¹⁰⁵ Just in terms of people who use tissue, one of the things we're quite keen to record, and I'm not sure whether the MRC is actually recording this, is whether the people who are requesting tissue are new to requesting tissue from brain banks? I think that's quite a valuable thing to record. One of the things we do is try to help the people who come to us with a tissue request that doesn't look particularly good, by feeding back information to help them to develop their tissue request and ask for the right things and the right numbers because it's addressing the point that people think it's very hard to work with human tissue. If we can show that we're increasing the number and capacity of researchers who are prepared to work with human tissue we will get the new ideas because these are people coming from doing their studies on *Drosophila*, zebra fish, all these transgenic studies, and they'll say: 'Actually, why can't I do that in human tissue as well?' So I think that's quite an important thing that we try and support, and perhaps we can at least record it.

Jenkinson: We're not systematically recording whether each user is new but certainly with the database we've seen that a lot of the people registering for that database are young investigators; they're not people we would normally

¹⁰³An early histological technique in neuropathology was the H&E stain. The acidic dye eosin is used to stain basic (in the chemical sense) structures pink; the basic dye haematoxylin is used to stain acidic structures purple or blue.

¹⁰⁴Silver stains are used to identify nerve cells and their processes.

¹⁰⁵Bomfim *et al.* (2012).

associate with brain banking who already know who to talk to about acquiring the tissue. So I think the database is reaching a new audience and actually the type of iteration you describe where the bank manager or administrator works with the person requesting the tissue to make sure that they're getting the right samples from the right location from the right number of donors is actually the really important added value experience that the banks offer and we can't underestimate the value of that. So actually having a system where people could just order tissue straightaway through the database isn't what's important, it's making that connection and making sure that they're getting the right samples that they need for their study.

Perry: I think it's probably true to say that many people who work on flies do not understand what Brodmann areas are, or the cyto-architectonic subtleties of the thalamus, so this is probably very important.

Esiri: I just wanted to make the point that the committees that decide how funding should be allocated also come into the equation here because if people who commit money for research are not themselves in favour of research on human tissues being performed, that's going to get in the way of even keen researchers who want to do it. So there's also a perception there that perhaps needs to change.

Perry: Can I respond to that? I think it's hugely important to recognize that all of these things are driven by peer review and that relates to my comment earlier about whether the PR that refers to the use of human post mortem tissue is good enough:¹⁰⁶ if the research isn't perceived as being a significant step forward then it's always going to be seen as something in the background. As we captured in our comments right at the beginning of the meeting, it's not clear sometimes whether human post mortem tissue studies are really setting the pace for the research. I think Djordje's comment is quite important – are the animal models the drivers of how we think a disease is understood? People used to refer to Alzheimer's transgenic mice in the title of their papers. Now they refer to 'Cure for Alzheimer's disease' in a paper and it turns out it's research in mice or flies.¹⁰⁷ I think that those working with human tissue not communicating the value of what they do is actually detrimental.

¹⁰⁶ See page 59.

¹⁰⁷ See, for example, Franco and Cedazo-Minguez (2014).

Esiri: Well, the other thing that I was going to say in relation to communicating what you do is that we have tried, particularly Brenda has tried hard with the Brain Bank for Autism, to get articles and interviews into the public domain about what we're trying to do because we've been so aware of the need to educate people. It's terribly hard to get people to carry these articles and Brenda actually can talk to this more than I can, she has a lot of experience of trying.

Nally: Yes, I have and, as you say, very limited success but where we have been successful it has yielded a tremendous public response, a very positive public response.

Perry: So this is trying to publish in national newspapers?

Nally: Yes, primarily.¹⁰⁸ I think one of the basic issues that we haven't mentioned and which does come into discussion with journalists and with members of the public, is the effect of attitudes to, and feelings about, death, which is inevitably associated with this whole area and sometimes negatively associated with it. So very often that's an area that journalists want to look at.

Perry: They would like to explore the issues around death?

Nally: Explore public attitudes to it and how that might affect responsiveness to research appeals. I'm very aware that the research into autism faces very different issues and that emerged very clearly in this discussion today – issues about difficulties in reaching donors and the huge need for brain donation and the fact that research is being held back by a lack of tissue. I think that's very different in autism research from all the other areas we've discussed. But, yes, I think there is a resistance in the media and I'm sure people are interested in this issue and aware of people's resistance to issues connected with death. Also, professionally, people working in public services and also some charities who act as gatekeepers to the public and to the community that we are trying to reach, have their own personal resistances and their own sensitivities to the issues that concern people who are most directly affected by it – the issues I talked about earlier on about resistance to this research as being unnecessary and not in the area they would want it to be.¹⁰⁹

Perry: Karen, do you have anything you'd like to add to that? You're a gatekeeper too between the patient and research.

¹⁰⁸ An article on the UK Brain Bank for Autism was published in *The Guardian* two days before the annual World Autism Awareness Day held on 2 April. See Gentleman (2013).

¹⁰⁹ See the discussion on pages 31–33.



Figure 21: Ms Karen Shaw

Shaw: And researchers and medics.

Perry: And death, you're right there. We've hardly used the word 'death' at all. It's probably quite important. When you have these discussions with people about donation, is death actually an important part of the conversation or is it that you simply avoid that bit and you talk about what's going to happen afterwards?

Shaw: It can be either. When I said to you earlier about approaching people in an individual way, I think that's quite important. So, yes, some people may want to talk about it in the context of them dying; other people absolutely don't want to and would rather avoid that part of it and think about when they're no longer going to be here and it's going to be the relatives' responsibility. So everybody's quite different. One of the clinics that we do at Queen Square is the progressive supranuclear palsy (PSP) clinic. We have a palliative care consultant as part of a multidisciplinary team and I can work alongside her so we can explore issues of death and then about donating for research, but on other occasions we don't have that and I don't talk about death. It really depends on who the person is and which way they are wanting to take it.

Perry: If you were going to give some advice to Seth, for example, who is going to start a new PR campaign for brain banking - 'only the right brains in the right bank', 'the very best bank for your brain' – should the word 'death' appear? If we're going to discuss post mortem tissue, should the word 'death' appear?

Shaw: You mean in the kind of promotion?

Perry: Yes. 'When you die you can do something useful' Maybe that's not quite the way to put it but... 'When you die', 'after your death'...

Shaw: Maybe, I think euphemisms are totally unhelpful.

Perry: I'm interested, you say yes; not everybody else says yes. Then why don't the press want to take your articles that deal with this? If everybody here thinks that's fine, that's just what people expect.

Lantos: Perhaps because we don't have the right handle on it. The press endlessly deals with, and the BBC is obsessed with, assisted death. It's spelled out quite clearly to the point that they describe in detail people travelling to a clinic in Switzerland where they are being, at their request, killed.¹¹⁰ So I don't think that the public in general is averse to talking about death and I don't think that it should be a problem.

Can I come back to the wider problem of the future that you just mentioned, but which we haven't discussed yet? I think the success of the brain banks, apart from the competence of those who run them, depends on two major factors: one is outside funding, and the other is public perception and support. This is where I seem to detect a slightly negative attitude on our behalf – we don't think that our work on the brain is actually of interest to the public. If you were to ask the man on the Clapham omnibus, or in a few years' time those on Crossrail,¹¹¹ which organ they would find most interesting, on account of its shape and function, I would say most people would choose the brain. Now that is only the normal brain. However, considering diseases of the nervous system, the public is interested in their prevention and cure; a few years ago it would have been a very different matter. Now we can say that some of the most frequent diseases involve, in one way or another, the brain. As a trustee of Alzheimer's Research UK we

¹¹⁰ Assisted suicide is illegal in the UK but is permitted in some circumstances in clinics in Switzerland (e.g. Dignitas). Between 2008 and 2012, 126 people from the UK travelled to Swiss clinics to die; see Gauthier *et al.* (2014).

¹¹¹ Crossrail is a new 73-mile railway line currently under construction to serve Greater London, tunnelling under central London. It is scheduled to open in 2018.

found that our funding, despite the recession, went up considerably because the public became aware of the devastating effect of Alzheimer's disease. So I don't think that there should be a problem, in principle, to make the public aware that actually brain tissue is being used. Every so often on a Thursday morning on the *Today* programme there is a report of a medical breakthrough, referring to *The Lancet* or *New England Journal of Medicine* and it quite often relates to a genetic discovery of one or another neurological disease. The public may not be aware that without the use of human tissue these discoveries would not have been possible. So I am actually more positive about future possibilities of spreading knowledge. I think we have to communicate and for this reason the Wellcome Trust, for instance, could make a series of documentary television films, if not already made, on the use of human tissue from the beginning of research to the present day: about the discoveries that would not have been possible without using human brain tissue.

Gveric: I can say no to death in a new way because there is no real need to discuss death at any point. Death is obviously part of life, as it is, and for brain banking it's basically that practical turning point when you can get the brain. So we have developed language already for dealing with death; we're talking about a lasting gift and it's just part of all this charitable culture of donating something, whether it's money or whether it's part of you, when the time comes. And that's really about it. I've spoken to many, many people with MS and PD and have never mentioned death and they never asked about death apart from some practical issues about funerals and so on. So death is fine and most of the people are fine with it at a certain point in their life. So I guess we can just carry on as we have so far.

Shaw: I think euphemisms such as 'when the time comes' are not particularly helpful.

Gveric: It works very well. And we are extremely happy with that.

Perry: Karen, you don't use that kind of language?

Shaw: No.

Perry: So what do you say?

Shaw: When you die.

Perry: Why do you not like those euphemisms?



Figure 22: Professor David Mann

Shaw: Because I've heard doctors using euphemisms: 'when the time comes' and actually I've seen patients getting the wrong end of the stick on that one; and 'maybe we could have a piece of your brain when the time comes' and the relative and the patient have thought that you mean some kind of therapeutic input in a bit of their brain. They didn't realise it meant taking the brain when they died. So it can be misconstrued, I think.

Mann: Another common euphemism again is that we're reluctant to talk about taking the brain as a whole; we hedge around and say: 'We would like brain tissue' as though it's some kind of nebulous amount, and we can solve everything on a pin prick of tissue. We don't like to say: 'We'll take the whole brain.' I don't understand why, but that's the kind of medical euphemism that goes around, that pervades everything in life, anything to do with medicine; doctors speak in euphemisms.

Brayne: Just to say that I agree with the sort of clear, clean language, to use the neurolinguistic programming term. When we were developing the donation programme we moved away from talking about 'pieces of tissue', we went to explicit description of how the brain is taken out because actually what it did was flush out all those misconceptions about what people think happens at post mortem. As regards talking about death and not beating about the bush, our experience in the older population – it may be different for different age

groups – was that it was on the whole welcome, and that people appreciated the opportunity to talk about their own death as they had not been able to raise it with their families. It was an opportunity for them to decide and to discuss whether they wanted to be cremated or buried and all of those sorts of things. That honest language triggered a whole load of other positive outcomes.

Francis: Yes, certainly in the BDR our experience is completely congruent with that. People will correct you if you're not honest, and they will say: 'yes, of course I'm going to die, I just want to sort it out.' Even if you approach it cautiously, older people remain incautious. They will tell you exactly: 'Well, I'm not going to need it, am I?' It's actually a surprisingly common response, so I don't think there is an issue about mentioning death. As you say, Carol, it's the practicality – they want to know whether they are going to be scarred? We tell them they can have an open casket if that's what they want because removing the brain in a mortuary is not going to interfere. Even if you need to take the spinal cord it's inevitably done from the back and you can still have an open casket. And people think: 'Oh right, okay, that's fine; I understand that process.' It gets rid of these misconceptions – a 'piece of tissue', are we back to biopsies? It's important that we're honest with people.

Perry: The discussion about 'piece of tissue' brings me back to something that David started with. Every day all over the UK there are dozens of neurosurgical units discarding bits of human brain tissue. You were saying earlier, David, how your early studies had benefited from taking tiny samples of fresh human tissues with which you can do all sorts of things that you might not otherwise do. It has always puzzled me that there isn't a part of brain banking that involves the capture of small, half-centimetre cubes of post-surgical tissue, which I would have thought were invaluable. You could learn an enormous amount. Have you stopped doing this kind of thing, David?

Mann: Oh yes, a long time ago. I think the problem with taking cerebral biopsy is clearly the effect of the trauma in removing it. In that particular study we were taking something like 1–2cm cubes of tissue, but out of that 2cm cube of tissue probably 50 per cent was probably not usable because it was cauterized.¹¹² There are practical problems, therefore, with using cerebral biopsy tissue. Interestingly, there have been a couple of papers out recently looking as to whether one can make, or to what extent one can make, an accurate diagnosis of dementia from simulated cerebral biopsies from post mortem tissue, taking small amounts out

¹¹²See, for example, Neary *et al.* (1986).

to see how representative of the disease that might be.¹¹³ Whether that might be part of a groundswell of opinion that one should move back towards doing small cerebral biopsies for diagnosis, I don't know. It seems to be quite an important issue that has surfaced in the literature.

Lantos: I think you raise a very important issue because by brain banking we automatically talked only of post mortem tissue and that is not the case. Some of the most interesting material we have are temporal lobe biopsies for epilepsy. That is important not only because it is from living patients and being a different type of tissue but also because, unlike dementia and other neurodegenerative brains that involve an advanced age group, we are here dealing with a much younger generation of people. In addition, we are also collecting tissues from brain tumours. Brain tumours in children, I think, are the second most common tumour type; so there is also emotional involvement on behalf of the parents. Going back again to what has become my hobbyhorse, actually brain banking should not be necessarily boring and something that the public doesn't notice.

Francis: Picking up the point about biopsy and David's comment about what you could get from somebody in their sixties as a biopsy and what might be safe and agreeable to any ethics committee which was investigating that, as I mentioned the control tissue we used to have was from people who were undergoing surgery for deep seated cranial tumours. Now my understanding is that the procedures have changed so much that they're not removing normal tissue in order to gain access to these any more; they're using much more sophisticated approaches. We also had tissue from the Brook General Hospital in London which was actually for subcaudate tractotomy so they were putting in radioactive yttrium rods into pathways underlying the frontal cortex, and then they would take out small pieces of tissue and we were investigating these. We were investigating depression, intractable depression.¹¹⁴ That's not done here now but I think it is still done in one or two places in the USA so this tissue is potentially available. I think the amount of tissue is much less. Temporal lobectomies and so on, okay that's a very specialized area, do form part of a wider brain bank, so to speak, but they will be much rarer than they were, say, 20 years ago.

¹¹³Venneti *et al.* (2011); King *et al.* (2013).

¹¹⁴See Bridges *et al.* (1994); Clarke *et al.* (1995); Clarke *et al.* (2011); Francis *et al.* (1989); Pangalos *et al.* (1992).

Perry: So my attempt to get lots of fresh human tissue is obviously going to fail. There are a couple of other topics I'd like to touch on before we close. One of them is our relationship with industry. We have, over the years, had a fluctuating relationship with industry in neuroscience and people will know that in neurodegenerative disease it has waxed and waned, waned quite a lot recently and we hope that it's now going to be revitalized. In multiple sclerosis, industry stepped back and then when things started to happen and looked hopeful from a therapeutic perspective, it came back again. How do we feel that industry should use our brain banks? Djordje, you've got an excess of brains; are industry clamouring to use your excess of brains?

Gveric: They are actually; we have a lot of people who are interested. However, we also have something called 'Terms and Conditions' which prevents us from giving it to absolutely every single company in the world, including the NIH in the United States. Obviously intellectual property (IP) is the hot issue between brain banks and the pharmaceutical industry.

Perry: For all of us here: what is the issue?

Gveric: The issue is that there's obviously a line referring to intellectual property in terms and conditions for every single tissue request, saying that they need to inform us of something that might be commercialized, something they might be making profit from, and so on. That's the real problem: whether someone who is signing the contract in a pharmaceutical company will agree to it. There's a lot of negotiation and renegotiation going on, obviously very complex if it starts involving the company, Imperial College lawyers, and charity lawyers as well.

Perry: So the donor says: 'I give my tissue; I don't care who uses it as long as it's for the benefit of humanity', and then the bank says: 'No, no, industry can't use this because they might make a profit out of it.'

Gveric: No, we're not saying that, we're just saying that you have to sign terms and conditions so that if anything comes out of it we want you to share it with the people who funded it. That's the only issue.

Perry: Let me play devil's advocate: is the donor aware that you're going to do that?

Gveric: I'd say no.

Perry: Is that right? Is that ethically right?

Gveric: It's ethically right. That's a big question, you know. We might go back to the example of HeLa cells and who benefits from that.¹¹⁵ I've quite often asked this question – whether a relative can expect anything out of the research that comes from using the tissue of their loved ones. I'm not sure. I don't have the answer to this. I just know that we stick to these regulations that are hampering efforts to give tissue to pharmaceutical companies. But if we come up with an agreement, we quite often modify these things and they sign them.

Perry: If you were going to give your bit of brain to a pharmaceutical company would you think it would be fine that it was used for the benefit of humanity?

Gveric: It's absolutely fine.

Lantos: You should not forget that if there weren't profit from pharmaceutical companies there wouldn't be the Wellcome Trust.¹¹⁶

Perry: I'm not against it, I'm just interested.

Jenkinson: I think that some of the terms and conditions that you're describing around IP relate to particular charity conditions that are in place in your bank. In my experience, in a lot of the interactions that I've seen with industry, the problem is not so much the terms and conditions that the bank are asking industry to sign up to, it's the terms and conditions that industry are then asking the banks to sign up to when supplying them that tissue. There have been cases recently where industry have wanted to get hold of tissue but then have specified within that that they owned that tissue and that goes against the spirit of the donation in the first place.

Perry: The tissue or what they learn from the tissue?

Jenkinson: The tissue.

Perry: I see, okay.

¹¹⁵ HeLa cells form the oldest human immortal cell line most commonly used in scientific research. They were originally taken without permission from, and named after, cervical cancer patient Henrietta Lacks in 1951. See Skloot (2010).

¹¹⁶ Sir Henry Wellcome (1853–1936) created the Wellcome Trust in his will dated 29 February 1932. It endowed two research charities, one to support the history of medicine and the other to support research in medical sciences. The Trust owned the umbrella organization, the Wellcome Foundation, which had been formed in 1924 by Sir Henry Wellcome to include his libraries, museums, research laboratories, and the pharmaceutical company of Burroughs Wellcome & Co. until it was partially floated on the stock market in 1986, eventually merging with Glaxo in 1995, and becoming part of GlaxoSmithKline in 2001. For a history of the pharmaceutical company, Burroughs Wellcome, see Church and Tansey (2007).



Figure 23: Professor Carol Brayne and Dr Djordje Gveric

Brayne: The reason they want to own the tissue is that then they will be able to make profits on what they've discovered, is that right?

Jenkinson: It's the specification that they actually own the tissue that causes problems because it's a donation.

Brayne: This is a fascinating area, a really difficult one, and there are other areas where similar issues arise clearly in remote geographies, populations with very interesting genes etc. etc. Bronwyn Parry did go into this in some detail in her project, which was about the nature of ownership and the way that material is morphed into different things, and when you add IP, then who owns it? I think the collective custodian or steward – stewardship, was the model that came out from all of that work.¹¹⁷ The problem is that the pharmaceutical approach doesn't fit that stewardship on behalf of humankind.

Perry: Can I ask you just to pause there, so before you go to the next step. The stewardship model, which came out of the Nuffield Council on Bioethics report on *Human Bodies: Donation for medicine and research*,¹¹⁸ it begs the question: who benefits? As Peter just pointed out, if everybody benefits, because the company actually makes a new drug, what's the problem? Somehow I just don't

¹¹⁷Parry and Gere (2006).

¹¹⁸Nuffield Council on Bioethics (2011). The report considered the ethical, social, and legal issues concerning the donation of bodily material for medicine and research.

understand how you can just turn around and say, ‘Yes, but it’s them. It’s them over there. We don’t want them to do something that they might make some money in order to help lots of other people. But we’d be very happy to do it in lots of other ways.’ I don’t quite understand.

Brayne: It’s more that it remains under the bank’s stewardship, that’s the problem. It is incumbent the bank holds the ethical approval effectively so you can’t just sign it over to a pharmaceutical company.

Perry: It depends on who and how they gave it, doesn’t it? If I give my brain for the good of humanity – full stop. If Djordje gets hold of it he won’t give it to industry. If I give it to Seth and he keeps it in a cupboard then he can give it to industry. I don’t understand this, why not?

Brayne: I suppose it’s the definition ‘for the good of humanity’. It’s a question of whether you are steward of the material for the common good; if you are steward of the material is it incumbent on you to know what happens with that tissue? I think the zeitgeist is that one should know what happens with the tissue and be able to track it. The finance I think is not so relevant. It’s the ‘what is being done’ with that tissue and is it for the good of humanity?

Reynolds: I suppose in 30 years I’ve been approached four or five times by industry wanting psychiatric post mortem cases and my approach has always been: ‘No, I’m not in a position to give them to you or sell them to you but you can support a project within the lab that we can monitor ourselves.’ On two or three occasions that has been the outcome, after some period of thought back at the company.

Perry: So is that an ethical fudge?

Reynolds: Perhaps it is, although I think the question of stewardship, or the problems with stewardship are avoided, and it means that the research should progress.

Francis: Can I suggest another task for Seth? I would be happy to try and organize this through BDR but it would probably be better coming from the MRC; that is, perhaps if we have an ethics study day where we invite industry, ethicists, lay people, and make the point, ‘I’m giving my brain, why can’t it be used in industry?’, that sort of approach. I strongly feel, as you do, that if somebody is making that donation we should not stand in their way. But Carol makes a good point that the way that the Act is written at the moment is that we cannot transfer ownership and the HTA will be down on us like a ton of

bricks if we transfer it to somebody and we have no control over the disposal of that tissue. Now, I'm planning to use Gavin's model in a project that I want to do with a pharmaceutical company. It can work but are we bending the rules to our own advantage by then attracting funding to university to do the project? And will the pharmaceutical company, or whoever they are, take all the data that you get? That in some way is fine because data is not the human tissue. So that could work or there could be some other way of getting around it. I think a group of ethicists – not too many otherwise we'll have too many opinions – but actually an ethical debate where the pharmaceutical industry is present as well, and in the MRC Steering Committee we certainly have representatives from the pharmaceutical industry who can comment on this.

Jenkinson: I don't know if we need a group of experts to get together really, it's already clear that this tissue absolutely can go to industry. There are examples of where this has worked. The difficulty comes down to individual terms and conditions and I'm not sure we're going to get an industry standard template that they have to use – let's just note that it is the terms and conditions the company sends to the bank that have caused the problem.

Love: Certainly in our limited experience of industrial requests the two critical things are: I don't think we can ethically release tissue without being told what it's going to be used for because all of us operate within some constraints. So, for example, the terms and conditions of our research ethics committee approval are, that this is research which is going to have, or has, the potential to be of benefit to people with dementia and/or their families. So we have to know something about what they are going to do to just make sure that we are conforming to the purposes for which we're established, for which we have approval. The other thing which we need to be careful about is the principle of sharing of data. We've had quite a lot of discussion in previous meetings with the MRC that if you supply tissue to people and they generate data, they can use that data to commercialize a drug or whatever it is – that's absolutely fine – but the raw data that enriches all of those donations should come back to the brain bank. And certainly that's something people have been keen on in the past. I think the same standards should apply to industry. I don't think that either of those things should prevent pharmaceutical companies from gaining information from the tissue and then using it to test ideas that they formulated in mice and then commercialize a product. I don't think those are barriers.

Perry: I think that we should debate these issues. I'm not for one second saying that we should allow industry or anybody else *carte blanche* to do what they want to do. I think it is important in the nature of this kind of conversation that if somebody donates tissue, what are the limitations to what it is used for? I think it is a hugely important issue that the data that is collected from any type of analysis from a particular brain comes back to a database relating to that brain; this is the most useful way forward. Unfortunately I think right now what happens is that bits of tissue go to different places and the data are never assimilated in some way. If all this information came back to a source we would have a richness that would be truly valuable. I agree with you, we have to use these network data sources the right way. I don't want anyone to imagine that I think industry, or anybody else, should do what they want to do. I want to know for the purposes of discussion: what are the rules and the limits that we have in place? I do think that the sorts of things that Paul and also Gavin have up their sleeves are good ways to do it. It takes advantage of the skills of industry, and the financial clout that industry may have, to make sure that tissue is used and then the information is released to the community.

Mann: Going back to Djordje's point, it may be an industrial misconception of the term 'ownership'. Perhaps they think that we, as brain bankers, actually own the tissues we supply, whereas in fact we don't. There's no such thing as tissue ownership according to HTA. We are custodians of the tissue. We don't own it. We may look after it and preserve it, distribute it and use it, though ultimately we don't own it and there's no way that industry can actually own any tissues either. As you say, if we're working with industry, they have to have that appreciation that they cannot own the tissue, but they can work with us through a joint custodianship of the tissues but, ultimately, we need to know, as Seth has said, what has happened to that tissue, how it's been used, how it's been disposed of, has it been used ethically etc. etc.

Reynolds: Back to the issue of data: I'm surprised you feel that most brain banks are not insisting that data is fed back.

Perry: No, they insist, the issue is whether it happens or not.

Reynolds: Certainly back in the 1980s it was instituted in Cambridge that those receiving tissue should feedback all the data and usually that was the case – usually more data than we could handle. I think the Stanley Medical Research Institute in the US do this extremely well; they have everything on



Figure 24: Professor Gavin Reynolds

an open database, or open to all users, so there's a lot of opportunity for data mining there.¹¹⁹ I would hope that the MRC would be doing this with their network anyway.

Love: As rapidly as it can.¹²⁰

Francis: Just one thing about ownership, David. If companies try us or anybody else and we're too slow or there are terms and conditions, what happens is that they will go and buy the tissue – you can buy human tissue for research and essentially you have, or the company has, ownership of that tissue. So we're

¹¹⁹The Stanley Neuropathology Consortium Integrative Database was established as a web-based tool to explore the neuropathology data from the Stanley Medical Research Institute to facilitate research into schizophrenia, bipolar disorder, and depression. See Kim and Webster (2010); and the website at <http://sncid.stanleyresearch.org> (visited 24 September 2014).

¹²⁰Professor Seth Love wrote: 'There isn't a specific narrowly focused policy statement on the integration of research data but the MRC has included the statement "An ambition of the MRC Network over the next few years is to develop better systems for data storage and management, that will facilitate the integrated analysis of clinical, neuroradiological, molecular genetic, neuropathological and neurochemical data across the Network" in its description of the future plans for the MRCUK Brain Banks Network (www.mrc.ac.uk/research/facilities/brain-banks/future-plans/ (visited 15 October 2015)).' Email to Ms Caroline Overy, 15 October 2014.

competing against something that we know very little about but there are companies who will supply human tissue to other companies. I'm not sure what the ethics are; where they're getting it; are these criminals in China or something? I've no idea. I really don't know where they're coming from. So there is this situation out there and that's what companies are doing because they have a commercial agreement with another company to buy tissue.

Perry: Interactions with industry was obviously an exciting area to lead us towards the end of the day. The future of brain banking is more, bigger, better, bolder, under tight control, and information comes back to source. As Gavin says it does happen and I think it happens to some extent but not to the full extent that we hope it will. I think the results from brain banking are a huge and fantastic resource, and a fascinating resource. If there's one thing that I'm left with a concern about, it is the PR. I think our outreach of what is learnt from the study of brain tissue could be integrated perhaps with what's coming out of the imaging. There are fantastic imaging tools and somehow if we joined this up in the right way with brain banking, people could understand more about how post mortem tissue contributes to advance understanding not only of the diseased brain but understanding the healthy brain. Without it there would still be huge gaps in our knowledge. One also has to remember that there are structures of the human brain that don't exist in other species. In non-human primates there are areas that match the human brain but once you study other vertebrates there are areas that do not. There are some special aspects of human brains and I think we also have to remember that many of the human diseases that people here and others study are peculiarly human. For example, there are claims to have generated autistic mice but I'm not sure that it's quite so easy to judge whether this is indeed the case. Since we're closing in on the end of the meeting, is there anyone who feels they would like to add anything, or say anything about human brain banking in the last 20 or 30 years, that has been missed?

Mann: As a Yorkshire man I'm going to talk about value for money and brass – where's t'brass for it all, lad? If we're going to develop brain banking over the years to build up the resource and continue to use and improve it, it needs support. Support is tangible, let's admit it. It is tangible and a resource that can be easily pulled away from us. What happens then?

Love: I feel like poacher turned gamekeeper here. I feel confident that support will be forthcoming if we show that we don't just sit back and wait for it to come. We have to demonstrate continually that we're doing things that are

useful, providing scientific value. If we continue to do that I'm sure we will continue to be supported. If we don't do that we don't deserve to be supported.

Lantos: This would require another four-hour discussion.

Perry: Three minutes.

Reynolds: Can I just say in some ways this session was very much meant to be a look backwards and we've talked a lot about the future. I've heard things from Seth and from others that I've actually heard over the past 20 to 30 years and there have been so many promises in the past that brain banking is the future. Back in the 1980s brain banking was the future and brain banking has shown itself to be effective and to be innovative and to give us new and important data but we've never really, really had a proper commitment from the Wellcome Trust, from the MRC that provides that strength that brain bankers have been looking for in their work.

Perry: Gavin, I'm not sure I want to go there at this late hour.

Moody: Can I say for the record that the banks in the Network, the ones that MRC supports, have just secured a further five years of support from MRC. I appreciate there is charity funding and there are other types of bank but surely they are on a firmer footing now than they ever were in the past?

Reynolds: My point was really that this had been promised so much in the past and it is fantastic if it is happening now but there have been three decades of really underfunding that has restricted brain banking development.

Perry: Gavin, I think there's actually a great message from Seth which is, why does imaging get lots of money? Because people like it and perceive that it has delivered important results. Whether you like what it delivers, there is a lot of debate around that too. It would be true of any area of science so I think the message about the PR associated with brain banking is that it's hugely important.

Finally, thank you all for coming and the last word is to Tilli.

Tansey: I'd also like to thank you all very much for coming and for sharing your views and opinions, and thank Hugh in particular for being such an engaged and at times provocative chairman. Thank you.

Appendix 1

Brain Banking Timeline¹²¹

1950: Professor Nick Corsellis establishes the first brain collection in the UK at Runwell Hospital in Essex.

1953: The MRC awards Professor Corsellis a research grant; the MRC's support for research on the Corsellis collection continues for the next four decades.

1957: Using donated brain tissue, Professor Arvid Carlsson demonstrates that dopamine is an important neurotransmitter and that low levels cause symptoms of Parkinson's disease. His ground-breaking research leads to the development of l-dopa treatment.

1964: The MRC publishes the UK's first ethical principles to be observed by those undertaking medical research on patients.

1973: Professor Corsellis studies the brains of 15 former boxers and discovers the presence of amyloid plaques, a sign of dementia pugilistica, brain injury associated with boxing.

1974: MRC-supported scientists Dr Ted Bird and Professor Leslie Iversen show that a loss of gamma-aminobutyric acid-containing neurons in the basal ganglia is characteristic of Huntington's chorea.

1976–77: MRC-funded researchers, in parallel with two other research groups, discover the loss of choline acetyltransferase in cerebral cortical tissue from individuals affected by the plaque and tangle hallmarks of Alzheimer's disease.

1984: Researchers George Glenner and Caine Wong identify 'a novel cerebrovascular amyloid protein' known as beta-amyloid – the chief component of Alzheimer's brain plaques and a prime suspect in triggering nerve cell damage.

1986: CC75C starts a population-based brain donation programme linked to MRC Cambridge Brain Bank.¹²²

¹²¹ Timeline provided by Dr Joanna Jenkinson emphasizing MRC contributions.

¹²² Entry added by Professor Carol Brayne.

1988: The MRC sets up Cognitive Function and Ageing Studies 1 (CFAS 1) to investigate dementia and cognitive decline in a representative sample of more than 18,000 people aged over 65 years. The study has been valuable in public policy decisions and in long-term projections.

1990: Wellcome Trust-funded research and brain collection identifies a deficit of a marker for GABAergic neuronal innervation to be reduced in schizophrenia, leading in 1997 to the identification of deficits in parvalbumin-containing neurons - the most robust neurochemical finding in the disease.¹²³

1991: MRC-funded research shows that decreased hippocampal expression of a glutamate receptor gene occurs in schizophrenia.

1991: A husband and wife team of researchers (Heiko & Eva Braak) undertake a detailed and painstaking examination of a large post mortem series of brains to establish a pattern of Alzheimer's disease development as it spread from region to region. This staging of the disease is now used as a benchmark for disease severity, allowing changes that occur early in the disease to be studied and hence to be a focus of attention.

1996: Professor James Ironside identifies a new variant strain of Creutzfeldt-Jakob disease using neuropathological examination, and suggests a link to BSE.

2005: The MRC Sudden Death Brain and Tissue Bank opens, providing researchers with access to the healthy brain tissue required for comparisons with tissue affected by central nervous system conditions in research.

2006: Research on donated brain tissue shows that TAR-DNA binding protein 43 (TDP43) is the major disease protein in two neurodegenerative conditions –amyotrophic lateral sclerosis and frontotemporal dementia.

2007: MRC researcher characterizes gene Neuregulin 1, whose dysregulation has been linked to schizophrenia, and identifies a functional promoter variant associated with the condition.

2008: Using post mortem brains, scientists show that neurons in the fusiform gyrus area of the brain, involved with facial perception, are fewer and smaller in cases of autism.

¹²³ Entry added by Professor Gavin Reynolds.

2009: The MRC establishes the UK Brain Banks Network to coordinate the provision of brain tissue and to help tackle the shortage of samples available for research into neuroscience and mental health disorders.

2013: The MRC launches a database of brain samples from more than 9,000 donated human brains held across the Network of ten UK brain banks to enable researchers to search promptly for, identify, and request the tissue required for their work.

Appendix 2

The MRC Sudden Death and Tissue Bank¹²⁴

The MRC Sudden Death and Tissue Bank was set up in Edinburgh in 2005 in response to a need in the medical research community for access to ‘control’ tissue – that is the non-diseased tissue with which to compare diseased tissue when investigating abnormalities.

Access to human tissue had become a contentious issue in the light of events leading to the Redfern and Isaacs reports and the subsequent loss of public confidence in the post mortem process.

The tissue bank started with a 24-month pilot to develop a mechanism by which relatives of individuals who had died suddenly and been autopsied under the Procurator Fiscal Service could be sensitively approached so that discussions surrounding tissue retention for research could be initiated.

A key element in this has been the development of transparency; relatives are given a very strong voice in the retention process and are given the option to make tissues available to medical researchers.

Ninety-eight per cent of relatives approached supported research and gave authorization for tissues to be used for medical research purposes and positive feedback from relatives was received. The pilot study was followed by further funding from the MRC and, to date, the high success rate has been retained.

¹²⁴ Text provided by Dr Joanna Jenkinson.

Biographical notes*

David Bowen

PhD (1940–2011) studied chemistry and microbiology at the University of Reading and obtained his PhD from the University of Pittsburgh in 1964. Following a postdoctoral post at the University of Michigan he returned to the UK in 1968 to work at Unilever. In 1970 he was appointed to the Department of Neurochemistry at the Institute of Neurology in Queen Square, where he focused on the neurochemistry of Alzheimer's disease. His studies of the post mortem changes in choline acetyltransferase activity led to the development of therapies for patients with mild and moderate Alzheimer's disease. See Palmer, Sims and Francis (2011).

Professor Carol Brayne

MD MSc FRCP FFPH (b. 1957) is a Professor of Public Health Medicine and Director of the Cambridge Institute of Public Health at the University of Cambridge (since 2008). She graduated in medicine from the Royal Free Hospital School of Medicine, University of London, in 1981 and went on to train

in general medicine, gaining Membership in 1984. She moved on to study epidemiology with a Training Fellowship with the Medical Research Council and received an MD in 1991, studying ageing and dementia. Since the mid-1980s her main research area has been longitudinal studies of older people following changes over time in cognition, dementia natural history, and associated features with a public health perspective. She is lead principal investigator in the group of MRC CFA Studies which have informed, and will continue to inform, national policy and scientific understanding of dementia in whole populations. She initiated the concept of population-based brain examination and worked with the Cambridge Brain Bank and the Department of Psychiatry in the 1980s in pioneering work to develop methods which worked for the respondents in cohort studies. The acclaimed Mind Over Matter exhibition (supported by a Wellcome grant) centred on brain donors from the CFA and Cambridge City over 75s cohort studies.

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

Professor (John Arthur) Nicholas Corsellis¹²⁵

MRCs LRCP FRCPsych FRCPath FRCP (1915–1994) qualified in medicine at the London Hospital in 1944, and spent much of the next few years in sanatoria and hospitals recovering from tuberculosis. During his illness he studied neuroanatomy and pathology and following his recovery he joined the staff of Runwell Hospital, a long-stay mental hospital in Essex, where he went on to become Consultant Neuropathologist. In 1976 he was appointed to the Chair of Neuropathology at the Institute of Psychiatry, a post that he held until his retirement. It was at the Runwell Hospital that he established his brain collection, retaining the brains of patients who had had post mortem examinations, collecting ‘control’ brains as well as those that were of diagnostic interest. In addition to his work on dementia pugilistica, he is also known for his recognition of focal cortical dysplasia as a cause of epileptic seizures, the first description of limbic encephalitis, characterized by inflammation of the brain, systematic studies on temporal lobe epilepsy, epilepsy surgery in general, and Alzheimer-type changes in senile dementia. For further information see Kasper *et al.* (2010); Crow (2000).

Professor Margaret Esiri

DM (b. 1941) is Emeritus Professor of Neuropathology at Oxford University and continues to work part-time on research related to neurodegeneration and dementia, a subject that has interested her for over 30 years. Earlier in her career she was an MRC Senior Clinical Fellow and then Reader, later Professor, of Neuropathology at Oxford University and Honorary Consultant Neuropathologist at what are now the Oxford University Hospitals. She is an Emeritus Fellow of St Hugh’s College, Oxford. Most of her work has been based on studies of autopsied human brain tissue generously donated with full consent for research.

Professor Paul Francis

PhD (b. 1958) has degrees from Reading University. In 1982, he joined the laboratory of Professor David Bowen to study the biochemistry of Alzheimer’s disease. In 1995, he moved to King’s College London and was appointed Professor of Neurochemistry. His group’s current research interests focus on neurochemical correlates of cognitive and non-cognitive changes in dementia and biomarkers. He led the IMI demonstration project, AddNeuroMed, around model

¹²⁵ Biography using material provided by Dr Joanna Jenkinson.

development and translational biomarkers for dementia. He is Director of Brains for Dementia Research (BDR), a significant initiative in brain banking by the AS and ARUK and is a member of the MRC UK Brain Banks steering committee. He is a member of the Alzheimer's Association ISTAART council. Recent research funding comes from a variety of charities and pharmaceutical companies. He has published extensively on Alzheimer's disease and related disorders.

Dr Djordje Gveric

PhD (b. 1965) studied medicine at the University of Sarajevo (former Yugoslavia). He obtained a MSc in immunology at King's College London and received a PhD in neuroimmunology from the University of London. From 1994 until 2006 he worked at the Institute of Neurology where he was involved with the MS Society Tissue Bank and conducted research into pathogenesis of multiple sclerosis as a member of Professor Louise Cuzner's group. In 2008 he joined Imperial College as Manager of the MS and Parkinson's Tissue Bank.

Professor James Ironside

CBE FRCPATH, FRCPEdin, FMedSci, FRSE (b. 1954) graduated in Medicine from the

University of Dundee in 1979. He was Senior Lecturer then Reader in Pathology at the University of Edinburgh and Honorary Consultant Neuropathologist at the Western General Hospitals Trust, Edinburgh from 1994 to 2000. Since 2000, he has been Professor of Clinical Neuropathology at the University of Edinburgh and Honorary Consultant Neuropathologist and the Lothian University Hospital Division and Tayside University Hospitals Division. He is Director of Laboratories in the National CJD Research & Surveillance Unit, which identified the new variant form of CJD in 1996, and is currently a member of several advisory committees on CJD to the UK Government, the WHO, European Union and other international bodies. He was Director of the MRC Network of UK Brain Banks from 2009 to 2013.

Dr Joanna Jenkinson

PhD (b. 1977) received a PhD in fungal genetics from the University of Exeter, then undertook her Defra-funded, postdoctoral work on the evaluation of the field scale trials of GM crops. She then joined the Biotechnology and Biological Sciences Research Council, initially working for the Plant and Microbial Sciences Committee and

then as a Programme Manager for the Sustainable Agriculture Strategy Panel where she ran a number of international calls that were jointly funded by DFID. She joined the Medical Research Council in 2008 and has since held a range of different posts within MRC Head Office, with responsibility for scientific areas ranging from genetics and cell biology through to neuroimaging. MRC Programme Manager responsibilities within the Neurosciences and Mental Health Board have included, until November 2013, developmental neurobiology and brain banking; currently she leads on the MRC's mental health and addiction portfolios.

Professor Emeritus Peter Lantos
MD, PhD, DSc, FRCPath, FMedSci (b. 1939) qualified in medicine at the Medical University of Szeged in Hungary in 1964. He was awarded a Wellcome Research Fellowship in 1968 at the Middlesex Hospital Medical School, London. He completed his PhD, University of London, in 1973, became a Member of the Royal College of Pathologists in 1975, and Fellow ten years later. He was appointed Senior Lecturer and Honorary Consultant at the Middlesex Hospital Medical School in 1976, and Professor of Neuropathology at the Institute of

Psychiatry in 1979 with Honorary Consultant contracts to the Maudsley, King's, St Thomas's and Guy's hospitals. Until his retirement he was Director of Neuropathology services at King's Clinical Neurosciences Centre. His research interest concentrated on neurodegenerative diseases, including Alzheimer's disease and movement disorders, particularly multiple system atrophy in which the diagnostic hallmark lesion is referred to as Papp-Lantos inclusion. For over 20 years he ran the Brain Bank at the Institute of Psychiatry. He served on and chaired many national and international committees of neuropathology and neuroscience. He was co-editor, with David Graham, of two editions of *Greenfield's Neuropathology*, and author of some 500 medical publications. In 2001, he was elected Fellow of the Academy of Medical Sciences. After retirement, he became a trustee of Alzheimer's Research UK, and author of a childhood memoir, *Parallel Lines*, and a novel, *Closed Horizon*, both published by Arcadia Books London, in 2006 and 2012, respectively.

Professor Seth Love
PhD MBChB FRCP FRCPath (b. 1955) trained in medicine at the University of the Witwatersrand,

graduating cum laude in 1978. After completing internships, he moved to London, where in 1980 he joined the Department of Neuropathology at Queen Square. This was initially as a PhD student but he became interested in the diagnostic work of the department and decided to train as a neuropathologist. He completed his PhD in 1984 and his neuropathology training in 1985. He then spent two years as a Research Fellow at UCSD before returning to the United Kingdom in 1987, to a consultant post at Frenchay Hospital in Bristol. In 1995 he was awarded a Personal Chair in Neuropathology in the University of Bristol. He is Director of the South West Dementia Brain Bank, President of the British Neuropathological Society, serves on multiple editorial boards and grant review committees, and was appointed Director of the UK Brain Banks Network in 2013. He is the lead editor of *Greenfield's Neuropathology*, and Editor-in-Chief-elect of *Brain Pathology*. His current research is supported by the Medical Research Council, Alzheimer's Research UK, Alzheimer's Society, British Heart Foundation, and BRACE, and is largely focused on Alzheimer's disease and related causes of dementia.

Professor David Mann

PhD (b. 1948) studied zoology at the University of Durham, before completing his PhD in Neuropathology from the University of Manchester in 1972. His doctoral and postdoctoral work established a career interest in neurodegenerative diseases and brain banking. In 1976, he was appointed Lecturer in Neuropathology at the University of Manchester, and was promoted to Professor of Neuropathology in 1998. He is Honorary Professor of Neuroscience at Salford Royal Hospitals NHS Foundation Trust, and Honorary Professor of Neuroscience at Beijing University of Chinese Medicine. He is a Fellow of the Royal College of Pathologists. He is coordinator of the Manchester Alzheimer's Disease Research Centre within the Alzheimer's Research UK Network, and Director of the Manchester BDR Brain Bank. He has been a regular committee member of the British Neuropathological Society.

Dr Catherine Moody

PhD (b. 1957) received a PhD in pharmacology from the University of London, and her early postdoctoral career was in biomolecular research in London and the United States. She joined the Medical Research Council in 1991 and has since held a range

of different posts within MRC Head Office, with responsibility for scientific areas ranging from basic molecular work through to clinical studies. From 2004 until 2007 she gained experience of ethical, social, and legal issues while on secondment as Deputy Director to the Nuffield Council on Bioethics. MRC programme manager responsibilities within the Neurosciences and Mental Health Board group since 2007 have included imaging, brain banking, and dementias research.

Ms Brenda Nally

BA DSA (b. 1941) worked in a range of public sector services and Higher Education professional training courses over a 30-year period, which led to a strong focus on the promotion of better services for disabled people, particularly through partnership with them and their families. Between 1993 and 2006, this focus turned to autism, working in the north of England and Northern Ireland for the National Autistic Society in project management and regional coordination. Since 2007, she has focused on the development of the UK Brain Bank for Autism & Related Developmental Research at Oxford, working as outreach coordinator of this programme. Her initial postgraduate qualification was in social work.

Professor Hugh Perry

MA DPhil FMedSci (b. 1952) is Professor of Experimental Neuropathology at the University of Southampton (since 1998). He completed his DPhil at the University of Oxford (1977) and remained there as a Locke Fellow of the Royal Society (1982–1986) and Wellcome Trust Senior Research Fellow (1986–1995). His research interests are in the field of neuroimmunology; his recent work focuses on interactions between the immune system and nervous system, and in particular how systemic infection and inflammation play a role in driving the progression of neurodegenerative disease. He has published more than 300 peer-reviewed papers. He has sat on research advisory and funding panels for a number of different groups and chaired the Cellular and Molecular Neuroscience panel of the Wellcome Trust (2004–2007). He has acted as a consultant for biotechnology and pharmaceutical companies in the area of neuroinflammation and neurodegenerative disease. He was elected a Fellow of the Academy of Medical Sciences (2005), and was Deputy Chair of the Nuffield Council on Bioethics. He is Chair of the MRC Neuroscience and Mental Health Board (2012 –).

Professor Gavin Reynolds

PhD (b. 1952) studied chemistry at the University of York and received a PhD in biochemistry from the University of London. His postdoctoral work in London and Vienna established his long-standing interests in the neurochemistry and pharmacology of schizophrenia and other neuropsychiatric disorders. He developed these research interests further while ‘brain-banking’ with the MRC in Cambridge and following an appointment in 1985 as Wellcome Lecturer at the University of Nottingham. In 1990 he moved to the University of Sheffield and in 2004 took up the Chair of Neuroscience at Queen’s University Belfast. He is now Honorary Professor in the Biomedical Research Centre at Sheffield Hallam University and Professor Emeritus at Queen’s University Belfast. He was President of the British Association for Psychopharmacology (2008–2010).

Ms Karen Shaw

RMN (b. 1964) trained in psychiatric nursing and moved into neurology whilst practising as a dementia nurse specialist and coordinating a multidisciplinary memory clinic. She joined the Queen Square Brain Bank for Neurological Disorders at

UCL Institute of Neurology as research/brain donation nurse in December 2000, where she provides expert information and advice to healthcare professionals, and counselling and support to patients, relatives, and members of the public in relation to brain donation. Her role in the brain bank is to ensure that the rationale for donation is fully understood by patients and families during life, and that the pathological diagnosis and research findings are sensitively related to the family after the donation. On the occasions when a genetic mutation is indicated in a donated brain she provides genetic counselling to the relatives and ensures the results are appropriately received within a clinical neurogenetics service. She is interested in personal, cultural, and societal perceptions of the (donated) brain, and has carried out research exploring the experiences, beliefs, and attitudes of donor relatives to brain donation (Eatough, Shaw and Lees (2012)).

Professor Tilli Tansey

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

Marine Laboratory in Plymouth, the MRC Brain Metabolism Unit, Edinburgh, and was a Multiple Sclerosis Society Research Fellow at St Thomas' Hospital, London (1983–1986). After a short sabbatical break at the Wellcome Institute for the History of Medicine (WIHM), she took a second PhD in medical history on the career of Sir Henry Dale, and became a member of the academic staff of the WIHM, later

the Wellcome Trust Centre for the History of Medicine at UCL. She became Professor of the History of Modern Medical Sciences at UCL in 2007 and moved to Queen Mary University of London (QMUL), with the same title, in 2010. With the late Sir Christopher Booth she created the History of Twentieth Century Medicine Group in the early 1990s, now the History of Modern Biomedicine Research Group at QMUL.

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

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