WELLCOME WITNESSES TO TWENTIETH CENTURY MEDICINE

MAKING THE HUMAN BODY TRANSPARENT:
THE IMPACT OF NUCLEAR MAGNETIC RESONANCE AND MAGNETIC RESONANCE IMAGING

RESEARCH IN GENERAL PRACTICE

DRUGS IN PSYCHIATRIC PRACTICE

THE MRC COMMON COLD UNIT

WITNESS SEMINAR TRANSCRIPTS EDITED BY:
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WITNESS SEMINARS
IN THE HISTORY OF TWENTIETH CENTURY MEDICINE

The past

In 1990 the Wellcome Trust's History of Twentieth Century Medicine Group was established to develop and strengthen links between the biomedical research community and medical historians, and to promote and facilitate the study of twentieth century medical history. Overseen by a Steering Committee,[1] the group has endeavoured to satisfy these requirements by initiating a series of seminars and symposia, running an international Summer School meeting, and producing a regular *Newsletter*.[2] Throughout, we have attempted to bring members of these different communities together, to emphasise the potentials of working jointly, and to encourage the creation and deposit of archival sources for present and future use. A particularly effective way, we believe, to meet many of our objectives, has been the development of a programme of Witness Seminars, meetings to which individuals associated with a particular set of circumstances or events are invited, to discuss, debate, agree or disagree about their reminiscences. This format came to our attention in 1993, when we learned that the Institute of Contemporary British History used such meetings to address issues of recent political history, and by way of an experiment we organized a meeting on the subject of *Monoclonal Antibodies.* Encouraged by the positive responses to that seminar, and to the publication of a detailed report and the transcript,[3] we repeated the experiment with a meeting on *Renal Transplantation*. We subsequently decided to develop such meetings to explore, in particular, aspects of late twentieth century biomedical science, and during the academic year 1994-95 a number of shorter (two hours long) seminars were held, each focusing on a narrowly defined topic. A further meeting, *Ashes to Ashes* was integrated into a two-day symposium on the history of smoking and health.[4] All or parts of most meetings have been published (the exceptions being *Renal transplantation* and *Oral contraceptives*), as shown below. From 1996 onwards, meetings were routinely arranged as full afternoon seminars, and it is the transcripts of four of these that are presented in the present Volume. A further five, held from 1997 to 1998 and also listed below, are currently being transcribed and edited.

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[1] Between 1996 and 1998 the Steering Committee comprised Dr Tilli Tansey (Chairman and Organizing Secretary), Sir Christopher Booth, Dr David Gordon, Dr Stephen Lock, Dr Lara Marks, Professor Vivian Nutton and Professor Tom Treasure.

[2] For further details of the Group's activities, and to receive the *Newsletter*, please contact Mrs Wendy Kutner at the Wellcome Institute for the History of Medicine, London.

[3] Tansey E M, Catterall P. (1994) Monoclonal antibodies: A witness seminar in contemporary medical history. *Medical History* **38**: 322–327; *idem* (eds) (1995) Technology transfer in Britain: the case of monoclonal antibodies. *Contemporary Record* **9**: 409–444.

[4] Lock S P, Reynolds L A, Tansey E M. (eds) (1998*) Ashes to Ashes – The history of smoking and health*. London: Wellcome Trust, 198-220.

1993	**Monoclonal antibodies**[6] Organizers: Dr E M Tansey and Dr Peter Catterall
1994	**The early history of renal transplantation** Organizer: Dr Stephen Lock
	Pneumoconiosis of coal workers[5] Organizer: Dr E M Tansey
1995	**Self and non-self: a history of autoimmunity**[6] Organizers: Sir Christopher Booth and Dr E M Tansey
	Ashes to ashes: the history of smoking and health[4] Organizers: Dr Stephen Lock and Dr E M Tansey
	Oral contraceptives Organizers: Dr Lara Marks and Dr E M Tansey
	Endogenous opiates[6] Organizer: Dr E M Tansey
1996	**Committee on Safety of Drugs**[6] Organizers: Dr Stephen Lock and Dr E M Tansey
	Making the body more transparent: the impact of nuclear magnetic resonance and magnetic resonance imaging[7] Organizer: Sir Christopher Booth
1997	**Research in General Practice**[7] Organizers: Dr Ian Tait and Dr E M Tansey
	Drugs in psychiatric practice[7] Organizers: Dr E M Tansey and Dr David Healy
	The MRC Common Cold Unit[7] Organizers: Dr David Tyrrell and Dr E M Tansey
	The first heart transplant in the UK Organizer: Professor Tom Treasure
1998	**Haemophilia: aspects of clinical management** Organizers: Dr E M Tansey and Professor Christine Lee
	Obstetric ultrasound: historical perspectives Organizers: Dr Malcolm Nicolson, Mr John Fleming and Dr E M Tansey
	Post-penicillin antibiotics Organizers: Dr Robert Bud and Dr E M Tansey
	Clinical research in Britain, 1950–1980 Organizers: Dr David Gordon and Dr E M Tansey

The present

Once a subject has been agreed by the Steering Committee of the Group, a suitable chairman is sought, and we start to discuss the meeting with possible contributors. Inevitably such approaches lead to suggestions for other appropriate participants, and during the months preceding a meeting we compile a detailed database of contacts to invite. It may become apparent at this stage that some topics cannot be included because of the lack of suitable witnesses. An early problem is to ensure that we invite all the appropriate people, and unfortunately we are not regularly able to bring overseas participants to our meetings. Key individuals can be inadvertently omitted simply because they are so 'obvious' no one suggests they should be invited. Other proposals may unintentionally reflect bias towards particular labs, Universities or specialities. We consult our scientific colleagues in the Wellcome Trust for advice, and use MEDLINE, SCIENCE CITATION INDEX, and other databases to search for participants. Each meeting's invitation list is constantly updated and checked for possible omissions.

We also search, when appropriate, for the voices that are rarely heard. Although we made the deliberate decision not to invite patients to Drugs in Psychiatric Practice, because of the vast variety of drugs and conditions to be discussed, we did so for Haemophilia, a meeting focused on only one condition. For the Common Cold Unit seminar we were able to locate former volunteers and members of the administrative staff; local Family Planning Association doctors and nurses attended the predominantly scientific seminar on Oral Contraceptives; similarly for Research in General Practice we invited practice nurses involved in specific research projects, although none were able to attend.

Throughout we promote informality and flexibility, we neither expect nor encourage participants to arrive with prepared scripts, and we do not usually allow slides or other visual material to be shown, as this may disrupt the flow of the meeting – we suggest that illustrations, graphs or figures are photocopied and placed on every chair, so material can be referred to easily and when appropriate during the course of the meeting. Our further experiences of running Witness Seminars confirm the view expressed in the Introduction to Volume One of these transcripts: that each meeting develops its own unique agenda and dynamics, and no two have ever been the same.

The entire proceedings of the meeting are recorded, the tapes are transcribed and the unedited transcript is sent to every participant with the request that they check their own contribution and provide biographical details. Minor comments are incorporated into a master document, the editors turn the spoken word into readable text, add biographical and bibliographical footnotes, and also include additional material or comments from participants as footnotes. The final scripts are again sent to every contributor, accompanied by copyright assignment forms. Any subsequent comments are further incorporated as appropriate, and the complete transcript is sent to other colleagues to read for sense and

comprehensibility. Our aim is to make the substance of these meetings available to the informed non-expert, and a frequent concern is how much specialist vocabulary does such a reader require? In some instances (*Nuclear magnetic resonance*, *Common Cold Unit* and *Drugs in psychiatric practice*) we have added a brief glossary, although we hope that even if the precise technical details remain obscure, the significance and general sense of the transcripts are clear.

We intend the documents that result from these meetings not only to inform those with a general interest in the history of modern medicine and medical science, but also to emphasise to the participants, their contemporaries and colleagues that events of the recent past, of their own working lives, are of proper and necessary concern to historians. For historians we hope that these accounts will provide new insights, fresh material for study, and prompt additional, possibly new, themes for research. Each, in a different way, provides a detailed view of a particular event, or series of events. The subject matter ranges widely – to date we have promoted seminars that have included discussions on disease classifications and treatments (e.g. *Pneumoconiosis*,[5] *Autoimmunity*,[6] *Common Cold Unit,*[7] *Haemophilia*); technological developments in diagnosis and treatment (e.g. *Monoclonal antibodies,*[6] *Nuclear magnetic resonance*,[7] *Obstetric ultrasound*); clinical practice (*Renal transplantation*, *Research in General Practice*,[7] *First heart transplant in the UK*, *Clinical research in Britain*); drug developments (*Oral contraceptives, Endogenous opiates*,[6] *Drugs in psychiatric practice*,[7] *Post-penicillin antibiotics*); and the role of Government in health care (*Ashes to Ashes*,[4] *Committee on Safety of Drugs*[6]).

That straightforward catalogue does not adequately represent the variety of material presented in each meeting. For example, in the present volume alone, the locations discussed range widely, from laboratories in the pharmaceutical industry (*Drugs in psychiatric practice*), in government research institutes (*Common Cold Unit*) and industrial engineering companies (*Nuclear magnetic resonance*), to general practitioners' consulting rooms (*Research in General Practice*), specialist hospital clinics (*Nuclear magnetic resonance)*, and even into the open air, as infected volunteers at the Salisbury Hospital took country walks a set distance apart from other participants (*Common Cold Unit*). Broad general themes also emerge, for example, who should fund basic research and its subsequent application is a constant issue (e.g. *Nuclear magnetic resonance*, *Drugs in psychiatric practice*, see also *Monoclonal antibodies* and *Endogenous opiates* in Volume One); the ethical issues of drug trials (e.g. *Drugs in psychiatric practice*, *Research in General Practice,* see also *Committee on Safety of Drugs* in Volume One), and of human experimentation and equipment trials (*Common Cold Unit, Nuclear magnetic resonance*), are frequently

[5] P D'Arcy Hart, edited and annotated by E M Tansey. (1998) Chronic pulmonary disease in South Wales coalmines: An eye-witness account of the MRC surveys (1937-1942). *Social History of Medicine* (in the press).

[6] Published in Tansey E M, Catterall P P, Christie D A, Willhoft S V, Reynolds L A. (1997) (eds) *Wellcome Witnesses To Twentieth Century Medicine.* Vol I. London: Wellcome Trust, 135pp.

[7] Included in the present volume.

raised; as are questions about the classification and definition of diseases (e.g. *Research in General Practice*, *Drugs in psychiatric practice*, see also *Self and non-self* in Volume One, *Pneumoconiosis*[5] and *Ashes to Ashes*[4]).

Witness seminars can have a very immediate effect on the community from which the participants are drawn: to the frequent amazement of our contributors, they discover that 'history' embraces their own working careers. This realization can have several consequences: one is active participation in the meeting itself, another is in assisting the editorial process, a third is the increased deposit of conventional archives. We have encouraged the deposition of written, photographic and film archives (mainly into the relevant departments of the Library of the Wellcome Institute for the History of Medicine), and also directed instrument collections to suitable curators.

The future

The Steering Committee receives suggestions for such meetings, from scientists, clinicians and historians, and we are keen to proceed with this programme and develop it further, providing we continue to meet our objectives. We are also eager to take more advantage of the opportunities offered by these seminars: ideally we would like to follow up meetings with further, more focused interviews with individual participants, to include accounts from those not able to attend the meetings, and to arrange other satellite interviews and archive collecting, using the Witness Seminars as the nuclei of larger, more cohesive, projects. Unfortunately, given current resources we cannot do this ourselves, although we encourage others to do so, wherever possible. We hope therefore that the publication of these transcripts will act as a stimulus to those interested in twentieth century medical history and promote further collaborations.

Acknowledgements

Many people are involved in the organisation of these meetings and their subsequent publication. Mrs Wendy Kutner helps organize and run all the activities of the History of Twentieth Century Medicine Group, and she is assisted by Mrs Lois Reynolds and Dr Daphne Christie, who also undertake much of the editorial and production work associated with converting the meeting into a readable volume. Several colleagues have generously read the completed transcripts for general sense, and we are very grateful to Mr Wilfred Baldeo, Dr Dianne Dixon, Mr William Schupbach, Dr Hugh Thomas, Dr Trevor Turner, and Dr Lise Wilkinson, for their helpful comments and advice. We also thank Wellcome Trust staff from the Audiovisual, Information Systems, Publishing and Reprographics Departments, and the Photographic Library, and our transcriber Mrs Jaqui Carter. We are grateful to them all, and especially to those who have participated in our

Witness Seminars, answered our queries and often provided additional material and memories. Finally, I gratefully acknowledge the Wellcome Trust for its financial support.

Tilli Tansey
Wellcome Institute for the History of Medicine

MAKING THE HUMAN BODY TRANSPARENT:
THE IMPACT OF NUCLEAR MAGNETIC RESONANCE AND MAGNETIC RESONANCE IMAGING

The transcript of a Witness Seminar held at the Wellcome Institute for the History of Medicine, London, on 2 July 1996

Edited by D A Christie and E M Tansey

This meeting examined the original discovery of nuclear magnetic resonance and its application in spectroscopy and in magnetic resonance imaging during the past half century. Chaired by Professor Robert Steiner the meeting considered the scientific and technical developments, and also the biological and clinical applications of these new technologies. It also discussed issues relating to the support and impact of industrial research. Of particular interest were the inter-relationships between manufacturers, Government agencies and medical specialists in acquiring and evaluating new equipment, and devising safety and clinical criteria.

MAKING THE HUMAN BODY TRANSPARENT:
THE IMPACT OF NUCLEAR MAGNETIC RESONANCE AND MAGNETIC RESONANCE IMAGING

PARTICIPANTS

Professor Raymond Andrew
Sir Christopher Booth
Professor Graeme Bydder
Professor David Delpy
Professor David Gadian
Dr John Galloway
Professor John Griffiths
Mr Gordon Higson
Professor Sir Godfrey Hounsfield
Professor Ian Isherwood
Professor Donald Longmore
Professor John Mallard
Professor Sir Peter Mansfield
Professor George Radda
Professor Osmund Reynolds
Professor Sir Rex Richards
Professor Robert Steiner (Chair)
Dr Paul Tofts
Professor Tom Treasure
Professor Sir Martin Wood
Professor Brian Worthington
Professor Ian Young

Others present at the meeting and apologies: Dr Francis Doyle, Dr Peter Luyten, Sir John Maddox, Professor Roger Ordidge, Dr Frank Smith, Sir Derek Roberts.

Sir Christopher Booth:[1] The History of Twentieth Century Medicine Group was set up a few years back by the Trustees, now Governors, of the Wellcome Trust, who were interested in looking historically at the sort of scientific work that they had funded in the twentieth century. Not much work had been done professionally at that stage on twentieth-century history so this was a new development for the Wellcome Institute for the History of Medicine and has been run predominantly by Tilli Tansey[2] who is the Historian of Modern Medical Science here.

The second point was why this particular topic? I remember discussing this question with Sir Peter Medawar[3] and he told me that he was absolutely horrified by all administrators, but particularly by those who worked at the MRC,[4] and that he could imagine in the 1950s one of you chaps going up before the Council and saying, 'I want a research programme at the MRC which will make the human body transparent.' You can imagine what all the old grey hairs round the table at Head Office would have said at that time. They wouldn't have believed a word of it, or believed it was remotely possible. It has happened and nuclear magnetic resonance (NMR) has made a major contribution to medicine, as well as its contribution of course, to biochemistry and other fields of science.

Your chairman today is very well known to you all – Professor Robert Steiner – and without more ado I will hand over to him.

[1] Sir Christopher Booth was the first Convenor of the History of Twentieth Century Medicine Group, Wellcome Institute for the History of Medicine, from 1990 to 1996 and Harveian Librarian at the Royal College of Physicians from 1989 to 1997.

[2] Dr Tilli Tansey is Convenor of the History of Twentieth Century Medicine Group and Historian of Modern Medical Science at the Wellcome Institute for the History of Medicine.

[3] Sir Peter Medawar FRS (1915–1987) was Jodrell Professor of Zoology and Comparative Anatomy at University College London from 1951 to 1962. He shared the 1960 Nobel Prize in Physiology or Medicine with Macfarlane Burnet for the discovery of immunological tolerance. Between 1962 and 1971 he was Director of the National Institute for Medical Research at Mill Hill, London, remaining on its scientific staff until 1984.

[4] The Medical Research Council (MRC) was established in the UK in 1920 as the successor body to the Medical Research Committee, founded in 1912.

Professor Robert Steiner:[5] This is my first experience of a Witness Seminar and I assume that for most of you the same applies. Since I have got strict instructions from Chris Booth and his team I can at least proceed with the management of this afternoon's proceedings with some knowledge. I very much hope that all of you have the appropriate documentation for what is expected. It will be a very informal meeting, we may get all the important historic facts presented and I will give everybody in this room a chance to make their points.

We will start by asking Professor Raymond Andrew to speak about the basic history of NMR and then try and have the main topics outlined in some detail. First spectroscopy, Sir Rex Richards and Professor George Radda from Oxford will be the opening speakers, followed by Sir Martin Wood, who was the founder of Oxford Instruments. His work was fundamental in magnet development and so was his collaboration with the Oxford team and others in centres around Britain.

After a break for tea we will deal with imaging in the same way as spectroscopy. The two opening speakers will be Professor Ian Young and Professor Graeme Bydder from the Hammersmith team, followed by Sir Peter Mansfield and Professor Brian Worthington from Nottingham, followed by Professor John Mallard from Aberdeen, Professor Donald Longmore from the National Heart Hospital and Professor Ian Isherwood from Manchester.

Following the opening speakers I very much hope that other members of the meeting will participate in a lively discussion. Let's start straight away with Professor Andrew and he will tell us all about the original history of the NMR discovery.

Professor Raymond Andrew:[6] Thank you Mr Chairman. I have been asked to give a general historical introduction and there has been so much history that to cover it in ten minutes is something of a tall order. Anyway, here goes.

Medical doctors who have become interested in magnetic resonance imaging (MRI), during the past 20 years sometimes express surprise that the basic phenomenon on which MRI was founded was described 50 years ago. Nuclear magnetic resonance was discovered at the end of 1945 by two independent groups

[5] Professor Robert Steiner (b. 1918) was Professor of Diagnostic Radiology, University of London, from 1961 to 1983, now Professor Emeritus. Former Editor of the *British Journal of Radiology*. Past President of the British Institute of Radiology and past President of the Royal College of Radiologists.

[6] Professor E Raymond Andrew FRS (b. 1921). In 1984 was elected to Fellowship of the Royal Society for contributions to NMR and shortly afterwards shared the Royal Society's Wellcome Medal and Prize with Jim Hutchison, John Mallard and Peter Mansfield for contributions to NMR imaging. Elected President of the Groupement AMPERE in 1974 (see note 114 below) and served as the first president of ISMAR (the International Society of Magnetic Resonance founded in 1971) from 1983 to 1986. In 1983 he started *Magnetic Resonance in Medicine* as Editor-in-Chief and retired from the editorship in 1991. Currently Research Professor, University of Florida.

both led by future Nobel Laureates, Purcell, Torrey and Pound at Harvard, and Bloch, Hansen and Packard at Stanford.[7]

The golden jubilee of NMR at Harvard was celebrated last December with an all-day seminar where many pioneers gave papers. Purcell and Torrey are now rather frail, in their eighties, and Purcell gave his talk from a wheelchair, receiving a standing ovation from the 200 people present.

The discovery of NMR in 1945 had what might be termed a pre-history. In 1936 and again in 1942 Professor Gorter[8] in The Netherlands looked for NMR in several crystalline solids without success. He later attributed his negative results to choosing materials with very long relaxation times. Both Bloch and Purcell understood the relaxation problem and took steps to avoid it.

The first British pioneer in NMR was Dr Bernard Rollin in the Physics Department, the Clarendon Laboratory, at Oxford. Immediately after seeing the first publications in early 1946, he built a novel NMR spectrometer and by November the same year had published his first NMR paper in *Nature*[9] which I think was pretty good going. His work is, I believe, less widely known than it deserves to be, partly because he would never travel outside Oxford. In fact, he would only speak at a conference if the conference was held in Oxford. Soon afterwards, also in Oxford, Rex Richards began to apply NMR to chemical problems and he acknowledged Rollin's advice in his early papers.

At the time of the discovery of NMR, I was a research student at Cambridge, working on superconductivity with Professor David Shoenberg. In 1947, Felix Bloch paid us a visit, soon followed by Bob Pound and by Nicolaas Bloembergen[10] and it was clear that NMR was an exciting new subject. So later, in 1947, when applying to the Commonwealth Fund for a Fellowship, I proposed to work on NMR at Harvard and I had a most wonderful postdoctoral year in Ed Purcell's laboratory. As a consequence I believe I am now the longest-serving NMR practitioner still working in the field.

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[7] Professor Edward Mills Purcell ForMemRS (1912–1997) was Professor of Physics at Harvard University from 1950 until his retirement in 1980. He shared the 1952 Nobel Prize in Physics with Felix Bloch of Stanford University. Working with R V Pound and H C Torrey, Purcell first observed nuclear magnetic resonance on 15 December 1945. In 1948 he became Associate Editor of *Physical Review* and was appointed to a full professorship in 1949. He was the senior fellow of the Society of Fellows at Harvard University from 1950 to 1971, and was elected a Foreign Member of the Royal Society in 1989. See Purcell E M, Torrey H C, Pound R V. (1946) Resonance absorption by nuclear resonance moments in a solid. *Physical Review* **69**: 37–38. Bloch F, Hansen W W, Packard M E. (1946) The nuclear induction experiment. ibid. **70**: 474–485.

[8] Professor Cornelis J Gorter (b. 1907) published several articles on his unsuccessful attempts to detect the phenomenon of NMR. See for example Gorter C. (1936) Negative result of an attempt to detect nuclear magnetic spins. *Physica* **3**: 995–998.

[9] Rollin B V. (1946) Nuclear magnetic resonance and spin lattice equilibrium. *Nature* **158**: 669–670.

[10] Nicolaas Bloembergen (b. 1920) was one of the recipients of the 1981 Nobel Prize in Physics for his contribution to the development of laser spectroscopy.

The discovery of the chemical shift and spin multiplets between 1949 and 1951, which led to the development of high-resolution NMR spectroscopy, had a tremendous impact on chemistry, biochemistry and other disciplines. In the quest for improved resolution and sensitivity the proton NMR frequency was steadily advanced from 30 MHz to 60, to 100 MHz and then with the aid of superconducting magnets, ever onwards and upwards to 750 MHz (17.5 Tesla). Oxford Instruments played a leading role in this development. With these high-resolution NMR instruments, molecular biologists have been able to determine the structures of proteins, enzymes, nucleic acids, carbohydrates and they've been aided by the development of two-dimensional, three-dimensional, and higher dimensions of NMR spectroscopy discovered and developed by Jeneer, Ernst and colleagues.

Turning to applications in biology, Felix Bloch[11] liked to say that he did the first biological NMR experiment in 1946 when he put his finger into the probe coil of his nuclear induction apparatus and got a strong proton NMR signal from it. However, the first serious high-resolution NMR studies of living systems began with the publication in 1973 of the ^{31}phosphorus spectra of intact red blood cells by Moon and Richards[12] and in 1974 of the ^{31}phosphorus spectra of a freshly excised rat leg muscle by Hoult and colleagues.[13] The first Richards I mentioned just now was J H in California and the second was R E (Sir Rex) in Oxford. In both cases, spectral lines could be assigned to individual metabolites and provided a monitor of metabolism. I am not going to follow this trail, because I am sure that Rex Richards and George Radda will talk about this important development after me. Instead, I want to pursue the parallel trail of magnetic resonance imaging, MRI.

In contrast with the steady onward march of NMR spectroscopy from physics through chemistry and biology to medicine, NMR imaging represents a distinctly different application of NMR which appeared rather suddenly on the scene in 1973. In 1973, Paul Lauterbur at Stony Brook published in *Nature*[14] the first NMR two-dimensional image of a heterogeneous-structured object, namely two tubes of water. He pointed out the simple fact that in a field gradient each nucleus responds with its own NMR frequency determined by its position. The NMR spectrum is the one-dimensional projection of nuclear density along the gradient direction. Applying the gradient in a series of directions, he devised an algorithm to generate a two-dimensional NMR image as in X-ray computerized tomography

[11] Felix Bloch (1905–1982). See Bloch F, Hansen W W, Packard M E. (1946) op. cit. note 7 above.

[12] Moon R B, Richards J H. (1973) Determination of intracellular pH by ^{31}P magnetic resonance. *Journal of Biological Chemistry* **248**: 7276–7278.

[13] Hoult D I, Busby S J W, Gadian D G, Radda G K, Richards R E, Seeley P J. (1974) Observation of tissue metabolites using ^{31}P nuclear magnetic resonance. *Nature* **252**: 285–287.

[14] Lauterbur P C. (1973) Image formation by induced local interactions: examples employing nuclear magnetic resonance. *Nature* **242**: 190–191.

(CT) scanning. Also in 1973, Mansfield and Grannell at Nottingham obtained one-dimensional images of several plates of camphor.[15] They were thinking, at first, of applications in crystallography and to other regular or approximately regular structures. Then in 1975, they extended their ideas to more general non-periodic structures.

Just as in NMR itself, so also in MRI there was a pre-history before these final discoveries. In 1951, Gabillard in France investigated the dynamic NMR response of liquids in simple glass structures in a field gradient and showed that the NMR signal was the Fourier transform (FT) of the spatial structure.[16] Then in 1956, Walters and Fairbank at Duke University studied the distribution of ^{3}He in three opaque, vertically arranged containers, one above the other but deep inside a low-temperature cryostat, by applying a field gradient from top to bottom and getting an NMR profile of the ^{3}He.[17] In 1972, Damadian filed a patent in which he proposed, without detail, a method for scanning the human body by NMR which was based on his pioneering observations in 1971 that T_1 and T_2, the two relaxation times, were significantly longer in cancerous rat tissue than in corresponding normal tissue.[18] The interactions between Damadian and Lauterbur were highly provocative and led to the publication of several books by their proponents.

Work on NMR imaging did not at first attract great attention. In Britain, research was carried forward initially in two centres – in Nottingham by Peter Mansfield's group and by our own group which included Waldo Hinshaw and Bill Moore, and in Aberdeen by John Mallard and his colleagues Jim Hutchison and others. In the United States there were groups led by Lauterbur and by Damadian and later by Larry Crooks in San Francisco. In Europe, Ernst was active in Zurich. Soon afterwards, Electrical and Musical Industries Ltd (EMI)[19] in Britain was the first commercial company to enter the field, led by Hugh Clow and Ian Young. First investigations for all of these groups centred on fruit and vegetables and small animals, and then onto humans in 1977 and 1978. Mansfield obtained the first finger image in 1977,[20] we imaged the first hand, wrist and arm,[21] Damadian and

[15] Mansfield P, Grannell P K. (1973) NMR 'diffraction' in solids? *Journal of Physics C: Solid State Physics* **C6**: L422–L426.

[16] See for example Gabillard R. (1952) A steady state transient technique in nuclear resonance. *Physical Review* **85**: 694–695.

[17] Walters G K, Fairbank W M. (1956) Phase separation in He^3–He^4 solutions. *Physical Review* **103**: 262–263.

[18] Damadian R. Apparatus and method for detecting cancer in tissue. US Patent 3 789 832 filed 17 March 1972, patent issued 5 February 1974.

[19] Electrical and Musical Instruments (EMI) (Middlesex) traditionally made records and home entertainment equipment, having pioneered electrical (in place of mechanical) recording in the 1920s and television in the 1930s. A research laboratory, Central Research Laboratories (CRL), was established in the 1930s.

[20] Mansfield P, Maudsley A A. (1977) Medical imaging by NMR. *British Journal of Radiology* **50**: 188–194. See also Mansfield P, Morris P G, Ordidge R J, Pykett I L, Bangert V, Coupland R E.

then Mallard the first chests,[22] Clow and Young the first human head in 1978,[23] and Mansfield the first abdomen.[24]

Physicists are not experts in human anatomy and quite soon physicians were recruited and became actively involved. Professors Coupland and Worthington at Nottingham and Dr Frank Smith in Aberdeen. And, of course, Professor Damadian was himself medically qualified. The EMI work was transferred to General Electric Company (GEC)[25] and to the Hammersmith Hospital in Professor Steiner's department, where Professor Bydder was working with Ian Young, and it became a centre of clinical MRI development.

From 1980 MRI developed exponentially and is now an accepted modality of clinical radiology. Today all major hospitals are equipped with MRI whole body scanners, an estimated 10 000 systems worldwide. Most use a large superconducting magnet and we should recognize the great technical contribution of Oxford Magnet Technology (OMT) in supplying the world with magnets in those earlier years, from the first one installed at the Hammersmith Hospital onwards. Now new horizons are being unveiled with the development of functional MRI. Not only can we think about MRI, but MRI can watch us thinking about MRI. Furthermore, MRI can watch us thinking about MRI recording our thoughts on MRI, and so on, to the n-th degree.

In closing, I would draw attention to the publication earlier this year (1996) by Wiley Publishers to coincide with the fiftieth anniversary of NMR, of the new *Encyclopedia of NMR* in which you may find a number of detailed historical articles. There is also a special jubilee issue of *Progress in NMR Spectroscopy*, which contains four historical articles on NMR in solid-state physics, in chemistry, in biology and in medicine.[26]

(1980) Human whole body imaging and detection of breast tumours by NMR. *Philosophical Transactions of the Royal Society* **B289**: 503–510.

[21] Hinshaw W S, Andrew E R, Bottomley P A, Holland G N, Moore W S, Worthington B S. (1979) An *in vivo* study of the forearm and hand by thin section NMR imaging. *British Journal of Radiology* **52**: 36–43.

[22] See for example Damadian R. (1980) Field focusing NMR (FONAR) and the formation of chemical images in man. *Philosophical Transactions of the Royal Society* B**289**: 489–500. Mallard J, Hutchison J M, Edelstein W A, Ling C R, Foster M A, Johnson G. (1980) *In vivo* NMR imaging in medicine: the Aberdeen approach, both physical and biological. ibid. 519–533.

[23] Clow H, Young I R. (1978) NMR imaging. *New Scientist* **80**: 588.

[24] Mansfield P, Pickett I L, Morris P G. (1978) Human whole body line-scan imaging by NMR. *British Journal of Radiology* **51**: 921–922.

[25] General Electric Company (GEC) of England (no relation to the US GEC), was established in 1892 through a merger of the Thomson–Houston Company and Edison General. GEC of England acquired Picker in 1982.

[26] Grant D M, Harris R K. (eds) (1996) *Encyclopedia of Nuclear Magnetic Resonance*. Chichester: John Wiley & Sons Ltd. Mattson J, Simon M. (1996) *The Pioneers of NMR and Magnetic Resonance in Medicine: The story of MRI*. New York: Bar-Ilan University Press. Emsley J W, Feeney J, Sutcliffe L H. (eds) (1995) *Fifty Years of NMR. Progress in NMR Spectroscopy* **28**: 1–135. See also Blume S S. (1992)

Steiner: Is there anybody in the audience who wants to comment or make any additional observations?

Professor Ian Young:[27] One tiny point. You didn't mention Odeblad.[28]

Andrew: Deliberately so. There are some even earlier people to mention. Shaw and Elsken and Johannssen before them.[29] Odeblad did a number of interesting investigations – high-resolution NMR in Stockholm – but this was when only very low-resolution equipment was available and that's why I actually said, 'The first serious high-resolution NMR studies of living systems'. I think that much more was obtained from the results starting with 1973 and 1974.

Young: The reason I mentioned it was because he actually measured relaxation time constants (T_1, T_2) which preceded Damadian[30] by many years.

Andrew: I am glad you raised that, because I think his work hasn't perhaps had the recognition it should have had and I perhaps should have mentioned it. I would have needed another minute.

Professor Sir Peter Mansfield:[31] Just a small point, but it's in connection with Raymond's [Andrew] mention of Oxford Instruments and Oxford Magnet

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Insight and Industry: On the dynamics of technological change in medicine. Cambridge, MA: MIT Press, ch. 6, The constitution of magnetic resonance imaging, 190–224.

[27] Professor Ian Young FRS (b. 1932) is Chief Scientist of the NMR division of Picker International Inc. He worked for EMI Ltd between 1976 and 1981, and for GEC plc, from 1981 until the creation of Picker International in 1982. An Aberdeen physics graduate, he was awarded an honorary DSc by the University in 1992. He has been visiting Professor of Radiology, Royal Postgraduate Medical School, since 1986 and Honorary Fellow of the Royal College of Radiologists since 1990. He has published over 100 papers in MRI and holds over 40 separate patents.

[28] Erik Odeblad worked on the NMR properties of biological samples including a wide range of human tissue, fluid, and secretion at the Karolinska Institute in Sweden. See for example Odeblad E, Lindström G. (1955) Some preliminary observations on the proton magnetic resonance in biologic samples. *Acta Radiologica* **43**: 469–476. Huggert A, Odeblad E. (1958) Proton magnetic resonance studies of some tissues and fluids of the eye. ibid. **51**: 385–392.

[29] Thomas Shaw and colleagues used NMR to monitor the water content of foods as early as 1951. See for example Shaw T M, Elsken R H, Kunsman C H. (1953) Moisture determination of foods by hydrogen nuclei magnetic resonance. *Journal of Agriculture and Food Chemistry* **36**: 1070–1076.

[30] In 1971 Raymond Damadian reported that NMR could be used to discriminate between malignant tumours and normal tissue. See Damadian R. (1971) Tumor detection by nuclear magnetic resonance. *Science* **171**: 1151–1153. See also note 18 above.

[31] Professor Sir Peter Mansfield FRS (b. 1933) has been Professor Emeritus of Physics, University of Nottingham since 1994. In 1983 he was awarded the Gold Medal of the Society of Magnetic Resonance in Medicine and was its President between 1987 and 1988. He was created an Honorary Member of the Society of Magnetic Resonance Imaging in 1994, Honorary Member British Institute of Radiology in 1993 and Honorary Fellow of the Royal College of Radiologists in 1992. He received

Technology. I think perhaps it may get expanded when Sir Martin speaks, but in fairness to them they were actually involved in the development of magnets and I think we, rather than your group at Nottingham, used an Oxford magnet which was a resistive magnet. I think it was one of, if not the first, resistive magnets to take a whole body, operating at 0.1 Tesla (1000 gauss). I think you were concentrating on the superconductive part of it, which was of course a subsequent development.

Andrew: No, no that's perfectly true. The earliest MRI whole-body experiments were done mostly on resistive magnets. Damadian actually used superconducting magnets and I am not sure how the dates go there. But he made his own magnets, yes, that's right. And we certainly used a Walker resistive magnet and you used an Oxford one. I don't think Oxford Magnet Technology was created at that point.

Steiner: Any other comments from anybody on the opening talk?

Professor Sir Godfrey Hounsfield:[32] I think the introduction of 2-D Fourier transform[33] was one of the biggest steps we had on the technical side.

Steiner: Would you like to enlarge on that?

Hounsfield: For quite a long time people had been using my CT reconstruction – the r-theta system which, of course, introduced very bad phase mistakes when it was used on NMR. It was only when the 2-D Fourier transform system was used that pictures were 100 per cent correct. This was a great step forward.

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the Mullard Medal and Award, Royal Society 1990; ISMAR prize 1992; gold medal from the European Association of Radiology in 1995; and Rank Prize 1997. With E L Hahn he was joint editor for *NMR Imaging* (1991) and with P G Morris, wrote *NMR Imaging in Biomedicine* (1982).

[32] Professor Sir Godfrey Hounsfield FRS (b. 1919) was head of Medical Systems at Thorn EMI from 1972 to 1976 and has been Consultant to Thorn EMI Central Research Laboratories since 1986. In 1969 he invented the EMI Scanner computerized transverse axial tomography system for X-ray examination which revolutionized X-ray diagnosis and for which he received the Nobel Prize in Physiology or Medicine in 1979. See Hounsfield G. (1973) Computerized transverse axial scanning (Tomography). 1. Description of system. *British Journal of Radiology* **46**: 1016. Ambrose J. (1973) 2. Clinical application. ibid. **46**: 1023–1047.

[33] Ernst R R. (1965) Sensitivity enhancement in magnetic resonance. I. Analysis of the method of time averaging. *Review of Scientific Instruments* **36**: 1689–1696. Ernst R R, Anderson W A. (1966) Application of Fourier transform spectroscopy to magnetic resonance. ibid. **37**: 93–102.

Andrew: I did mention contributions to the 2-D Fourier transform. I was thinking more in terms of spectroscopy when I first mentioned it, but it was implied for MRI too.

Professor John Mallard:[34] Could I make a comment on that? We did our early work immediately following Lauterbur's paper. Because we had been working in nuclear medicine, we had built a CT scanner for radioactivity, now called single photon emission tomography, our computers were geared up with all the CT programs and when Lauterbur's paper came out we quickly built a very small permanent magnet system for a mouse and using the CT reconstruction produced the mouse image we showed at Raymond Andrew's conference. Jim Hutchison himself showed it (Raymond Andrew confirmed it was March 1974). We then ground away to build a whole-body imager using an Oxford Instruments vertical field four-coiled resistive electromagnet supplied in 1976 (and still being used in the department) and we also used the same configuration from Oxford Instruments for our Mark 2 version. In 1979 we could get images with very bad movement artefacts, and it wasn't until March 1980 that we were able to come up with the first two-dimensional Fourier transform used in imaging, which most people call the spin-warp imaging. We used volunteers, including ourselves, from March until August, and we did our first patient using that technique on 26 August 1980, the patient was in the care of Frank Smith. I think he is going to be here at the meeting somewhere and I think really that was the breakthrough which made MRI clinically useful.

Professor Sir Martin Wood:[35] Just in response to some of the comments that have been made. I think that the first magnet we made in which a body could be placed, was indeed the one that we supplied to you, John [Mallard].[36] When the

[34] Professor John Mallard (b. 1927) was Professor of Medical Physics in the Department of Biomedical Physics and Bioengineering at the University of Aberdeen from 1965 to 1992, now Professor Emeritus, FRSE 1972. Amongst other honours he shared the Royal Society Gold Medal in 1984; and Mullard Medal, 1989. Together with W A Edelstein and J M S Hutchison at the University of Aberdeen he was involved in the refinement of the two-dimensional Fourier transform method first developed by Richard R Ernst from the Swiss Federal Institute of Technology in Zürich. See notes 33 above and 133 below.

[35] Professor Sir Martin Wood FRS (b. 1927) was the founder of Oxford Instruments plc in 1959 and its Chairman until 1983. He was Chairman of the National Committee for Superconductivity at SERC/DTI from 1987 to 1992 and Director of ISIS Innovation Ltd, CONECTUS, Newport Technology Group Ltd and others. He was awarded the Mullard Medal from the Royal Society in 1982.

[36] Sir Martin Wood wrote: 'Just for the record, I would like to say that all the early developments of NMR and MRI and spectroscopy magnets were done by the original Oxford Instrument Company. As these activities grew, they were transferred to specialized divisions or subsidiaries – Oxford Magnet Technology in the early 1980s, and the NMR division in the 1990s'. Letter to Dr Daphne Christie, 17 May 1998.

instruments came into use, and exactly what they are used for we can't always tell, but we can tell when we ship them out of the door, so to speak. I think there had been a number of magnets. I can remember in particular a 270 MHz NMR magnet that we supplied to Dr Challis in Nottingham, which I believe was used by a number of other people for some early imaging experiments, probably yourself too, Peter [Mansfield]. No? You didn't use that one? But when it came to putting a whole body into it, the first one we made was a vertical field magnet – a resistive magnet with water-cooled copper coils, not a superconducting magnet. The coils lay in the horizontal plane with a sufficient gap in the middle to be able to slide a fairly thin person across horizontally in the centre of the field. I believe we supplied the first one to you John [Mallard] in 1976 and the first horizontal field resistive one to Nottingham the following year. It was in the next two years or so that somehow the fever surrounding these developments grew and we built the first two superconducting magnets in 1980 which we supplied, one to EMI, which eventually finished up in Hammersmith, and one to Pfizer in San Francisco. Then the next one went to Technicare,[37] again in America, and I won't go any further than that.

Mansfield: Pardon me for correcting you on the dates, but the whole-body magnet that was supplied by OMT to Nottingham actually arrived in 1977.

Wood: Was it around Christmas Day? I remember frantic telephone calls from you during a Christmas party in Oxford, saying, 'Where the hell has that magnet got to?'

Mansfield: It wasn't actually Christmas day. I was at a party in Nottingham at the time and I had to run around and muster a group of people to help, because I think there was only a driver who arrived with the magnet and I don't know how he expected us to get it off, but we had to hump it off.

Wood: We had the same trouble in getting it on at the other end too!

Mansfield: That all happened in 1977. It was put together very quickly and we got our first image in April 1978. I went off to a conference in the States and presented that work, which was the image that Professor Andrew referred to, namely the abdominal scan.[38]

[37] Technicare, the parent company of Ohio Nuclear, was taken over by Johnson & Johnson in 1978, from which point a major investment in magnetic resonance imaging was made.

[38] op. cit. note 24 above.

Steiner: I think we ought to move on now to spectroscopy and Sir Rex Richards and George Radda will introduce the topic.

Sir Rex Richards:[39] My active interest in NMR goes back to 1947. I am glad that Raymond mentioned Bernard Rollin who was a very innovative and eccentric physicist who had made NMR measurements very, very quickly by an extremely simple and elegant method so soon after the original description. When I went to see him, to say that I was thinking of having a go at this, he was very derisive and said that there was no point whatever in chemists messing about with this subject. But when I said that I was going to have a go anyway he was extremely helpful and gave me a lot of very valuable advice.

He was, in fact, terrified of chemistry, I think, because later on when he was doing some pure quadrupole resonance measurements he designed his apparatus with a receiving coil which snugly fitted the standard 100 g bottle in which BDH supplied their chemicals. He just ordered up chemicals and when the bottle arrived he dropped it into his apparatus and made the measurement. He then took the bottle out and put it back up on the shelf. It never occurred to him to take the top off or that the stuff in the bottle might not actually be what it said on the label! Anyhow, that is what he did. In those very early days, they were times of very limited funds, so it was very much a matter of make-do and mend. Raymond [Andrew], I am sure, was in the same position. All the electronics that I built were made from components extracted from surplus radar sets from wartime equipment and although I was actually very lucky and able to buy a Tickford magnet with a four-inch pole face it wasn't much good and I had to use a magnet which I built myself. The yoke was made from cast iron at the local Cowley iron works, and machined by the Pressed Steel company who in those days used to make motor car bodies, and the coils I wound myself by hand. That sort of apparatus was very limiting and I spent quite a lot of time trying, unsuccessfully, to measure relaxation times by the progressive saturation method, a method in vogue at the time, but it didn't come to anything. So I turned to dipolar broadening in solids and I don't want to talk about that, because it's not relevant to this discussion.

[39] Sir Rex Richards FRS, FRSC, Hon FBA, Hon FRCP (b. 1922) was Dr Lee's Professor of Chemistry at the University of Oxford from 1964 to 1970 and Warden of Merton College, Oxford, from 1969 to 1984. He was Chairman of the Oxford Enzyme Group from 1969 to 1984, Director of IBM-UK Ltd from 1978 to 1983 and Oxford Instruments Group from 1982 to 1991, and Chairman of the British Postgraduate Medical Federation from 1986 to 1993. Other honours include President of the Royal Society of Chemistry from 1990 to 1992 and Trustee of the Ciba Foundation from 1978. He received a Medal of Honour from the Rheinische Friedrich-Wilhelms University of Bonn in 1983 and Royal Medal from the Royal Society in 1986.

However in the very early 1950s, I think it was or at the end of 1949, the chemical shift was discovered by Proctor and Yu,[40] you must remember I am coming to this as a chemist and so I am looking at it from a different point of view from Raymond [Andrew]. The chemical shift was discovered by accident – I think it was in ammonium nitrate, they were looking for nitrogen resonance, and were rather surprised to find two nitrogen resonances in the ammonium nitrate solution. Almost immediately afterwards, some surprising multiple structure was noticed in the fluorine resonance of the antimony hexafluoride ion and various ingenious explanations of that were given, one of them I think Raymond [Andrew] gave. Shortly afterwards when Erwin Hahn was doing spin-echo experiments he noticed in some proton resonances a mysterious modulation on the spin echoes.[41] The Harvard people, I think it was Ed Purcell particularly, realized that this was due to scalar coupling between the magnetic moments within the same molecule, which has come to be known as spin–spin coupling.[42] Once the idea of the chemical shift and spin–spin coupling had been discovered, to anybody like me who'd come from a spectroscopic background, the potential of NMR for chemistry was absolutely obvious.

But, of course, the technique was technically demanding for a chemist. It required strong magnetic fields, they had to be homogeneous and stable if you wanted to do proton resonances, to parts in 100 million – a formidable engineering task – and the number of people who were prepared to tackle this and make their own instruments could be counted on the fingers of one hand. But fortunately, there was a very important development in Varian Associates, an instrument engineering company run by two brothers who had been specializing in manufacturing microwave sources during the war, and had made a great deal of money from them. With the very visionary views of Russell Varian, one of the brothers – who was a physicist – it was decided to manufacture spectrometers to do high-resolution NMR and they produced a series of instruments based on a large electromagnet with 12-inch pole faces and a power supply driven by what the Americans called tubes. These instruments were made for high-resolution studies, first of all at 30 MHz for protons and gradually increasing the field up to the limit that you can get with an iron magnet, which corresponded to about 100 MHz for protons. This was an extremely important development from the point of view of chemists, because although these instruments were expensive, and they were quite difficult to manage, they did bring high-resolution NMR to the chemical

[40] See Knight W D. (1949) Nuclear resonance shift in metals. *Physical Review* **76**: 1259–1260. Proctor W G, Yu F C. (1950) The dependence of a nuclear magnetic resonance frequency upon chemical compound. ibid. **77**: 717.

[41] The spin echo was developed in 1950 by Erwin Hahn (b. 1921) because of the need to sustain the NMR signal over extended periods of time for the measurement of NMR phenomena. See Hahn E L. (1950) Spin-echoes. *Physical Review* **80**: 580–594.

[42] Ramsey N F, Purcell E M. (1952) Interactions between nuclear spins in molecules. *Physical Review* **85**: 143–144.

community and it released the technique from the grip of the physicists who had not got any idea what to do with it. [Laughter] I was told to make provocative remarks! And this left the chemists not having to worry about how to make these quite difficult magnets, but just to see what they could do with them, and of course it proved extremely valuable.

The instruments were, however, too expensive, and too limited in what they would do for those of us in Oxford who were working in this business and it occurred to me that a very cost-effective solution to high-resolution work would be to use a permanent magnet. One of the problems of an electromagnet is that you have to supply it with a lot of power to get the field you want and also stabilize it very elaborately, and then you have got to get the power out with water-cooling and so on. With a permanent magnet you can get over all those things. And I was very lucky, I'd scraped together a few hundred pounds here and a few hundred pounds there, until I'd got £2000, and I persuaded the Mullard Company to build a permanent magnet for high-resolution work, which they did. It had a field of about 7 kilogauss (that's 0.7 Tesla to young people here) and it proved to be extremely stable both in field strength and homogeneity and we built a high-resolution spectrometer around that, which we used for all sorts of chemical experiments. That instrument was the basis of a very simple and relatively inexpensive instrument manufactured by the Perkin Elmer Corporation and distributed widely to chemists. But the technique in those days was still quite severely limited to rather strong solutions of chemicals, and to chemicals with only a modest number of atoms in them. The reason was that the technique had poor signal-to-noise ratio; signal strengths were weak, and the spectra were rather complex, because quite often the spin–spin coupling interactions were comparable with the chemical shifts between the nuclei involved, so that one worked in a situation of strong coupling and the spectra didn't look simple.

The only way out of this was to increase the magnetic field and there was no hope of doing that with an iron magnet, but that became possible in the early 1960s with the discovery by an engineer in America of the so-called type 2 superconductors. Varian quickly exploited this and manufactured a high-resolution 220 MHz instrument based on a niobium–zirconium magnet. I discovered after going to Varian Associates a little while later that it was an extraordinarily primitive device, but nevertheless they manufactured and sold quite a number of them. They were frightfully expensive. Their stability of resolution was poor and they weren't very flexible, and it has always amazed me that they never bothered to do any further work on the design of that superconducting magnet. But just at about that time Martin [Wood] here went to the United States, I can't remember just when it was but he'll tell you, and he came back with some niobium–zirconium wire, wound a magnet at home and achieved a field of 4 Tesla. I got to hear about this and it seemed to me that this was a wonderful opportunity for us to see whether

we couldn't do as well as Varian. I went to the Science Research Council (SRC) and they had the imagination to give us quite a generous grant to build two superconducting magnets. The idea was that Oxford Instruments would build the magnets – one was to be a small model magnet to try out various design ideas that we had and the other was to be a magnet that we would use. And I am not going to say any more about it, because I expect Martin [Wood] will tell you that story.

About that time, integrated electronic circuitry was coming on stream and then very large-scale integration and, of course, that meant that computers of modest cost and modest size, but considerable power, were becoming available. As soon as that happened, Fourier transform became a practical proposition for NMR spectroscopy. We had tried to do Fourier transforms in my lab at Oxford in the early 1960s, by having a digital storage device to store the spectra, which we called a CAT in those days (computer of average transients), and then reading the results of that on to paper tape and carrying it across to the computing lab, and having a Fourier transform done. It was absolutely frightful because the paper tape punch wasn't very reliable and every time there was a drop out, of course, it appeared as terrific sine waves running across the spectrum and it really wasn't on. But the incredible rate at which computing power increased and the way the cost came down had a huge effect on NMR spectroscopy, because Fourier transform gives you two orders, and in favourable cases even three orders, of magnitude improvement in signal-to-noise. At the same time much higher magnetic fields of superconducting magnets also gave a big improvement in signal-to-noise. The signal-to-noise goes up as something like the three halves power of the field, so that's a great gain, and the combination of Fourier transform and higher magnetic fields was a complete revolution in NMR and changed the whole outlook of the ways in which it could be applied. And that brings me really to protein spectroscopy and spectroscopy in biochemistry and I am going to leave that because George [Radda] is here and he can talk about it.

Perhaps I could say one more thing, and that is that NMR continues to be a source of a tremendous amount of information and it's worth asking why. The reason is the huge information content that there is in almost any NMR spectrum. There are five or six independently measurable parameters for every distinguishable nucleus in a sample. It is a huge amount of potential information in the NMR spectrum and I don't myself believe that we have exploited all of that, by any means, even yet, and if I was 25 again I would still be having a go at that.

Wood: The involvement of Oxford Instruments in this business was really quite accidental. It started in the middle 1960s, after we had set up Oxford Instruments in 1959 as a spin-off from the high magnetic field department in the Clarendon Laboratory, the Physics Department of Oxford University, where I had worked for some years. The idea was to design and manufacture magnets for the academic

world in general. I don't think there was anybody in Oxford Instruments who knew anything about NMR. There was no track record of research in NMR known to us. There was probably nobody who knew what those three letters stood for even! We were just magnet makers. We used to call ourselves upmarket plumbers in those days before the type 2 superconductors had been developed and came onstream in the 1960s. We were just winding water-cooled copper coils, using the technology out of the Clarendon Laboratory, where there was a 2 megawatt generator and we made high-field coils without much homogeneity, because for the work they were required it wasn't necessary.

To follow on Sir Rex's [Richards] story, in the very early 1960s, I went to a conference at the Massachusetts Institute of Technology (MIT) which was really a workshop for magnet makers and magnet users – not an NMR conference at all. It so happened that there had been some tremendous developments in superconducting materials in the few months prior to that conference and to give time for these papers to be delivered, they ran an extra session on Saturday afternoon. You know what Saturday afternoon sessions at the end of a week's conference are usually like – most people have gone home and the rest are tired or bored – but this was an extraordinary meeting. It took place in the Kresge Auditorium in MIT and the place was absolutely full. There were representatives from the Bell Telephone Laboratory, the Lincoln Labs, Westinghouse, the Radio Corporation of America (RCA)[43] – all the big American companies who'd jumped in on the extraordinary new developments that had arisen. A man called John Kunzler had discovered an inter-metallic material, niobium-tin (Nb_3Sn), which remained superconducting, even when carrying a very high current density in a magnetic field approaching 9 Tesla. This was an extraordinary breakthrough on the material front of superconductivity research, and everybody got very excited. We came home from that conference and bought a pound weight of niobium–zirconium wire which was a superconducting material which soon became commercially available and we wound a magnet with it.[44] I remember taking it into the Clarendon Laboratory, and lifting the battery out of my car, as a source of current, and taking it upstairs to the laboratory where Professor Kurti[45] produced enough liquid helium to test it in, and we cranked it up to 4.2 Tesla. To reach this field without all the electrical machinery of the Clarendon Laboratory was unheard of. We were used to ringing up the Chief Engineer of the Oxford Power Station and asking for permission to turn the 2 megawatt generator on. Then with pure

[43] RCA (Radio Corporation of America) was established in 1919 when American Marconi was taken over by General Electric.

[44] This was the magnet referred to earlier by Sir Rex Richards.

[45] Professor Nicholas Kurti FRS (b. 1908) first held a research position at the Clarendon Laboratory in Oxford between 1933 and 1940. He later became Professor of Physics University of Oxford from 1967 to 1975, now Emeritus. The Clarendon Laboratory of Oxford is famous for housing the first helium liquefaction plant in Britain (1933).

water in the 100-ton reservoir on the roof circulating, we could begin to energize a magnet. You could say that it was a lot of fun – but it was certainly a lot of work developing high fields in the conventional way in those days. Suddenly the new superconductors were making this all very much easier – they were leading to a technological revolution in magnet world.

We saw that this was a major turning point for our company, and over the next few years we moved away from making copper coils for other laboratories around the world and changed over to generating high magnetic fields using superconductors. For that reason, and because the Clarendon Laboratory continued to use its conventional high magnetic field facility, regular contacts with Oxford University declined a little, and our relationships grew rapidly with other parts of the world where high-powered magnets were not yet available. Hence our surprise one day, when we had the telephone call from the Department of Physical Chemistry in Oxford, as we normally dealt with physicists. Here was a chemist ringing us up and saying, 'Would we like to talk about building a high homogeneity magnet'. We didn't even know how to spell high homogeneity. [Laughter] Most of our physicist customers wanted us to construct magnets which gave the highest field usually within some very small volume and with little interest in field homogeneity. So Rex [Richards] came to see us and looking back historically, that was an immensely important meeting for us. Previously everything – every single thing we'd ever made – had been specially designed for some research physicist for some particular experiment. Here was the first occasion when there was a possibility of making two things alike. And then perhaps a third, and a fourth, and a fifth. It was the collaboration which helped us so much. We knew how to generate high magnetic fields and the University helped us – Sir Rex in particular – in developing the high homogeneity aspect. A partnership began, which continued for many years with us developing each new generation of magnets, jointly with funds which Sir Rex got from the Science Research Council and elsewhere. He always gave us an enormous amount of credit in all the research papers that his department published, and that brought in lots of orders from elsewhere, which enabled us to develop the company and initiate the R&D required for the next NMR magnet. It was a sort of virtual spiral that went on and it continues to this day. The world's first 750 MHz magnet has been in operation now in Oxford for just over a year now.

Two or three things have come out of all this – quite different things. One is, of course, the imaging side of it which has become far and away the biggest single commercial application of superconductivity and it's interesting that that was never predicted until quite late – the middle to late 1970s. Even at the beginning of the 1980s there was considerable doubt in many circles as to whether this was really going to take off. We were obviously looking at the emerging applications of our technology and we went to a number of conferences and brought back all sorts of

reports of peoples' hopes and doubts. There was one in Nashville in about 1980 (correct me please, people who went to the conference) in which the messages came out first of all that MRI probably was going to be less important than whole body NMR spectroscopy – *in vivo* spectroscopy. This was a message that came over from the radiological fraternity who saw *in vivo* spectroscopy as something totally new and, very interesting, with a fantastic future, whereas imaging was something they knew all about anyway with X-ray. They didn't particularly want to learn a new technology. Secondly, they were thinking that if MRI was going to develop substantially the main application would be in fairly cheap small systems. It turned out, a year or two later, that both those predictions were completely wrong. We always had the problem, which I can admit to this small audience, of not always knowing the details of the fundamental scientific side, and yet having to be present and ready to make the equipment. We had to listen to what was said to us concerning the likely way things were going to go, but always trying to take our own view, sitting precariously on the fence – so that we could go in a different direction, if it went that way, as it often did.

Another interesting thing concerns the BTG (British Technology Group) income.[46] Having had enormous income from various other patents such as the cephalosporins and so on, which are now nearing the end of their lives, the income they now get from their patent portfolio on NMR and MRI is beginning to be one of the biggest, if not *the* biggest, single source of income to them. Substantial grants are now being fed back carefully into the scientific community.

I might add a comment, Rex, to what you said about Varian. The way commercial things work out in the long run is interesting as we are now in bed with Varian and we make all the magnets for the NMR systems which they sell. They are extremely good at making the spectrometers, and we make the magnets, and that collaboration is now working very well. There is also a semi-humorous, anecdotal side to the industrial picture which, of course, doesn't emerge normally. For instance, we had a quite famous Christmas party in 1977 – you talked about it Peter [Mansfield]. You weren't the only person on the telephone, ringing up and saying, 'When's that magnet going to be delivered?' If you are in our sort of business, supplying equipment to the research community, in which all customers want to be out in front, it's very difficult to convince any one person that actually we have responsibilities to other people too. There are always terrific pulls in different directions. There are also budgetary considerations – you have got to make certain deliveries before the end of December, the end of the calendar year. A lot of university labs are locked up at Christmas and not opened until well into January. If they happen to be open during a Christmas party, that can be a possible

[46] British Technology Group (BTG) is the successor body to the National Research Development Corporation (NRDC). The BTG was formed in 1981 by combining the NRDC with the National Enterprise Board (NEB). See note 153 below.

window for a delivery to an enthusiastic customer and not only to NMR and MRI customers![47]

It goes on and on. We are now working on a 900-MHz system and everybody's talking about a gigahertz magnet. I don't think there is any particular importance in that number, but it's a thing to focus on.

Steiner: Thank you very much. We will come back to you again when we discuss imaging. Now George [Radda], biology please.

Booth: Could I just ask a question at this stage? Having listened to those two views, one is fascinated by the link between what you might term sealing wax and string work in the university and an imaginative commercial organization, Oxford Instruments, and then funding from the Science Research Council, which must have been quite unusual at that time. The question I really want to ask you both is: was this structure in Oxford, namely a university department with a problem, a sympathetic development in commerce, and then the backing of the Research Council, was that unique to Oxford? Could it have happened anywhere else?

Richards: I think so, yes. Everybody in the 1950s, in this sort of business, was working on the same basis. We all built our own instruments and everything was done as inexpensively as possible, so Oxford was not peculiar in that respect. On the other hand, neither were we badly placed. We have very good workshop facilities in Oxford and the permanent magnet that I built first was supported by small grants, I think it was a few hundred pounds from Shell, and a few hundred pounds from what was known as the DSIR (Department of Scientific and Industrial Research), later became the SRC and, I forget, there was a few hundred pounds from somebody else. But that was how we all worked. It wasn't particularly unusual, and then by the time the 1960s came, of course, the university support was very much more generous than it had been and although the grant that I received to build these first two high-resolution magnets was quite a large grant, it wasn't a terrific amount of money. I mean it was nothing like as much as would be needed to build a mass-spectrometer, for example, which chemists were using all the time. So it wasn't extraordinary. The point was the lucky juxtaposition of Martin's [Wood] company and our interest at the time.

[47] Sir Martin Wood wrote: 'I can remember that Christmas party well with telephone calls from Nottingham, and an old vehicle loaded with a very heavy magnet.' Letter to Dr Daphne Christie, 17 May 1998.

Mansfield: The magnet that we keep talking about that got delivered just before Christmas in 1977, the audience may be interested to know now resides in a special display area in the Science Museum at Kensington.

Professor George Radda:[48] To go on from Rex [Richards] really, the biology started in the 1970s when Rex and my group started to work together while he was still in the physical chemistry lab. I remember the first studies we did were with chlorine resonance and looking at its binding to proteins, followed by caesium and its binding to membranes, and then Rex fortunately moved into the Department of Biochemistry, when he became Warden of Merton [College, Oxford], and the collaboration started to build up.

Richards: Can I interrupt you George? That move was an extremely lucky one and only happened because I became Warden of Merton, and Rodney Porter[49] who was so very kind to me actually caused the main cloakroom and lavatory on the ground floor of the Biochemistry Department to be refurbished and turned into my laboratory.

Radda: We did three sorts of experiments when you moved in. One was caesium NMR, then we did some lithium NMR with membranes and started to do phosphorus NMR to look at membrane structures. And while people were doing that, my group was interested in enzyme regulation and trying to see how small ligands can change conformations and how these enzymes might then behave *in vivo*, which we hoped to be able to predict after those studies. It was during one of those discussions, that on the basis of what we learnt in solution studies on the enzyme we could say how those enzymes work in the muscle, that somebody said, 'Let's try and work it out', and we did our calculations and we decided that we were two orders of magnitude out. That is, the solution studies didn't really tell us how things behaved *in vivo*. And a very bright graduate student of mine, Steve Busby, suggested to David Bell – who was killed – and I think David Hoult was already there, 'Well you are doing all this phosphorus on membranes, why don't

[48] Professor George Radda FRS (b. 1936) has been Chief Executive of the Medical Research Council since October 1996 and British Heart Foundation Professor of Molecular Cardiology at the University of Oxford since 1984 (on leave of absence). He was a founder member of Oxford Enzyme Group between 1970 and 1986 and President of the Society for Magnetic Resonance in Medicine from 1985 to 1986. He was awarded the Gold Medal from the Society for Magnetic Resonance in Medicine in 1984.

[49] Professor Rodney Porter (1917–1985) was Whitley Professor of Biochemistry at Oxford University and Chairman of the department from 1967 until his death. Porter shared the Nobel Prize in Physiology or Medicine in 1972 with Gerald M Edelman for their research on the chemical structure of antibodies. See Perry S V. (1987) Rodney Robert Porter 1917–1985. *Biographical Memoirs of Fellows of the Royal Society* **33**: 445–489.

we look at the metabolites in a living organ like a piece of muscle, then we can immediately tell what is happening.' Everybody pooh-poohed the idea, but nevertheless they went away and did the experiment. That was the first *in vivo* tissue experiment, at the end of 1973, on a living piece of muscle, which was published in 1974.[50] That was in one of Rex's early superconducting magnets which had a 22-mm bore, and was able to take a 10-mm sample tube and I think we realized very quickly that if you were going to do any serious biology and keep the muscle and other organs alive you need something much bigger. Rex took us to Oxford Instruments and asked them if they could design what was then called a wide-bore magnet, 11-cm bore, at 4.2 Tesla, and of course they could do it they said and it is going to cost us £25 000, which in 1975 wasn't a trivial amount of money. On a speculative project, that might work for the study of intact organs or beating hearts, and we realized that that wasn't the sort of thing that you would get out of a Research Council, because the committee would look at it and they would say, 'You haven't done the preliminary experiments and how do you know it is going to work?' So I went to the British Heart Foundation (BHF), and said, 'Look, I think I could have a beating heart inside a magnet of that sort and find out the biochemistry of the heart during a heart attack.' And they sent Sir John McMichael[51] down, who was Professor of Cardiology, who you must have known, he was in medicine at Hammersmith, and he came down with Peter Slight and we had this 3-mm tube with a little mouse heart beating in it and we put it in an old spectrometer and we watched it for about 20 minutes and saw the signal building up. Then we said to Sir John, 'Now we'll turn the oxygen off, that's a heart attack, and you can see those signals go away', and he got so excited that he went back to the BHF and said, 'We must support this, it's going to be tremendous', and so that's how our first wide-bore magnet was delivered in 1976. By this time several other groups in the States cottoned on to the idea that you could do *in vivo* spectroscopy – Bill Jacobus for example at Baltimore was doing similar work.[52]

Based on that, we'd done two or three years of work on heart, kidneys and various other things until a bright postdoc cottoned onto the idea that rather than surrounding the object with a coil which would make it difficult to look at a complex system like a whole animal, if you put a surface coil next to the object that you want to study, you might still get high-resolution signals. Jo Ackerman and colleagues used the first surface-coil experiment on a living animal in that

[50] op. cit. note 13 above.

[51] Professor Sir John McMichael FRS (1904–1993) was Professor and Director of the Department of Medicine at the Postgraduate Medical School at Hammersmith between 1946 and 1966, then Director of the British Postgraduate Medical Federation from 1966 to 1971. His research interests were predominantly in the field of cardiology and he was the first in Britain to apply the technique of cardiac catheterization. See Dollery C. (1995) Sir John McMichael 1904–1993. *Biographical Memoirs of Fellows of the Royal Society* **41**: 283–296.

[52] Jacobus W E, Taylor G J, Hollis D P, Nunnally R L. (1977) Phosphorus nuclear magnetic resonance of perfused working hearts. *Nature* **265**: 756–775.

wide-bore magnet in 1979 with a paper that was published in 1980.[53] And at that point in 1979 Britton Chance (from Philadelphia), who had been working with us on the perfused organs, came over to do some experiments on the brain.[54] After an experiment on a living muscle in an animal I took him back to Heathrow and his plane was delayed, so we were sitting around at Heathrow and he said, 'You know, if we can do that on a living muscle on an animal, surely we ought to be able to do that on a human, and wouldn't it be great if I could stick my leg into that magnet and could map out where the blood circulation is not good and we could tell the surgeon where to amputate.' It was a terribly simple idea and we said, 'All we need is a 2-Tesla horizontal magnet with a 30-cm bore and the experiment is on.' We both went to Oxford Instruments simultaneously to say we would like a horizontal bore, 30-cm magnet, 2 Tesla, which we can use to study spectroscopy in human muscle and we both got magnets at about the same time. Again, the British Heart Foundation helped us out to buy it and Oxford Instruments always contributed to the cost of that sort of thing. And these were the first magnets here in England and in the United States, that were capable of doing spectroscopy on human muscle.

Our first patient was studied in February 1981 and turned out to be a real star, because the patient had phosphorylase deficiency and it was so easy to pick up by the lack of acidification during exercise, because the muscle tissue couldn't produce lactic acid, that we were very easily able to identify McArdle's disease. That paper was published in the *New England Journal of Medicine* in 1981 as the first spectroscopic study of a patient.[55] I think we discussed that at a very important meeting in 1981 in Winston–Salem. I think Ian [Young] was there, and you [Mallard] were there, when the Society of Magnetic Resonance in Medicine (SMRM), a new society, was formed. There were a number of people there who sat down and said, we have to have a Society of Magnetic Resonance for Medicine, with imaging, and spectroscopy included.

Following these early human studies, we considered the possibility of a high-field, 2-Tesla, 80-cm bore magnet. There was a critical meeting in Oxford and I have got a note of that actually here – 28 November 1979 – held at Wolfson College on 'The Applications of NMR to Medicine', and that conference on that day was designed to convince the Department of Health that spectroscopy was going to be something worth supporting. The people present there, apart from the

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[53] Ackerman J J H, Grove T H, Wong G G, Gadian D G, Radda G K. (1980) Mapping of metabolites in whole animals by ^{31}P NMR using surface coils. *Nature* **283**: 167–170.

[54] See for example Chance B, Nakase Y, Bond M, Leigh JS Jr, McDonald G. (1978) Detection of ^{31}P nuclear magnetic resonance signals in brain by *in vivo* and freeze-trapped assays. *Proceedings of the National Academy of Sciences USA* **75**: 4925–4929.

[55] Ross B D, Radda G K, Gadian D G, Rocker G, Esiri M, Falconer-Smith J. (1981) Examination of a case of suspected McArdle's syndrome by ^{31}P nuclear magnetic resonance. *New England Journal of Medicine* **304**: 1338–1342.

speakers, who were Rex and David Gadian and a clinician called Peter Bore, were Gordon Higson, Norman Slark, John Williams from the Department of Health,[56] many other officers from the Welsh Office and the Scottish Office, and a large number of clinicians from all over the country. We spent the day talking about whether in fact it's worth trying to do spectroscopy in humans as a clinical investigation tool. I think in the end we managed to convince the various people, MRC, Department of Health, and Oxford Instruments together, that this would be a worthwhile effort. So the first high-field, whole-body magnet was installed in Oxford at the John Radcliffe Hospital towards the middle of 1983 and that was the beginning really of the clinical investigations.

Now there was a key publication in 1983 from General Electric (GE),[57] with Dr Paul Bottomley as the first author, which showed that at 1.5 Tesla, where they were already doing imaging, you could do the spectroscopy and you could do it in the same machine.[58] There were other localization methods than the topical NMR and that you could use the techniques designed for imaging to get localized spectroscopy. I think that changed the field again very significantly, because people realized that you could not only do the two experiments in the same instrument, but, in fact, there were better ways of localizing the biochemical information that you got out. From 1983 onwards it grew and to phosphorus-spectroscopy people have added proton-spectroscopy, which is now on a very large number of clinically usable machines. Proton-spectroscopy is perhaps more routinely done than phosphorus-spectroscopy, certainly on the brain, and I believe in the United States that's now a reimbursable measurement.[59] Certainly our radiologists in Oxford are doing proton-spectroscopy as routine in brain and tumour studies. So this is more or less at the beginning, and from there on it grew into a much larger industry in terms of the biochemical research and biomedical research. Perhaps I should mention, because it is very appropriate, that the first application of phosphorus NMR spectroscopy in the brain was in fact done on babies by Ossie Reynolds in 1982 in this country and then Britton Chance came after on that as well. So the initial studies on babies then have been taken onto whole humans.

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[56] John Williams was principal Technology Officer and Norman Slark was the Superintending Technology Officer in the Scientific and Technical Branch of the Department of Health and Social Security at the time. Gordon Higson was present at the Witness Seminar and contributes later.

[57] General Electric, International General Electric of New York.

[58] Bottomley P A, Hart H R, Edelstein W A, Schenck J F, Smith L S, Leue W M, Mueleer O M, Redington R W. (1983) NMR imaging/spectroscopy system to study both anatomy and metabolism. *Lancet* **ii**: 273–274.

[59] A recognized healthcare cost that can be re-imbursed as a legitimate health expense, through US Health Insurance Companies.

Professor Osmund Reynolds:[60] I just wondered if it might be interesting to hear about how the baby studies got started and the reason was that those of us who worked in neonatal intensive care units were aware that there was a highish risk of brain damage in surviving infants and we wanted non-invasive methods for investigating the structure and the functions of the brain so that we could find out what were the causes, prevalence, timing and prognosis and so forth, of cerebral lesions. We had in fact introduced brain ultrasound imaging in babies in 1978, which gave us a lot of useful information, particularly about cerebral haemorrhage, which was one of the two main causes of damage to the brains of babies who needed intensive care. But that technique, and you wouldn't expect it to, didn't give you much information about the early events in hypoxic–ischaemic brain injury, which is actually the more important cause of long-term disability in survivors of intensive care. We were looking around for some new techniques which would non-invasively examine the brains of sick babies and there were a group of us, including Dave Delpy who's sitting on my left and most particularly Doug Wilkie[61] who was an old friend and who was involved in NMR spectroscopy of muscle in studies of frogs,[62] and wanted to get involved with humans. One day we agreed between the medical physicists, including Dawood Parker, and the rest of us, that that would be a good way to go, if it was possible. Near-infrared spectroscopy was another way to go, but that's a completely different story, but that was coming along at about the same time.

Anyway, as far as the NMR spectroscopy was concerned, before getting involved with humans, we thought we ought to do some animal studies. Actually, the penny dropped that to move in this direction was a really good idea one day when Doug [Wilkie] said that the bore of the Oxford Research Systems magnet for spectroscopy had got big enough so you could stick a human limb in it and then this penny dropped that if you could get a human limb in, you could get a human baby in and you could study the brain. That was when the notion came that this was actually going to be practical. We got in touch with Oxford Research Systems, which Doug was already in close contact with, and Dave [Delpy] and Dawood [Parker] and the rest of us packed up rabbits, blood gas analyzers and everything else, and went out and did the experiments together with Roy Gordon in a shed at Oxford Research Systems. We asked the question: if you reduce the oxygen supply

[60] Professor Osmund Reynolds FRS (b. 1933) was Professor of Neonatal Paediatrics at University College London Medical School from 1976 to 1996, now Emeritus. He received the Maternité Prize, European Association of Perinatal Medicine in 1994; the James Spence Medal, British Paediatric Association, 1994; and the Harding Award, Action Research, 1995.

[61] Professor Douglas R Wilkie FRS (1922–1998) held a personal chair in experimental physiology at University College London from 1965 to 1969, became Jodrell Professor of Physiology and Head of the Physiology Department from 1969 to 1979, and then Jodrell Research Professor of Physiology (Emeritus) at London University from 1979 to 1988.

[62] Dawson M J, Gadian D G, Wilkie D R. (1978) Muscular fatigue investigated by phosphorus nuclear magnetic resonance. *Nature* **274**: 861–866.

to the brain of a rabbit do the predicted changes in the phosphorus metabolites and intracellular pH occur, and are they reproducible? And the answer to that was yes.[63] They were done in 1981, and then we raised the money from four charities of which the biggest contributor was the Wellcome Trust, to buy a 20-cm magnet for UCH. The first baby's brain was studied on 22 October 1982 and we had been waiting actually to see if we could find a baby who we thought might have a unilateral lesion, and so would have a control hemisphere, and one day we found one that had something pretty suspicious looking on one side on the ultrasound image which we couldn't understand. The baby was born six weeks prematurely and appeared clinically to be extremely well. I can remember the discussions with the father, who was a US lawyer whose wife had had this baby by mistake whilst travelling through London, and trying to explain how it would be jolly useful if we could put the baby in a magnet please. Anyway it worked out and we got the first human brain spectra. What we found was a good control spectrum on one side and evidence of seriously deranged energy metabolism on the other.[64] The child is now 14 years old with a hemiparesis but a normal IQ and that's just an instance of how NMR spectroscopy gives you a good idea of prognosis.

We then went on to do hundreds of studies and have modelled in experimental animals the changes that we see in the brains of ill human infants, so that cerebro-protective strategies can be tested.[65] But that's how it all arose in the first place.

Steiner: Gordon Higson, your name was mentioned by George [Radda], any comments?

Mr Gordon Higson:[66] Robert, I suspect when you talk about imaging it might be a good time to talk about issues of funding and how it all worked over several years. George [Radda] was one of many people who were knocking on the door, asking for money at that time and I will try and sort it out when we have heard more about imaging.

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[63] Delpy D T, Gordon R E, Hope P L, Parker D, Reynolds E O R, Shaw D, Whitehead M D. (1982) Noninvasive detection of cerebral ischemia by phosphorus nuclear magnetic resonance. *Pediatrics* **70**: 310–311.

[64] Cady E B, Costello A M de L, Dawson M J, Delpy D T, Hope P L, Reynolds E O R, Tofts P S, Wilkie D R. (1983) Noninvasive investigation of cerebral metabolism in newborn infants by phosphorus nuclear magnetic resonance spectroscopy. *Lancet* **i**: 1059–1062.

[65] Reynolds O. (1996) Causes and outcomes of perinatal brain injury. In Magnusson D. (ed.) Nobel Symposium, *The Lifespan Development of Individuals*. Cambridge: Cambridge University Press, 52–75.

[66] Gordon Higson (b. 1932) was Director of the Scientific and Technical Branch of Department of Health and Social Security between 1980 and 1984 and Controller of Supply between 1984 and 1985.

Professor John Griffiths:[67] After I qualified in medicine I went as a DPhil student to George Radda's group, in 1971. There I had a minor part in a prologue to the first magnetic resonance studies on living tissues. My role was to spin-label the enzyme glycogen phosphorylase and then, from the electron spin resonance (ESR) spectrum, measure its conformational changes when effectors such as adenosine monophosphate bound to it. If you made crude extracts of muscle glycogen particles you could put this spin-labelled enzyme back into something approaching its natural environment, but when you added effectors such as adenosine monophosphate they were degraded by other enzymes. I was much too lazy to do all the necessary assays so I asked David Gadian and colleagues if they would put the glycogen particles with the spin-labelled enzyme into the NMR machine, so that the adenosine monophosphate and its breakdown products could be assayed simultaneously. In one lab I did the ESR experiment with Raymond Dwek, in another lab Steve Busby assayed the activity of the glycogen phosphorylase and in the MR lab all these compounds appeared magically on the MR spectrum in real time. Although I didn't realize it, this was very close to an NMR spectrum of a living muscle.[68]

I bowed out at that stage and David Gadian and colleagues in George Radda's laboratory then did the really neat experiments. First they put a homogenized muscle into the instrument and then they performed their landmark MRS study on intact muscle. I went on to work for some years in the Biochemistry Department at the Medical College of St Bartholomew's Hospital. Eventually I came back into the Oxford fold on an occasional basis in collaboration with Richard Iles. Working again with David Gadian in Sir Rex Richards' laboratory, in collaboration with Professor George Radda's group, we did MR spectroscopy of perfused liver in the late 1970s.[69]

My last anecdote concerns the time when, as you just heard from Professor Reynolds, UCL had put together a raft of charities to fund the new horizontal-bore MRS instrument at University College. Professor Radda's instrument had been funded by the British Heart Foundation so just about every charitable body in Britain as well as the MRC seemed to be involved in these programmes. I urgently wanted to begin MRS research in my new job at St George's Hospital but who would fund the instrument I needed? I sat down with the big directory of charitable trusts in the library to see what was left. And then I noticed that one of

[67] Professor John Griffiths (b. 1945) is Director of the Cancer Research Campaign (CRC) Biomedical Magnetic Resonance Research Group, and has been Professor of Medical Biochemistry at St George's Hospital Medical School, London, since 1986.

[68] See Griffiths J R, Dwek R A, Radda G K. (1976) Conformational changes in glycogen phosphorylase studied with a spin-label probe. *European Journal of Biochemistry* **61**: 237–242.

[69] Iles R A, Griffiths J R, Stevens A N, Gadian D G, Porteous R. (1980) Effects of fructose on the energy metabolism and acid–base status of the perfused starved-rat liver. A ^{31}P nuclear magnetic resonance study. *Biochemical Journal* **192**: 191–202.

the largest research charities in the country was the Cancer Research Campaign. Suddenly light dawned, and I realized that nobody in the whole world had ever done an MR spectrum of a cancer. Coming from medicine, I realized, of course, that there were all sorts of clinically significant properties of cancer, particularly hypoxia, which could be studied with MR spectroscopy.

The new horizontal-bore machine for human limbs that you have just heard about was also ideal for animals, so in 1980–1981, in the Oxford Research Systems factory at Oxford, Richard Iles, Roy Gordon and I did the first spectroscopy of cancers *in vivo*.[70] Then, of course, we had to find a tumour on a human limb that we could examine in one of these magnets. Normally, of course, if somebody has a tumour on the end of a limb the surgeons amputate it very quickly, but in 1982 one very sad case where this was impossible came our way from colleagues at the Royal Marsden Hospital. By the kindness of our collaborators at University College, particularly Doug Wilkie and Ernie Cady, we were able to obtain ^{31}phosphorus spectra.[71]

So that was the beginning of MR spectroscopy of cancer. With these two 'firsts' under our belt, we felt able to approach the Cancer Research Campaign. They agreed to finance our work, and have continued to do so to the present day.

Steiner: Thank you Professor Griffiths. David Gadian is next to comment.

Professor David Gadian:[72] Just another anecdote about Oxford around 1973–1974. It was, I believe, Christmas 1973 when I was looking after the magnet. It had to be filled with helium every three or four days in those days and we had awful problems with the field homogeneity. I remember coming in over the Christmas vacation and trying to shim the magnet yet again and having big problems. I was adjusting the superconducting shims, because we weren't making very much progress with the room temperature shims. It was Christmas and I went off somewhere, came back on the following day and saw a touch of ice and whatnot around the magnet. What I had done was to forget to switch off one of the superconducting shim coils and the magnet had quenched; it had run out of helium. I was somewhat embarrassed about all of this, in fact more than embarrassed, I was desolate, I was quite young. Anyway, I was embarrassed to

[70] Griffiths J R, Stevens A N, Iles R A, Gordon R E, Shaw D. (1981) ^{31}P-NMR investigation of solid tumours in the living rat. *Bioscience Reports* **1**: 319–325.

[71] Griffiths J R, Cady E, Edwards R H, McCready V R, Wilkie D R, Wiltshaw E. (1983) ^{31}P-NMR studies of a human tumour *in situ*. *Lancet* **i**: 1435–1436.

[72] Professor David Gadian (b. 1950) has been Head of Radiology and Physics Unit/RCS Unit of Biophysics at the Institute of Child Health, University of London, since 1993. Author of *Nuclear Magnetic Resonance and its Application to Living Systems*, 1982 (1st edn), 1995 (2nd edn). Oxford: Oxford University Press.

phone Rex [Richards] over the Christmas holidays, but I did so, and I remember him coming in, I think late 30 December or 1 January. Whenever it was, he took the magnet to bits, found that in fact the reason why we'd been having problems shimming the magnets was that one of the superconducting shims wasn't working. We got it working, connected it all up, and shortly afterwards as a result of this the spectroscopy was much improved because of the rewiring of the superconducting shim. I think that was the start of a rather golden period in the development of the phosphorus spectroscopy at Oxford.

Richards: I think it was Christmas day actually!

Gadian: It was pretty awful anyway.

Steiner: Any other anecdotes from anybody or any questions on spectroscopy or related subjects?

Mansfield: I wonder whether I could ask a question of one of the speakers? Ossie Reynolds mentioned that they put children in, I don't know whether it was a 4-Tesla or a 2-Tesla magnet, and I am just wondering whether you had any reservations about doing that at the time in terms of the possible unknown hazards of magnetic fields.

Reynolds: No I don't think we did. It was 1.89 Tesla and we obviously looked at everything that was published and available and couldn't convince ourselves that there would be any adverse biological effects. I don't know if Dave Delpy wants to say something about that, because he thought about the thing more than any of us.

Professor David Delpy:[73] We'd gone through every publication on hazards, which I think comprised about three or four publications at that time, and couldn't find anything that indicated that there would be a significant hazard and, of course, we have to compare the risks that we were possibly exposing the child to with the possible outcome if one was not able to diagnose cerebral hypoxic-ischaemic injury. I think on the balance of the possible benefits against what appeared to be a minimal risk the clinicians very bravely tried, as Osmund [Reynolds] mentioned, to persuade an American lawyer to be the first volunteer or to volunteer his child as the first infant.

[73] Professor David Delpy (b. 1948) has been Hamamatsu Professor of Medical Photonics, Medical Physics and Bioengineering at University College London since 1992.

Mansfield: Was the choice of the father of the child an important one?

Reynolds: No it was just by chance, but we had no repercussions from that. He and his family have stayed closely in touch.

Professor Graeme Bydder:[74] The National Radiological Protection Board (NRPB)[75] had issued their guidelines in 1980, which in terms of a contribution to those trying to do clinical NMR was an absolute godsend. Here was a serious organization who'd analysed the problems and had issued 2 Tesla as a guideline. It made it a lot easier.

Steiner: Before we go any further, George you wanted to say something.

Radda: Martin reminded me of an experiment that we did in 1983 when we'd started to put people into this 2-Tesla magnet and we weren't worried about the static field, but we were worried about what would happen if the magnet quenched, because in those days these things weren't quite as stable and occasionally it did happen. What would happen if the magnet quenched while there was a patient in a 2-Tesla system? So we decided that as the magnet would have to go back for some repairs anyway that we were going to do a deliberate quench with a properly controlled physiological experiment and we managed to persuade the Home Office[76] to allow us to put a pig, anaesthetized, which we wired up for electrocardiographs (ECGs) and heart monitoring and blood oxygen and whatever else, into this magnet. Then we measured the field strength change at various parts inside and around the magnet, and the helium content of the room and that was the most spectacular experiment we have ever done – it's one of the most expensive ones too, but, in fact, it showed that there were absolutely no

[74] Professor Graeme Bydder (b. 1944) has been Professor of Diagnostic Radiology at the Royal Postgraduate Medical School, University of London, since 1989 and Fellow of the Royal College of Radiologists since 1986.

[75] National Radiological Protection Board (NRPB). See Anon. (1980) Announcement. *Lancet* **ii**: 103. NRPB. (1981) Exposure to nuclear magnetic resonance clinical imaging. *Radiography* **47**: 258–260. NRPB *Ad Hoc* Advisory Group on NMR Clinical Imaging. (1983) Revised guidance on applicable limits on exposure during nuclear magnetic resonance clinical imaging. *British Journal of Radiology* **56**: 974–977.

[76] The Cruelty to Animals Act, passed in 1876, regulated the conduct and conditions of animal experimentation. Laboratories had to be registered with the Home Office and were subject to random inspection by Government officials, and individual researchers had to be licensed to perform designated work. In 1986 it was replaced by the Animals (Scientific Procedures) Act.

physiological effects of the quench on that pig lying in the magnet and we felt very much more comfortable after that putting people in.[77]

Steiner: Would you explain the quench?

Radda: Oh the quench is when you deliberately warm up the magnet so that it loses all its superconductivity and releases all the megajoules of energy that are trapped in it and the helium and nitrogen will all boil off and the magnetic field will drop from 2 Tesla to zero in a couple of seconds (maybe a bit more).

Dr Jean Guy: Was the pig allowed to recover consciousness?

Radda: No. We were not allowed to do that. We had to kill it.[78]

Professor Brian Worthington:[79] As everyone knows, there is a classical model of the development of any technological innovation including those in radiology. There's a period of technical development, which Raymond Andrew described so very well. There's then a period of preliminary evaluation of the technique and following from this there are often publications in which claims are made which, in retrospect, appear to be somewhat exaggerated. Often there is a period following this of profound disillusionment with the technique and then follows a period of realistic reappraisal and the technique comes into more widespread operation.

I want to just refer to this period of disillusionment which Sir Martin [Wood] alluded to. He said he had a note about the radiologist who had made adverse comments about the development of MRI. Now I was fortunate enough to be the first radiologist in the world to be involved in the development of MRI and when the problems in scaling up the small-bore systems to the whole-body systems had been achieved, we were able to carry out the first evaluation of MRI, happily for me, as a neuroradiologist, in the brain. One saw immediately enormous benefits to accrue in neuroradiology, in the multiplanar capability, the better contrast discrimination, the absence of artefacts. George Radda has mentioned the extreme enthusiasm there was for the technique after the Winston–Salem congress, when

[77] Doyle M, Rzedzian R, Mansfield P, Coupland R E. (1983) Dynamic cardiac imaging in a piglet. *British Journal of Radiology* **56**: 925–930.

[78] op. cit. note 76 above. Recovery experiments required additional authorization and it was the law that unless otherwise authorized, scientists had to kill animals once they had been anaesthetized.

[79] Professor Brian S Worthington FRS (b. 1938) has been Professor of Diagnostic Radiology in the University of Nottingham from 1981 to 1998. He was awarded the Gold Medal from the Society of Magnetic Resonance in Medicine in 1990, the Barclay Medal of the British Institute of Radiology in 1992, and the Trent Medal by the NHS Executive in 1997.

people saw, for example, Sir Peter's images of a rabbit heart beating in real time from echo-planar imaging (EPI). We saw remarkable improvements in quality in the 12 months, particularly from Waldo Hinshaw and the Hammersmith group.

Now, why was it then that at that time a period of disillusionment set in? This came from two quarters. It came from outside, from the radiological community who pointed to CT which had developed rapidly in the period from 1974 to the early 1980s: we'd seen imaging times come down from 300 seconds to subsecond times, we'd seen improvements in spatial resolution to sub-millimetric resolution in the early 1980s and the discrimination of contrast had improved from 6 to 2 Hounsfield units, so there was a dramatic improvement which the radiologists saw. This was unfairly being compared with MRI, an embryonic technique, that wasn't fully developed. But there were problems that the insiders saw but really didn't talk about too much. They were potentially solvable, but if the solutions had not arrived I am sure that we wouldn't be here today. Instead, we would be talking about MRI as a footnote in the history of radiology. And of those problems, first of all, the question of spatial resolution: could we exploit higher fields? A paper had come out from Professor Andrew and Paul Bottomley looking at the radiofrequency (RF) penetration problems, and above 0.3 Tesla there were going to be problems, although these were not insuperable.[80]

There were problems with contrast. As a neuroradiologist, I was appalled to see that the commonest primary benign tumour in the intercranial compartment, the meningioma, was invisible on MRI. A paper had just come out from Bradley in the States.[81] Graeme Bydder and I had struggled, manfully, to try and separate tumour from oedema, which was easily done with contrast in CT but we were having very great difficulty in MRI. Furthermore, with the techniques we had available, the speed was not in any way comparable to CT, and then there were constraints from the safety standpoint. The NRPB had issued their report in November 1980, and in it they had quite properly suggested that volunteers who had a history of epilepsy or who had had a cardiac arrhythmia should not be imaged, and in the section on imaging patients it says that these constraints should also apply to patients unless the clinician in charge agrees that they should be overridden. Now, as a neuroradiologist, looking at that, if one could not image patients who had a history of epilepsy, then really there was very little future for this technique. So, by mid-1982 there were some very difficult problems to be addressed. Fortunately, one had the confidence to believe that these were all

[80] See for example Bottomley P A, Andrew E R. (1978) RF magnetic field penetration, phase shift and power dissipation in biological tissue: implications for NMR imaging. *Physics in Medicine and Biology* **23**: 630–643.

[81] Bradley W G, Shelden M D. (1983) Nuclear magnetic resonance imaging. Review of early clinical experience. *American Journal of Surgery* **146**: 85–87.

solvable and would be solved and, indeed, happily they have been solved which is why we are here today.

Steiner: We might come back to you Brian when we talk about imaging. Ian, your turn.

Young: Two comments – one about Brian and the negativism. There's a little book, it's quite interesting, called *Insight and Industry* which was published quite recently, about three years ago, by a Dutchman, Stuart Blume,[82] in which he looks at the introduction of new technology into medicine and he takes as his examples ultrasound, thermography, CT X-ray and MR and, of course, these are the four examples where Britain managed to snatch defeat from the jaws of victory successively. He makes the point, in fact, that it was the British authors who were really the most negative of the lot – we were the most cautious and we were the most reluctant and we were, in many ways, perhaps the most withdrawn – and he contrasts our caution with the American euphoria. It's quite interesting actually for his comments on Brian's work.

The other thing that I was going to say is that I suspect I am the only person here who actually sat on the original NRPB Committee on Safety and in retrospect it is clear that we knew absolutely nothing. The one thing that had been published which was really relevant was Tom Budinger's paper and the one thing one knew about that paper, was that there was at least one massive numerical mistake and actually a number of other smaller ones.[83] The only person we had on the Committee who had any expertise was Ted Grant, from King's College London, who was the microwave and high radiofrequency (RF) expert and there was some confidence about that. We'd some vague ideas about what the numbers were, and Rick Saunders, who really should have been here as he was the man who pioneered this from the NRPB, pulled the whole thing together, though it was more or less completely drawn out of the skies. We thought there was no reason not to go up and therefore we went up. We thought that we were probably going to be all right for 2 Tesla and perhaps a bit more, so we went up to two-and-a-half. It was very interesting, of course, later on when the Food and Drug Administration (FDA)[84] came to publish their guidelines, I remember the actual sentence in which they discussed their reasons for choosing a dB/dt value which was half the one that we

[82] See Blume S S. (1992) op. cit. note 26 above..

[83] Budinger T F. (1979) Thresholds for physiological effects due to RF and magnetic fields used in NMR imaging. *Institute of Electrical and Electronics Engineers Transactions in Nuclear Science* **NS-26**: 2821–2825.

[84] The Food and Drug Administration (FDA) of the USA, founded in 1938, is the premier drug regulatory organization in the world, inspecting and licensing the manufacture of foods, cosmetics, pesticides as well as human and veterinary medicines.

had chosen. We had got no real basis for this, but as they put it, 'We have received two advisories as to what the level of dB/dt ought to be. One from the NRPB in Britain and the other from Professor Thomas Budinger, Donner Professor of Electrical Engineering, University of Berkeley. He was the one with a factor of ten error. And we have decided to choose Tom's.' That's why their level was below ours for many years.

But to illustrate our ignorance this is my story of how the '5 gauss line' came about – because there are probably at least 97 other ones. I told this story at a safety conference, with the FDA there, a couple of weeks ago. It's one of Gordon Higson's initiatives in a sense. John Williams[85] had a research student who was going to work for him for about six weeks one summer. I think it must have been in 1978 and John couldn't think of anything for him to do and finally he said 'Here is a list of all the pacemakers we know about and here's a magnet, find out which ones fail at what field'. John had told me about three weeks before that he thought that most of them had worked quite well down to about 5 gauss with one he thought would fail below 5 gauss. I was phoned up by the FDA one Friday afternoon my time, Friday morning in America, by a young woman who went on to become a clinician. She was then working for the FDA as a very, very, very junior physicist and this was the status they were giving the issue. This was the bottom of the pan – the FDA were really monumentally uninterested in the topic – but she enquired about stray fields and what they do. I said they are present around magnets and cause plenty of artefacts and problems unless you are careful. For example, they affect CRTs (cathode-ray tubes); and she said, 'Are they unsafe?' I said, 'I don't know'. We use them often enough. The only unsafe thing I knew about is this experiment John Williams had done at the Department of Health and Social Security (DHSS). He'd put magnets besides pacemakers and found 5 gauss mostly all right. And that's where the 5 gauss line came from. Quite as anecdotal and stupid as that and it's still there and nobody can get rid of it.

Higson: I remember some of these things: they start to trigger the memories. The NRPB of course was asked to look into the safety of MRI as soon as the Department of Health had decided to support the installation of the MRI machine at Hammersmith. Once we had decided we were going to be associated with people going into a device of this kind, we had to cover our backsides. We asked the NRPB to study the problem and assure us that it was safe and they did. As Ian pointed out, there was a lot of ignorance about at that time. There was an awful lot known about RF and the Department was very concerned because pacemakers were a very sensitive subject. Pacemakers were not then as sophisticated as they are now and we were besieged with reports of people on underground trains suddenly

[85] See biographical note 56 above.

collapsing because the train started or stopped and their pacemakers were affected. We were doing a lot of work into trying to improve the pacemakers and put up protective notices which went up in public libraries and other places, because people had then started to put in security systems to prevent books and clothes being stolen from libraries and stores; and security was also beginning to become a problem at airports and people were collapsing all over the place from problems with their pacemakers. We could see all these possible risks and there was a vast literature on RF safety levels, but unfortunately the accepted safety level in the Western world was three orders of magnitude greater than that in the Eastern world, which we didn't believe, but we couldn't disprove it. But there was no knowledge at all about magnetic field effects on people and especially magnetic field gradients and sudden changes in magnetic field strength, other than what happened to people with pacemakers travelling on the underground. So it really was a very sensitive area and we were very glad that the NRPB gave a report that enabled us to carry on at Hammersmith.

Steiner: I tell you the reason for this. I was a member of the NRPB at that time, when they were primarily interested in X-ray radiation problems. So they had to be persuaded to look at NMR in its application for diagnostic purposes in humans, which was when Dr Saunders came in with his studies and subsequent reports.[86] Now the NRPB is much more concerned about the effects of magnetic fields on humans. In the early days at Hammersmith it was quite a worry to watch Ian Young and Graeme Bydder often acting as volunteers with their heads in the magnet for hours on end.

Delpy: The discussion has now brought back a memory of our discussions, our agonizing over the safety aspects and, in fact, at the time the biggest worry was not over the static magnetic field, but rather the effects of the time varying magnet field on which there was little information. It has been pointed out there was a lot of literature on RF safety because, of course, RF is used in hyperthermia and has been for many years. The only reason that we were able to justify studying the babies was because we were interested only in spectroscopy, we were not imaging. We needed a way of localizing, of course, and at that time Oxford Research Systems had been pioneering the use of static magnetic field gradients in a method called topical magnetic resonance as another localized spectroscopy technique. For the first, probably the first 100 babies we studied, we used this localization technique which now of course has entered the footnotes of history. Nobody has ever used it since the time-varying gradient techniques have come along, but it was

[86] Saunders R D, Smith H. (1984) Safety aspects of NMR clinical imaging. *British Medical Bulletin* **40**: 148–154. op. cit. note 75 above.

the development of topical magnetic resonance which is now obsolete, that allowed us to safely study the baby's brains and get our first spectra.

Steiner: Any other comments about spectroscopy.

Booth: Could I just ask Sir Rex Richards: in a broad field of science where did spectroscopists stand in relation to molecular structure people, particularly X-ray crystallographers? Was there collaboration between you as people looking at molecules or were there two totally different areas of science?

Richards: There were various branches of spectroscopy. X-ray crystallography was used for finding molecular structures in crystals before the war and became better and better as computing powers improved. Then there were ultraviolet and infrared spectroscopy. Infrared spectroscopy was very much developed during the war. I did my DPhil with Tommy Thompson[87] in the days when we actually made our own infrared spectrometers. Infrared spectroscopy was a very powerful method of studying molecular structure, much used by organic chemists, in the 1950s and up to the middle 1960s at any rate, and by the middle 1960s they were beginning to abandon the infrared spectrometers in favour of NMR. But spectroscopy was very widely used and people weren't very specialized. I mean the organic chemistry department in Oxford has UV and infrared spectrometers, lots of instruments scattered about that people used and they were in very close touch with the crystallographers. Dorothy Hodgkin was working on insulin, vitamin B_{12} and penicillin in the periods during and after the war and she was always in the Dyson–Perrins Lab, with Sir Robert Robertson arguing about whether the penicillin was going to be the beta lactam structure or the oxazolone structure. So everybody was working together and these techniques were seen simply as valuable aids.

Radda: Can I just add to that, that in terms of NMR spectroscopy of course, its contribution to looking at large bimolecular structures and protein structures, Rex was the Chairman in setting up the Oxford Enzyme Group in the early 1970s, where the aim was precisely to see how NMR structures can be determined with NMR and compared with X-ray crystallography and the multidisciplinary group, the Oxford Enzyme Group, set up on that basis.

[87] Sir Harold Warris (Tommy) Thompson FRS (1908–1983). See Richards R. (1985) Harold Warris Thompson 1908–1983. *Biographical Memoirs of Fellows of the Royal Society* **31**: 573–610.

Richards: Yes, we had 18 members from nine different departments in Oxford and we met on alternate Mondays as a group.

Radda: A lot of the structural NMR was developed over a long period.

Richards: But these new techniques are not always embraced as enthusiastically as you might expect. I can remember stumping around the country in the 1950s, late 1950s even, giving talks about NMR, with sceptical people in the audience saying, 'Oh he's just using a steam hammer to crack a nut – this will never be of any real use.' There was a great deal of scepticism.

Booth: I think really the point I'm trying to get at is whether there was a conflict in a scientific sense between crystallographers and spectroscopists, because so often one finds new technology coming along and people in established technology do resent it. People like Perutz[88] accepted it straight away.

Richards: No. I don't remember any problems of that kind. I had a big disagreement with Dorothy [Hodgkin] over the structure of penicillin, because I was working on the infrared spectra and I was much too young, but I ought to have known better than to quarrel with a crystallographer.

Radda: I think it was always seen as complementary to crystallography, because it works in solution.

Richards: I don't remember problems of that kind, but of course people being who they are, I am sure that there were personal difficulties, but there were no particular problems that I recollect. People had their own views, they thought one method was better than another, but that's human nature isn't it?

Dr John Galloway:[89] I was at the MRC – that's why I am here today. The comment I was going to make was from the days when I worked in David Phillips' laboratory in Oxford, at the time of the Enzyme Group. What I could say

[88] Professor Max F Perutz FRS (b. 1914) was Director of the Medical Research Council Unit for Molecular Biology at Cambridge from 1947 to 1962 and Director of the MRC Laboratory for Molecular Biology since 1962. His work focused on determining the structure of haemoglobin and with Sir John Kendrew he was awarded the Nobel Prize for Chemistry in 1962.

[89] Dr John Galloway (b. 1942) is R&D and Education Manager at the Eastman Dental Hospital which is part of the UCL Hospital NHS Trust. As a new member of MRC Headquarters staff, he had responsibility for MRC funding for NMR as it started in the mid 1970s.

I think from the protein crystallographer's side was they had an impression of themselves as being rather plodding and unintellectual compared with spectroscopists and I think that was really quite a common view in that group which David Phillips[90] formed, and they used to make that sort of rather slightly disparaging comment about themselves, as opposed to the spectroscopists.

Richards: Well, of course it is a technique that requires a very great deal of time – it did in those days – it was extremely slow wasn't it?

Galloway: Yes, it was. At that time Dorothy Hodgkin was finishing insulin. I mean, she had been doing it for 35 years and we should remember that. David Phillips himself who had done lysosome – it had taken five years to get that structure out and they did think of themselves as being terribly laborious and plodding and they felt it, compared with spectroscopy, which seemed to be instant.

Richards: Well, there again, that's another case where the engineering development of computing completely transformed it. I think it is rather important to bear in mind that some of the really big leaps forward that occur are often due to engineering.

Young: One of my surprises, Rex, and I was going to ask you about this, was that Fourier transform infrared was around for about 11, 12 years before the first FT NMR seriously got going and they must have overcome the problem. It has always surprised me as to why there was this lag. Fellgett originally described this in his thesis in 1951.[91] People just never made the link.

Andrew: But the technology must have been there at some point.

Young: But there again you see, they were looking at high-resolution spectroscopy. It was used for high-resolution infrared spectroscopy, and it was quite normal to work for a year on one system, so the problem of collecting the data and then taking it, and computing it in a different place, was not a problem at all, whereas in NMR you were trying to measure half a dozen compounds in a day or in an hour

[90] Professor David Phillips (Lord Phillips of Ellesmere from 1994) FRS (b. 1924) was Professor of Molecular Biophysics at the University of Oxford, now Emeritus, and Fellow of Corpus Christi College, Oxford, from 1966 to 1990.

[91] Fellgett P B. (1951) *The Theory of Infrared Sensitivities and its Application to Investigations of Stellar Radiation in the Near Infrared.* PhD Thesis. Cambridge: Cambridge University.

or whatever, and it's quite a different thing. But the idea of doing FT spectroscopy in the infrared was quite well accepted.

Andrew: I think I realized how widely accepted high-resolution NMR was and how widely pervasive it was, when I found myself seven or eight years ago talking to a chap in a queue – we were queuing up for lunch in the Soviet Union, which it then was, and after we got talking I said, 'What do you do and where do you come from?' and he said that he had a Varian spectrometer and he was working at Ulan-Bator in Outer Mongolia. I thought it can't be long before we find one on the moon or at the North Pole.

Dr Paul Tofts:[92] I was working in Os Reynolds' group at University College London in the early 1980s. There's another first that took place in Ossie's group which is that we were able to measure absolute concentrations of metabolites *in vivo* using spectroscopy. Really, as a physicist, I thought we ought to be able to use this as a scientific instrument, make objective accurate measurements of physical quantities in people's brains and so we were able to do this. We measured the ratio of the phosphorus to the water signal in the brain and muscle of live rats. We then filled a test tube full of these tissues, and measured the absolute level of the signal, to find the water concentration. From this we estimated the absolute phosphorus concentrations, which came out at about 2 or 3 millimolar for ATP in both brain and muscle.[93] Then we did a literature search for chemical *in vitro* measurements of ATP concentration, and ours were spot on, within 5 per cent.

Griffiths: In analogy to the discussion we just had about the relationship of MR and crystallography, another field that has been impacted by biological MR spectroscopy is that of metabolism, a field that has become very, very unfashionable in the last 20 years. Probably because doing it by MR spectroscopy involves large, sexy bits of apparatus and lots of money, this is the one area where metabolic studies have managed to remain fairly near the forefront. Certainly, all the other areas of biology have been to a large extent blotted out by the huge developments in molecular biology-based techniques but physiological measurement by MRS seems to have retained its fascination.

Reynolds: One thing. I have just remembered, which David Gadian seems to be too modest to say anything about, that he, together with Mark Gardiner and his

[92] Dr Paul Tofts (b. 1949) has been Reader in Medical Physics at the Institute of Neurology in London since 1994 and Fellow of the Institute of Physical Scientists in Medicine.

[93] Wray S, Tofts P S. (1986) Direct *in-vivo* measurement of absolute metabolite concentrations using ^{31}P nuclear magnetic resonance. *Biochimica et Biophysica Acta* **886**: 399–405.

group, published the first abnormal NMR spectra from an inborn error of brain metabolism in histidinaemic mice. In that paper it was speculated that since those peaks were detectable, those for phenylalanine in the important inherited disease phenylketonuria should be detectable too, and so it subsequently proved.[94]

Gadian: Just another comment. I think we should refer to Doug Wilkie's and Joan Dawson's contributions on muscle fatigue which they did in collaboration with us in Oxford in the mid-1970s.[95] Doug unfortunately isn't here today, but it was a great privilege for us to gain his expertise as a muscle physiologist and his knowledge in the area. I think he was one of the first people from outside NMR to realize its potential and to apply it to a real problem, which was one of muscle fatigue.

Steiner: Any more comments from anybody? If not we will have a tea break and start the next session on MRI with Professor Ian Young and Professor Graeme Bydder.

Young: I am not sure why I am the first one to talk, but I was given a slightly different brief, and therefore I will begin the imaging story and its implications, which were not quite so predictable. I worked at the EMI Central Research Laboratories (CRL)[96] as a recording physicist. I knew something about recording data on disks and Hugh Clow made thin-film tapes and knew something about them. When the initial interest in NMR developed, EMI, which was not going to be outdone by anybody, decided they had to investigate it. Working on the principle that since we knew something about magnetics, we must know something about NMR, they said to Hugh [Clow], 'You will work this out theoretically', and to me, 'You will build the machines.' And this is how we started. We did the logical thing, which was to go and acquire all the expertise we could and we sought Peter's [Mansfield] help and we sought Raymond Andrew's help and we sought Bill Moore's help[97] and we did some work of our own and, in

[94] Gadian D G, Proctor E, Williams S R, Cady E B, Gardiner R M. (1986) Neurometabolic effects of an inborn error of amino acid metabolism demonstrated *in vivo* by ^{1}H NMR. *Magnetic Resonance in Medicine* **3**: 150–156

[95] op. cit. note 62 above.

[96] op. cit. note 19 above.

[97] Bill Moore who led one of the three teams at the University of Nottingham Department of Physics, built a whole body imager in the early 1980s. See Moore W S, Holland G N. (1980) Experimental considerations in implementing a whole body multiple sensitive point nuclear magnetic resonance imaging system. *Philosophical Transactions of the Royal Society* **B289**: 511–518. Hawkes R C, Holland G N, Moore W S, Worthington B S. (1980) Nuclear magnetic resonance (NMR) tomography of the brain: a preliminary clinical assessment with demonstration of pathology. *Journal of Computer Assisted Tomography* **4**: 577–586.

retrospect, when one thinks about it, one cannot imagine why we did some of the things we did, which were quite incredible.

We started with a 0.1 Tesla Walker magnet which we got actually at the very beginning of 1977; it came about three days into the New Year of 1977, so we were earlier than some, and we started off by putting the gradient coils outside the magnets and driving them from enormous thyristor units, known as resonant transfer thyristor drives, so we had about three or four hundred amp pulses hurtling around these vast gradient coils outside the magnet. And, not unpredictably, this didn't work and we ended up by rebuilding the magnet and putting the gradient coils inside while we used the original coils as shim coils. We went through a number of traumas and we finally got our first head image. There were two teams involved. There was myself and Colin Harrison and Mike Burl. Colin went onto IBM and Mike, after a spell with the BBC, is back with Graeme [Bydder] and me at Hammersmith. Hugh Clow and Peter Walters, who was his number two, together with W S Percival, formed the other team.

In late 1977 we got a bit bored one day so we thought we would put ourselves in the machine, see what happened and get some head images. And that was fine, except that the head image looked something like a dislocated lop-eared rabbit after somebody had put a cleaver through its brain. But the thing that really concerned Peter Walters was the violation of the machine and he tore around the place, denouncing us for having raped it! This caused a good deal of trauma. About that time, or shortly after, prior to us actually getting a respectable image at all, Gordon Higson, and I think it was this way round, suggested that the DHSS might look at proposals for the development of a serious NMR machine; something that could be evaluated clinically.

There were two of us in the race. There was GEC, for whom at that time Waldo Hinshaw worked, and this is not a very widely known thing. Waldo went from Nottingham to GEC Hirst Research Centre and then on to Massachusetts General Hospital, before ending up at Technicare. Waldo and his team were competing with Colin and myself and ours, and in the background all the time, John Williams (of the DHSS) was saying that there's this tremendous man in Nottingham and he's got this absolutely fabulous fast-sequence. Did we know, it takes an image in 40 milliseconds and what are you going to do about it? We got out our calculators, I think we even had a computer, it was a very old one, and we did the sums again and again and we concluded we just couldn't get enough signal-to-noise ratio at 0.1 Tesla – we just couldn't do it. So the proposal we made to DHSS, and how it was accepted I cannot imagine, was for a field cycling magnet working at 0.3 Tesla that was normally going to sit at 0.1 Tesla, being quiescent. Then it was going to go up to 0.3 Tesla to take an image and come back down again. And, in retrospect, this was quite the most horrendous concept, and only total ignorance could have allowed it to happen. That was fine, until 1 July 1978 –

when we got the contract, and we actually had the awful prospect of having to make this damn thing work. How were we going to do it? It so happened that about a week later Colin and I were still shocked and we were sitting in my office when he said that there was a superconductivity conference on (at Wembley, I think). He went along to this and found that there were two companies who were prepared to quote us for a magnet – one was called Oxford Instruments and the other was called Thor Cryogenics. We got two quotes, one from Oxford and one from Thor. I'll tell Martin [Wood] this now, as this is where all the real truths come out, that I thought the Thor quote was actually a good deal better than the Oxford one. The only problem about the Thor one was that they insisted on using a cryo-cooler and a refrigerator system, and for that they wanted an extra fifty-odd thousand pounds and there was no way that Bill Ingham (Director of CRL of EMI) was going to sanction that. I mean he was dubious enough about this whole enterprise anyway. The Beatles were in decline, EMI no longer had quite the same millions flowing in from them, and the CT scanner was suffering a bit, so that refrigerators were out. We could live with liquid helium, and we therefore went to Oxford and we signed a contract with about 17 lines of confidentiality agreements built in. The contract, and this I must remember, was actually a two-stage contract.

The first stage was a design and development contract. The design and development of a whole-body magnet, for the princely sum of £10 000. I am really asking Martin how much it is worth for me not to remind Thorn EMI[98] of this, because in fact we owned the whole-body design, or so we could maintain. And the rest of the contract was for £60 600 and this was the whole value of the magnet. The construction of that magnet was like everything else at that stage, beginning with endless confidentiality agreements for everybody because that was the way Ingham worked, he had been an ex-military electronics engineer. I will never forget the moment when Raymond Andrew phoned up about three weeks later, after all these things had been signed, and said that somebody's just come along and tried to sell me your magnet. I said, 'How do you know it's my magnet?' He said, 'Well you've such a funny bore diameter – it has to be your magnet – there can't be two people who have asked for the same thing.' He was right and there was a considerable hoo haa about that. But the building of that magnet was quite dramatic, as it was driven madly around the country. I don't think Rex and Martin really knew what was going on, and if they had, they'd probably have stopped it on the spot, because Oxford had never built anything even vaguely as big and they didn't know where to buy parts. However, the Director of Purchasing of EMI,[99] who went on to be your ex-boss Gordon [Higson], and a great source of trial both to you and me, was ex-Davey United. He

[98] Thorn EMI was formed by the merge of EMI with Thorn Electrical Industries.

[99] Tom Critchley (b. 1928), who worked at EMI between 1970 and 1980, was Under Secretary at the Department of Health and Social Security, subsequently the Department of Health, and NHS Management Board Member from 1986 to 1990.

knew about big power engineering so he organized the manufacture of this magnet which trundled across England and up to Scotland and back down again, where bits were added and welds made. It was welded out of round, so it had to be taken somewhere else and made round again. We had great fun with that thing and it finally turned up. In the end Oxford built two magnets virtually in parallel. The second one was for Pfizer which went to Larry Crookes, and the one for us. We kept saying, 'Hey, we were first and we are not worried about all the things you are worried about. We know how to deal with eddy currents and things of this nature.' And we did.

But, finally, the magnet turned up and was put in a room with all the windows painted out and we made the machine work. It was a 0.3-Tesla magnet, but we ran it at 0.26 and during this time we finally made the 0.1 Tesla function. The bit that was interesting was that the only clinician we could find to supervise us was a GP from Havant. We ended up by putting many people through. We had a demonstration day when we scanned ten volunteers in eight hours. We went to Hammersmith, and we went to all the big hospitals seeking help, but we couldn't find anyone. It was also during this time that we were finding out where this cryomagnet was going to go. And my first preference, and I hope Robert may forgive me for this, was that it should go to Atkinson Morley's, where Godfrey [Hounsfield] had put his first machine. I went to Jamie Ambrose[100] and asked him if he would like this first machine; and he said no. I said, 'Why not? It's marvellous, brand new technology. It's going to revolutionize everything' – I must have been naive and young and all the rest of it. And he said, 'There are two reasons. The first reason is that if it doesn't work I'll waste two years of my life finding out it is useless, and the second reason is that if it does work, I'll waste two years of my life showing wretched Americans around the machine, while they get in my way.'

The second choice was Hammersmith which became the second choice entirely due to the fact that my brother had done his PhD there. I have, with time, been fairly successful in planting machines wherever my brother has worked just to annoy him – he is actually a clinician – a proper doctor as he reminds me and I am an improper one! In the States I got one into the Mayo Clinic and one into the National Institutes of Health (NIH).[101] However I never got one into Aberdeen which is my main failing, because I am as much an Aberdonian as John Mallard is, and I never got one into the Hospital of the University of Pennsylvania (which is impossible for anybody except General Electric). We finally made the machine

[100] Dr James Ambrose was the neuroradiologist at the Atkinson Morley's, the Neurological hospital in South London, now part of the St George's Hospital group.

[101] National Institutes of Health (NIH) is one of the world's foremost biomedical Research Centers, and the Federal focal point for biomedical research in the US. The NIH is one of eight health agencies of the Public Health Service which is part of the US Department of Health and Human Services. It comprises 24 separate Institutes, Centres and Divisions

work and we decided we were going to transfer it to Hammersmith. I can remember how bizarre that was. We had to get it accepted by Gordon Higson, as that was the criteria for transfer. Robert was prepared to take it. We'd got a nice new building waiting for it, but the rule was that the DHSS had to agree to its transfer and the person delegated to do this was John Williams.[102] John informed us that he had still to do his Christmas shopping, and those of you who know John Williams will recognize the syndrome, but that he would accept it just before Christmas. He came down and he said he wasn't going to accept it, because we hadn't achieved brain contrast that was anything like as good as that from the 0.1-Tesla machine. The machine worked at 0.26-Tesla and he could see the images looked quite nice, but they weren't right, they didn't have any contrast. So he wasn't going to accept it. We knew the helium in the magnet was running out rapidly, and I decided I was going to warm it up over Christmas regardless. However we just couldn't get the contrast, we just couldn't get it and finally, in desperation, I said to Alistair Hall who, by then, had replaced Colin [Harrison] – that we were going to drop the field; we were going back to 0.1-Tesla, which we knew and loved. Alistair dropped the field and in so doing he partially quenched the magnet and the next day I spent pretty well all day in that machine while we desperately juggled the sequences to try and get the timing right. And we couldn't even use our own computer but had to rely on that operating the 0.1-Tesla system. I lay in that machine, knowing that it had no liquid in it at all. It was running on gas and we made it by five minutes, before the field finally collapsed on us. We got an image that John agreed had good contrast. So we were allowed to move the machine. We got it to Hammersmith and switched it on and we got nothing except noise across the images. The machine had gradient amplifiers, which were valve amplifiers, with 6 kilovolt rails. They drove about an amp so their operation was all volts and no current. The ampere-turns were all turns and no amps. CRL had clearly had an atmosphere that was dry enough; we just got away with the amplifiers. At Hammersmith the whole thing collapsed in a heap of corona, arcing, sparking, and all the rest, and we took it apart there and rebuilt it. The machine sat with its trunk up – it had an RF shield that looked like that. It sat up with its trunk up for about two months, while everybody who looked at it called it a white elephant and Robert [Steiner] worked out what he was going to do with the room when he took the machine out. It was about that time of course that EMI got out of the imaging business and I think I will probably defer to Gordon [Higson] to tell the story of how I nearly worked for GE and what the right field would then have been instead of 1.5 Tesla, because GE very nearly bought the project. The other manufacturers nearby did as well. Waldo [Technicare] wanted to buy it for the beer. Bill Edelstein [GE] wanted to buy it because it was going to be fun and he was going to be able to do stupid things earlier than he was able to in the end.

[102] op. cit. note 56 above.

The sale finally got stopped by Professor Longmore, I think. Either he or Bob Clayton, or both, were the people who stopped that little transaction. Again, Gordon [Higson] can probably verify this. Donald [Longmore] admits it.

Graeme [Bydder] started at the beginning of 1981. I think by the time that we got the machine together again we planned to set it up in 500 gauss steps, until we got back to 0.26 Tesla but at 0.15 he said, 'I've had enough, I am going to start putting patients in' and that was the moment which the machine finally became clinical. And it was the only NMR machine, probably, that's ever dropped its field. Mike [Burl] and I on a couple of occasions thereafter tried to put its field up again, but he would have nothing of it.

We went to Winston–Salem. In many ways that was the seminal meeting, I think. George [Radda] has alluded to its importance in things like the founding of SMRM.[103] In passing, as a sort of commentary, there are more charter members and past presidents of the original SMRM in this room, than I suspect you could put together anywhere else. You would have to work fairly hard to get anywhere near as many as we have here.

I think my part of the story really ends with the beginning of the clinical evaluation. This became a formalized thing with the Department of Health and the MRC involved. In many ways, since that time, it has been downhill all the way. But, as I say, in retrospect, why we did some of the things we did I just cannot imagine. It's quite extraordinary that it was ever made to work at all, thinking about it in cold blood thereafter.

Steiner: You have heard it said that there were sceptics and I certainly was a sceptic at that stage as you can imagine.

Young: As were many people. I remember Bill Moore practically going incandescent at the thought that we had bought a cryomagnet – he was furious. We had let the whole side down. John Mallard and Bill, in particular, the latter using steady-state free precession (SSFP), John using the spin-warp, had really designed machines that would work with poor fields and this was one of the targets – to make a dirt cheap machine to get underneath CT prices. At that time, Britain wasn't buying any CT scanners and the argument was, 'Let's make a cheap machine because this can be a cheap machine.' We really thought that we could make a resistive machine to sell for a quarter of a million pounds in 1980 and this is why we ran all the patients through, did all the volunteers in a day and all that sort of stuff. We were incredibly lucky in that the original sequence we used was driven equilibrium Fourier transform (DEFT) which was a steady-state sequence

[103] This was the 1981 Winston–Salem meeting discussed by George Radda earlier.

like SSFP, which Brian had been using. Retrospectively, both of these had virtually no contrast and if we had actually made DEFT work and Bill had gone on making SSFP work, it probably would have done damage to the clinical perception of imaging which could have taken years for it to have recovered from. We were amazingly lucky we couldn't make DEFT work. We just didn't have a good enough machine.

Steiner: Yes, before we look at other systems, can we just ask Graeme Bydder to carry on and explain how the clinical imaging of NMR developed at Hammersmith.

Bydder: Thank you very much, Professor Steiner. I joined the EMI group at Hammersmith Hospital on 1 January 1981 and thus was a relatively latecomer to MRI. At that time Ian Young and his team had just installed their new system at Hammersmith Hospital. Although it was the first cryomagnet-based system, there were a number of problems. EMI had sold their interests in CT and were looking for a buyer for their MR system. So people would arrive at work in the morning, and wonder whether they had a job. That was unusual in 1981, although more common at the present time. The Hammersmith X-ray Department had installed a CT machine from a rival company, Siemens. This system was much faster than the MR system. It could reconstruct an image in five seconds compared with the seven minutes for the MR system and it provided images of much higher spatial resolution. The patient handling of the MR system was acutely uncomfortable. The water-cooled valve amplifiers were highly unreliable and the sole copy of the operating manual went missing and was never seen again. We began patient studies on 25 March 1981, and I missed the diagnosis in each of the first three cases. This was unlike the head CT where James Ambrose had diagnosed a frontal tumour in his first case in 1971 and he and Sir Godfrey had danced their famous jig, following this event.[104] It was also unlike the body CT where Louis Kreel had diagnosed carcinoma of the pancreas on his first case in 1975.[105] Soon afterwards, the leader of the clinical group, Professor Frank Doyle, had a catastrophic stroke and soon following that, John Gore, the medical school physicist, left the group. We also knew at that time that Brian Worthington had published the first series of brain cases in September 1980 and had received over a thousand reprint requests for his article.[106] Frank Smith in Aberdeen was also energetically studying patients and had published results in both the *British Medical Journal* on oesophageal

[104] Hounsfield and Ambrose, jumping up and down in excitement, is reported in Süsskind C. (1981) The invention of computed tomography. *History of Technology* **6**: 39–80, quote on page 61.

[105] Kreel L. (1975) Computed tomography in the evaluation of malignant disease. *Transactions of the Medical Society of London* **92–93**: 139–144.

[106] See Hawkes R C, Holland G N, Moore W S, Worthington B S. (1980) op. cit. note 97 above.

carcinoma and the *Lancet* on the liver.[107] We also knew that the San Francisco group who received the second cryomagnet from Oxford Instruments was bound to make a success of their clinical work. At that time also there was greater interest in spectroscopy than in imaging and visitors would generally travel down the A40 to visit George Radda's unit at Oxford, without finding it necessary to view our imaging on the way. Soon afterwards, the magnet quenched and the system was down for five weeks.

Although there were few clinical results, and the EMI management would not allow us to publish them anyway, there were some rays of hope. Gordon Higson and John Williams of the DHSS seemed able to perceive some encouraging signs, even if others could not. The physicists and engineers of the EMI group, under the leadership of Ian Young, had stuck to their task remarkably well and Jacqueline Clarke had proved to be an able and diligent researcher. Professor Steiner was also an astute and very able head of the department and in addition the patients seemed to be prepared to put up with any amount of discomfort and inconvenience in the interests of research. So while the machine was down we became aware that there was, what the Americans termed, a back-to-back showdown planned between the US and the UK groups and that this was scheduled at Winston–Salem, North Carolina, on 1–3 October 1981. The previous meeting, as Sir Martin has eluded to at Nashville in 1980 had not been a success, at least in part because of the lack of clinical results. It was also becoming clear that while the T_1-weighted inversion recovery sequence was slow there was often an amazing degree of contrast between normal and abnormal tissues. Sometimes the contrast difference was so great that it was difficult to display the images. When the showdown came at Winston–Salem, it soon became obvious that other groups in the US and the UK had had their difficulties too. In fact, Bill Oldendorf[108] in his commentary on the meeting suggested that the poor showing of the US groups relative to those in the UK was due to the excessive numbers of physicists in the US working in defence, to the detriment of medical research.

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[107] Smith F W, Hutchison J M, Mallard J R, Johnson G, Redpath T W, Selbie R D, Reid A, Smith C C. (1981) Oesophageal carcinoma demonstrated by whole body nuclear magnetic resonance imaging. *British Medical Journal* **282**: 510–512 (see also note 134 below). Smith F W, Mallard J R, Reid A, Hutchison J M. (1981) Nuclear magnetic resonance tomographic imaging in liver disease. *Lancet* **i**: 963–966.

[108] W H Oldendorf, University of California neurologist, had done early experiments on X-ray tomography. Professor John Mallard wrote: 'Bill Oldendorf is a man whose important work tends to become overlooked.' Letter to Dr Daphne Christie, 28 May 1998. See for example Oldendorf W H. (1974) Spin-migration: an early attempt at radiographic transmission section scanning. *Bulletin of the Los Angeles Neurological Societies* **39**: 138–143. *idem* The quest for an image of brain: a brief historical and technical review of brain imaging techniques. *Neurology* **28**: 517–533. *idem* NMR imaging: its potential clinical impact. *Hospital Practice* **17**: 114–128.

By this time Picker International,[109] a subsidiary of GEC, had bought the system from EMI and we had sent off six papers. At the Winston–Salem meeting it also became clear that there was a considerable prize for whoever first performed the definitive MR study on the brain. The Massachusetts General Hospital group had the inside track, with an operating MR system, great strengths in neurology and neurosurgery, with over 80 beds in these fields, as well as the world's leading neuroradiologist, Juan Taveras. In contrast, we had two neurology beds, no neurosurgery at all and no neuroradiologist. Nevertheless, we thought the target worth pursuing and the clinicians actively sought patients, while we made arrangements to study them at any hour of the day or night. By the following January, we had over a hundred patients with conditions covering the main headings in neurology. But we then had a windfall. David Bailes had resurrected the spin-echo sequence which had previously failed to show disease in its short echo time form and increased the echo time to 40, 80, and then 120 milliseconds.[110] This caused a wide range of lesions in the brain to shine out with remarkable contrast. We had been fortunate enough to stumble on the most valuable screening sequence in NMR imaging in the brain, the T_2-weighted spin echo. Over a two-week period, we recruited a further 30 patients and sent the paper off to Juan Taveras, also neuroradiological editor of the *American Journal of Radiology* and editor of the *American Journal of Neuroradiology*. We thought that he would have every reason to be critical of our work, given his own hospital's efforts, but in fact he was strongly supportive and gave the paper high priority. It was published in August 1982 and described 140 cases, the largest published clinical series up until that time had been ten cases.[111] The first US clinical paper on NMR of the brain appeared the following month and described six cases. I could go on like this for the rest of the afternoon, but I think that I should stop at this stage. A more complete account of what I have said is included in the *Encyclopedia of NMR*[112] and there is also a photograph, including at least six people in this room from the Winston–Salem meeting.

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[109] Picker International was formed by GEC (*not* GE), which merged its existing medical interests with those of the American Company Picker, which it took over in 1982. Picker acquired the Hammersmith superconducting NMR technology from EMI.

[110] Bailes D R, Young I R, Thomas D J, Straughan K, Bydder G M, Steiner R E. (1982) NMR imaging of the brain using spin-echo sequences. *Clinical Radiology* **33**: 395–414. Bydder G M, Pennock J M, Steiner R E, Orr J S, Bailes D R, Young I R. (1984) The NMR diagnosis of cerebral tumors. *Magnetic Resonance in Medicine* **1**: 5–29.

[111] Bydder G M, Steiner R E, Young I R, Hall A S, Thomas D J, Marshall J, Pallis C A, Legg N J. (1982) Clinical NMR imaging of the brain: 140 cases. *American Journal of Roentgenology* **139**: 215–236.

[112] op. cit. note 26 above.

Steiner: Many thanks, Graeme. Well we have now got the facts of the problems at Hammersmith in the very early days to the rapidly evolving successful clinical evaluation. May I now turn to the other teams. Peter, what about Nottingham?

Mansfield: I am going to rely very much on picking up, if you like, some of the comments and statements that have been made by others.

You heard earlier from Professor Andrew that, as far as we were concerned in Nottingham, our first publication in imaging was in 1973, the same year in fact that Paul Lauterbur published. We had obviously been thinking about imaging before that, and a very extensive, unpublished correspondence exists between me and one of my students while I was in Heidelberg on sabbatical leave in 1972. In that correspondence I was trying, from a long distance, to get my student, Peter Grannell, to take on new ideas. Because he was writing up his PhD I had to persuade him to get on and do something about imaging.

But NMR imaging really started as far as I was concerned in 1972, over a cup of coffee. It always amuses people when I tell this story, particularly foreign people, because not everyone in the world has a coffee break in the morning and those that do sometimes take their coffee into their office. But in Nottingham, and I think this was largely due to Raymond Andrew who was Head of Department at the time, Raymond encouraged us every day to meet and discuss our work over a cup of coffee. I believe this has something to do with traditions at Oxford or Cambridge or both. It was out of a discussion of that type early in 1972, that the idea of imaging actually occurred to me but it took some time to evolve. If you want to know the blow by blow details of this, you will have to turn to the Historical Perspectives of a document which has just been published and I don't want to play on that too much.[113] But, anyway, in 1973 we published our first paper on imaging and from then on there were a series of papers on various aspects of imaging, including the method of slice selection which is, of course, now widely used by most MRI systems.[114]

I want to move on to a comment made by Professor Young, because at the time I didn't know that he was an employee at EMI. In 1975, we had published a paper in the journal *Physics in Medicine and Biology* and to many people, particularly outside the field of medical physics, it's a fairly obscure place to publish something. It was a paper with Peter Grannell who was the first author. The paper showed a one-dimensional profile of a finger – it wasn't an image of a finger – which we managed to produce. This got published and I thought that was the end

[113] Mansfield P. (1996) A personal view of my involvement in the development of NMR and conception and development of MRI. In Grant D M, Harris R K. (eds) (1996) *Encyclopedia of Nuclear Magnetic Resonance*. Historical Perspectives. Chichester: John Wiley & Sons Ltd, 478–481.

[114] Garraway A N, Grannell P K, Mansfield P. (1974) Image formation in NMR by a selective irradiative process. *Journal of Physics* **C7**: L457–L462.

of the matter.[115] But then I got a telephone call from some people at EMI who had apparently seen this paper and become rather excited about it. We had images that had been published in other places and of course there had been at Nottingham an AMPERE[116] conference in 1974 where there was actually a session on imaging. The EMI group had picked up this obscure paper and asked if they could come and talk to me about it, which they duly did. I can't remember the names of the people, maybe Ian [Young] will know. There were three people that visited us and on the basis of that visit, they shortly afterwards invited me to go to EMI to give a talk on imaging, really to try to get themselves up-to-date with what was happening in Nottingham.

I went along and gave the talk. Of course I knew that Godfrey Hounsfield had received a Nobel Prize for his work on the CT scanner. When I arrived there I was led to the lecture room which was about this size [≈ 10 × 7 m] and there were probably as many people in the audience [≈ 50]. I kept asking, I think it was Alan Blay, the person who received me and showed me round, where was Godfrey Hounsfield? – I don't think he'd got his knighthood at the time – so it was Dr Hounsfield. And Blay said, 'Oh well he'll be coming along, he'll be coming along.' I started to talk, I gave my talk which lasted about 50 minutes and still no sign of Godfrey Hounsfield. I kept saying that I must meet him. It would be a great honour to meet a Nobel Prize winner, I thought I may not get the chance again. I've got to see this fellow and still Blay kept saying, in a very defensive way, 'Well I'm afraid Dr Hounsfield is doing this or that' or, 'He is in a different building'. I was definitely getting the feeling that they were hiding him. And Blay said, 'Well you don't know Godfrey, but when he gets a bee in his bonnet about something, and I think he is going to get a bee in his bonnet about NMR imaging, he is likely to be distracted from CT. We don't really want him to be diverted this way. We want him to keep his nose to the grindstone on CT scanning, you see.' As I was being ushered out of the Shoenberg building that evening, just by the entrance, I began to think, my God, I am not going to meet this fellow.[117] In the foyer to the building they had the actual device which Sir Godfrey had built with his own hands. There it was in a glass case. I thought this is about as close as I am going to get to him. Just as I was about to leave, Godfrey came along the corridor – I did not recognize him of course. There was a chap called Froggitt, Alan Blay and myself and we were blocking the corridor. Godfrey wanted to get by and I think they would not have introduced me even then, but somehow they felt that their

[115] Grannell P K, Mansfield P. (1975) Microscopy *in vivo* by nuclear magnetic resonance. *Physics in Medicine and Biology* **20**: 477–482.

[116] AMPERE, Atomes et Molecules Par Etudes Radio-Electriques. Founded in 1952 in France as a forum to enable practitioners to discuss progress, methods and results in the applications of magnetic resonance in physics and chemistry. E R Andrew organized the 18th AMPERE Congress in Nottingham in 1970. He was elected President of AMPERE and served till 1980.

[117] See note 32 above.

visitor was going now, and he couldn't possibly keep Godfrey long. So they introduced us.

When I met him in the corridor it was about five o'clock and he didn't know anything about my talk. They'd been keeping it very, very quiet, so he said, 'Who are you, what are you doing?' I told him and he said, 'What is NMR? I don't understand this', so I said, 'You should have come to my talk.' He said, 'They didn't tell me.' He then said, 'Look have you got a while, can you come to my office?' So off I went to his office and I was there until about 7.30 – a two-and-a-half hour lecture he had from me. It was a replay, with additions, of my talk. I tell that really as an amusing story, and shortly after that I was invited back as a consultant to EMI to help them set up what eventually turned out to be the story that you heard from Ian [Young].

But I have also to tell another slightly amusing story. I went to EMI, many times after my first visit, probably once a month for several months. The fellow that I always used to meet at these meetings was a chap called Hugh Clow. There were two other fellows, Peter Walters, who has been mentioned, and Mr Percival (I don't know what his first name was – I don't think anybody knew what his first name was, he was always called Percy). Percy was the 'mathematician'. I used to spend many a happy hour with those three teaching them NMR and NMR imaging. I never ever met Ian Young although I gather he was lurking in the background somewhere. It was afterwards when he got involved in what came to be known as the, oh dear what was the project called? – he had a name for it.

Young: It was called Neptune.[118] It wasn't my preferred name – that wasn't allowed.

Mansfield: But it wasn't until Neptune that suddenly he bounced in the room one day and I instantly recognized him. It turned out that I knew him from years before in a different company. So it's sort of interesting how these things tie up and how many people in what one might consider to be unrelated fields all touch and impinge on the developments which eventually led to Neptune and, of course, to the project at Hammersmith.

I will move on from that to just simply say that this all happened in 1975, but in 1976 we developed a technique called line-scanning and looked at fingers. We produced a line-scan image of a finger rather than just a projection. This caused a great deal of excitement, because we were trying at the time, without initial success, to persuade the MRC to give us some money to build a whole-body

[118] In 1981 GEC, London, installed their prototype machine 'Neptune' operating at 1500 gauss provided by a superconducting magnet (Oxford Instrument Company), at Hammersmith Hospital in London.

imaging machine. There were a lot of advisors to the MRC at the time who were rather doubtful that one could scale things up from fingers to whole bodies. But in the end, they came up with the money, and of course we produced in 1978 a whole-body line-scan image of the abdomen.[119]

We heard during the course of these proceedings, I think starting with Brian [Worthington], that there were a lot of doubters and detractors and so on. But there were also some enthusiasts and champions. Donald Longmore[120] was one of these and he invited me in 1980 to address a meeting of cardiologists in York. I think it must have been shortly before we had produced the first ultra high-speed movie images now called echo-planar images, and these were first presented at Winston–Salem in 1981. They were presented there by Roger Ordidge who had been working with me on EPI at Nottingham and we imaged a live rabbit in the machine. Our home-built machine underwent some gyrations in development at that time. We had a whole-body imaging programme going on which was relatively slow speed. But we also had a smaller probe insert which had a 10- or 12-cm diameter bore. We could therefore image hands, wrists and small animals. So Roger Ordidge produced a series of snapshot images of the beating heart of a rabbit. These were real-time images and, of course, we were terribly excited.

We both went off to Winston–Salem to the conference and Roger gave the paper on this work.[121] The turn of events at the meeting was amusing and Brian Worthington alluded to this. The way things worked out Ian [Young] was the speaker before us, and then Roger followed. Ian was saying something about MRI being a slow technique and we are never going to do this, and never going to do that. Then Roger got up and presented these very fast movie images showing the beating heart in real time. That was a bit of a shock I think, for many people at that meeting. But, as I said earlier, Donald Longmore was a very, very strong enthusiast. I think he had seen these images somewhere and he came up to Nottingham to talk to us about potential applications and he's been a very strong supporter and proponent of high-speed imaging ever since. He and his team have gone on to apply these high-speed imaging techniques in a very clinical sense, which is, of course, really what imaging is all about. I am a physicist and I have always tried, as much as I can, to get involved on the clinical side. But at the end of the day, you need clinicians with strong conviction and I found his support and comments extremely gratifying in those early days. At the time I was working with medical colleagues in Nottingham. Rex Coupland was the Head of Human Morphology, so he was very good at producing dead samples of things for us to

[119] op. cit. note 24 above.

[120] See biographical note 139 below.

[121] Ordidge R J, Mansfield P, Doyle M, Coupland R E. (1982) Real time movie images by NMR. *British Journal of Radiology* **55**: 729–733.

image, but we didn't really have a strong interaction at that time, or as strong as I would have liked, with the consultants and the clinical radiologists.

After Winston–Salem we enlarged this 12-cm aperture up to 20 or 25 cm and started ourselves to take EPI seriously. I know the lads in the lab at the time were quite keen to push on with EPI and I think I was acting as a bit of a break. Maybe Roger [Ordidge] will have something to comment on this. But anyway we did expand the aperture and we started to look at heads. We have some very early data showing ventricular motion in the brain and CSF motion in the brain. Also we looked at sick babies. This was essentially clinical work in situations where we didn't want to sedate the patient. Babies do move and so high-speed imaging techniques seemed to fit in extremely well.

I could go on all day, but I won't. This is a snap-shot view of a particular short period in the development of NMR imaging. It does not go into the detailed thoughts that went into our original proposal for imaging nor does it go on to when we acquired superconducting magnet technology. All MRI development during the period I am talking about was actually done with the Oxford resistive magnet which has been mentioned many times in the first session. It was all performed with an electromagnet working at 0.1 Tesla.

Steiner: Thank you Peter. Can we now have the Aberdeen contribution; Professor John Mallard please.

Mallard:[122] NMR began for me way back in the late 1950s when I was at Hammersmith at the same time as Sir Christopher Booth and Robert Steiner. My job, and main interest at that time, was nuclear medicine and I was developing early rectilinear scanners and gamma cameras where radioactive uptake in tumours provides the imaging contrast. Earlier I had done my degree and PhD in magnetism under Professor L F Bates, who was a magnetism buff, so I was really looking hard for a use of magnetism in medicine. I didn't want to waste my magnetism background so I started measuring electron magnetic resonance signals from rat tissues, and we found that tumours gave different signals, some bigger than normal tissue, some smaller, and they were signals from free radicals. We published all this in *Nature* in the early 1960s.[123] So we realized that if we could measure the ESR signal from point to point, we could find tumours without the need to inject radioactivity, as in nuclear medicine, or contrast media, as in X-

[122] See biographical note 34 above.

[123] Cook P D, Mallard J R. (1963) An electron spin resonance cavity for the detection of free radicals in the presence of water. *Nature* **198**: 145–147; Mallard J R, Kent M. (1964) Differences observed between electron spin resonance signals from surviving tumour tissues and from their corresponding normal tissues. ibid. **204**: 1192.

radiology. We presented this at the First International Congress of Medical Physics at Harrogate in 1965, and it was published in *Nature* in 1967.[124]

I went to Aberdeen in 1965 and I was able to appoint two young postdocs, one was a physicist, Jim Hutchison from St Andrews and another, a biologist, Meg Foster, from Durham. They eventually got married and they both played a very important part in the development of MRI. Jim Hutchison and I tried very hard to make ESR imaging work on mice during the late 1960s but we were beaten by the strong absorption and scatter of the 100 MHz radiation.[125] Damadian's work then came out in 1971,[126] so that encouraged us to switch to NMR. We built an NMR spectrometer and Meg Foster got cracking on measuring the relaxation times of animal tissues and tumours. We published our results which were not so favourable as Damadian's at that time, and we were able to predict what NMR images might look like, if we could make it work.[127] And it turned out to be remarkably accurate.

Whilst this was going on, I had my nuclear medicine team building a tomographic scanner, a CT scanner, for gamma rays from radioactivity, and we had it working on patients in the late 1960s and I can remember also going to give a talk at the EMI laboratories in Hayes, but Sir Godfrey Hounsfield did come to that one! We published our first clinical gamma-ray CT series in 1973 on epilepsy, the same year as Sir Godfrey announced his X-ray CT scanner.[128] So when Lauterbur's paper came out at the same time,[129] we were all ready with our CT reconstruction programmes and we quickly built a small permanent magnet system and produced the famous mouse image which Jim Hutchison showed at the AMPERE conference in March 1974 in Nottingham.[130] That proved that NMR imaging could work and that T_1 would distinguish body tissues and pathology. We then lost more than a year, getting a grant of only £25 000 from the MRC to build a human imager. And because of our radioisotope experiences, we wanted to jump in at the deep end, to build a whole-body machine, all ready for clinical use,

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[124] Mallard J R, Lawn D G. (1967) Dielectric absorption of microwaves in human tissues. *Nature* **213**: 28–30. Mallard J R, Whittingham T A. (1968) Dielectric absorption of microwaves in human tissues. ibid. **218**: 366–367. Mallard J R. (1967) Inaugural lecture. Medical physics – what is it? Hybrid tea – numerically scanning clockwise. *Aberdeen University Review XLII* **137**: 12–29.

[125] Hutchison J M S, Mallard J R. (1971) Electron spin resonance on the whole mouse *in vivo*: a 100 MHz spectrometer. *Journal of Physics E: Scientific Instruments* **4**: 237–239.

[126] op. cit. note 30 above.

[127] Mallard J, Hutchison J M S, Edelstein W, Ling R, Foster M. (1979) Imaging by nuclear magnetic resonance and its bio-medical implications. *Journal of Biomedical Engineering* **1**: 153–160.

[128] op. cit. note 32 above.

[129] op. cit. note 14 above.

[130] Hutchison J M S, Mallard J R, Goll G C. (1974) *In vivo* imaging of body structures using proton resonance. In Allen P S, Andrew E R, Bates C A. (eds) *Proceedings of the 18th AMPERE Conference, Nottingham.* Amsterdam: North Holland Publishers, 283–284.

and also to image T_1.[131] Whilst we were building it, we saw all the other teams working up in size – fingers, oranges, peppers and heads and all that sort of thing and we didn't appear to be doing anything, it was very frustrating. We then had to get another grant and there was a very good meeting at the MRC in December 1976 which brought all the teams together. We took on more people, including an American, Bill Edelstein, who was at that time a PhD student at Glasgow. We carried on building our machine which had a vertical field of only 0.04 Tesla, from an electromagnet with four horizontal coils, with the patient horizontal, and this configuration gave an advantage of root two in sensitivity.

We reported early images of my own chest at a British Institute of Radiology meeting in November 1978 in Savoy Place at the Institution of Electrical Engineers.[132] It was recognizable, but it was badly spoiled by the movement artefact: we had lots and lots of meetings and arguments over this and it wasn't until we got to about February or March 1980 that our 2-D Fourier transform was originated, generally known as spin-warp.[133] We got good images of volunteers with that, including all of us. We spent a few months clearing up all sorts of details and we imaged our first patient cared for by the radiologist, Dr Frank W Smith,[134] who has already been mentioned, on 26 August 1980, a very great day. We found spinal metastases that weren't known about in that particular patient. They were subsequently confirmed by other methods and one week later I showed those images at Heidelberg at an International Atomic Energy Agency nuclear medicine imaging meeting.[135] So we believe we were the very first team to produce clinically useful images. On our machine, good images could be obtained of any part of the body, including T_1-weighted images.

Frank Smith was very enthusiastic. He sent and diagnosed over 900 patients in the next two years. The porters wouldn't bring the patients over to our building where the machine was, because they wouldn't be insured outside the hospital building, so we had to bring all the patients over ourselves. We had to convert the medical school soap store into a patient waiting area and so on, and so forth. A

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[131] In 1975 Dr Jim Hutchison introduced the inversion-recovery pulse sequence for obtaining T_1-weighted images. See Hutchison J M S. (1976) Imaging by nuclear magnetic resonance. In *Proceedings of the 7th L H Gray Memorial Conference, Leeds*. Chichester: John Wiley, 135–141.

[132] See note 127 above.

[133] UK patent number 2079946A, March 1981. Edelstein W A, Hutchison J M S, Johnson G, Redpath T W. (1980) Spin-warp NMR imaging and applications to human whole-body imaging. *Physics in Medicine and Biology* **25**: 751–756.

[134] Dr Frank W Smith was the consultant radiologist and specialist in nuclear medicine at the Aberdeen Royal Infirmary at the time.

[135] Mallard J R, Hutchison J M S, Foster M A, Edelstein W A, Ling C, Smith F W, Selbie R, Johnson G, Redpath T W. (1980) Medical imaging by nuclear magnetic resonance – a review of the Aberdeen physical and biological programme. In *Medical Radioisotope Imaging*, International Atomic Energy Agency, Vienna, 117–144. See also Smith F W, Mallard J R, Hutchison J M S, Reid A, Johnson J, Redpath T W, Selbie R D. (1981) Clinical application of nuclear magnetic resonance. *Lancet* **i**: 78–79, and note 107 above.

whole lot of world-first clinical series were published with Frank Smith,[136] and, of course, the machine was in use so much that we couldn't get any time on it to improve it, so we had to build another one (NMR Imager Mark 2 in the Aberdeen Royal Infirmary). From September 1980 onwards life was frenetic. We were besieged by Japanese companies that all wanted the know-how for next to nothing. The MRC wouldn't help us. There wasn't one British company interested in what we were doing, and this brings us to this disillusionment period again, and I think another factor in it was this dreadful crash of the X-ray CT and EMI at that time. It influenced all the radiologists and it certainly influenced the City of London, because I tried hard to get money for setting up a company.

In 1981–1982 I think I am right in saying that International General Electric (IGE) of New York[137] spent $112 million on R&D alone, developing their prototype. And they snapped up our Bill Edelstein, who went to them in the summer of 1980, so they got all our know-how for nothing.

I was asked to build a machine by the Professor of Radiology at Edinburgh. We struggled hard to set up a company (M and D Technology Ltd) to build them, we could only get £1.5 million from financiers in the City of London at that time. Company staff built three machines, one for Edinburgh, one for Bart's and one for Geneva. They all worked for ten years. They are now in museums. The Edinburgh one is in the National Museum of Scotland, the Bart's one is in the Science Museum at South Kensington, London. We went bump, because I couldn't get any more money to improve our model, but the Japanese company that had the know-how from us in 1981 in return for the money to build our second machine (NMR Imager Mark 2 in the Aberdeen Royal Infirmary), built and sold 145 machines in the Far East, over a period of five years, and it was just basically our machine improved (and 200 more of a more versatile, higher-field version later). So it could have been successful, if only we had had the backing. The University team built a Mark 2 at twice the field strength in 1981 and 1982 which was used between 1983 and 1993. Nine thousand patients were done on that. By 1985 we were old hat. We couldn't get our clinical papers published: we were told we were not 'state of the art' because equipment available elsewhere had moved on so much. So I will finish now by saying that my original goal of imaging free radicals is now being pursued in my old department by a combination of electron resonance with MRI called PEDRI.[138]

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[136] See for example Pollet J E, Smith F W, Mallard J R, Ah-See A K, Reid A. (1981) Whole body nuclear magnetic resonance imaging in medicine: the first report of its use in surgical practice. *British Journal of Surgery* **68**: 493-494. Mallard J R. (1986) Nuclear magnetic resonance imaging in medicine: medical and biological applications and problems. The Wellcome Foundation Lecture 1984. *Proceedings of the Royal Society* **B226**: 391–419.

[137] International General Electric (IGE) was the European trading designation of General Electric of the USA.

[138] This is a double resonance technique involving both electron spin resonance and nuclear magnetic resonance. See Lurie D J, Nicholson I, Foster M A, Mallard J R. (1990) Free radicals imaged *in-vivo* in

Steiner: The next speaker will be Professor Donald Longmore from the National Heart Hospital.

Professor Donald Longmore:[139] Professor Steiner, ladies and gentlemen, I have a slightly different approach to this. I am only a cardiac surgeon, not a clever physicist or indeed a radiologist. But in 1975 I was so disillusioned with cardiac surgery and my colleagues, who were using the new technologies for personal gain, that I set up a charity with a view to preventing heart disease. And I remind you that half of you in this room are going to die of blocked arteries, a quarter of cancer, 12 per cent of pneumonia and about 2 per cent of the things that magnetic resonance has been used for so far. This venture, having a charity supported by extremely important people and chaired by Lord Carr, put me on the spot. And I was fortunate to go and see Peter [Mansfield] in 1976 and I saw his first linear finger image and I was so excited by this, that driving home, I exceeded the magic hundred mile an hour speed limit and got a lot of spotty dicks on my licence. A few days later, I witnessed John Vane discovering prostacyclin at the Wellcome Foundation's research laboratories[140] and I thought now we have the two magic ingredients for secondary prevention of this major killing disease. One is an understanding of what's going on in the vessel wall and the other is the potential way of imaging it. So we had funding and we had the inspiration from Peter [Mansfield], but it was extremely difficult to overcome the extreme negativism of the radiologists who felt that magnetic resonance was a radiological tool and that it really wasn't any good anyhow. But I had a dream that we could put magnetic resonance machines into vehicles and go out and screen the population for a disease for which we don't know the causative factors and therefore can't apply preventive measures. We should be able to detect it at an early stage and apply preventive measures. And I am glad to say that the clinical trials of that are going on at this very minute.

Now the next thing after Peter Mansfield is the enormous generosity of Graeme Bydder and Ian Young, who let us butcher their machine, and put cardiac

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the rat by using proton-electron double resonance imaging (PEDRI). *Philosophical Transactions of the Royal Society* **330**: 453–356. It uses the Overhauser Effect, see note 141 below.

[139] Professor Donald Longmore FRCS(Ed) FRCR (b. 1928) is Professor of Magnetic Resonance in Medicine and Director of the MR Unit, Royal Brompton National Heart and Lung Hospital and has published many papers on magnetic resonance of the heart, and chemical-shift analysis of atheromatous plaques. He devised the phase shift method of measuring blood flow. See for example Rees S, Firmin D, Mohiaddin R, Underwood R, Longmore D. (1989) Application of flow measurements by magnetic resonance velocity mapping to congenital heart disease. *American Journal of Cardiology* **64**: 953–956. Keegan J, Firmin D, Gatehouse P, Longmore D. (1994) The application of breath hold phase velocity mapping techniques to the measurement of coronary artery blood flow velocity: phantom data and initial *in vivo* results. *Magnetic Resonance in Medicine* **31**: 526–536.

[140] Professor Sir John Vane FRS (b. 1927) worked at the Research Laboratories of the Wellcome Foundation in Beckenham, Kent, from 1973 to 1985. He discovered prostacyclin, the short-lived antagonist of platelet aggregation, and shared the 1982 Nobel Prize in Physiology or Medicine.

dating on it. I am not sure if Professor Steiner knew what was going on, but if he did, he didn't say anything, and allowed us, with their help, to crack the problems of using phase-shift to measure blood flow. Later we were able to image the blood vessel wall and to use chemical shift artefacts to analyse atheromatous plaques, and my belief is that magnetic resonance has been heavily distorted by the history. It has been distorted by the fact that it was a radiological tool and that it was easy to shove the brain in a machine and that that has actually pushed the thing off the proper course that it should have followed. Peter Mansfield's rapid imaging is absolutely fundamental for the cardiovascular system and very short echo times of microseconds are essential for the lung and all these problems have been cracked.

Looking a tiny bit ahead, I wonder whether spectroscopy, which when I started was the clever way ahead, and imaging was the childish way, I wonder whether spectroscopy will survive against the combination of high-resolution imaging and the Overhauser effect to measure oxygen tension.[141]

And finally, to deal with Professor Mallard's point, nothing has changed. We have a new British walk-in machine with all the latest technology and nobody in the City or the UK is the slightest bit interested in funding it. Nothing has changed. Magnetic resonance is still being used for the head, where it might be of interest, spectroscopy is still going on, the cardiovascular system which is going to kill half of us, is grossly neglected, but I have to say that the generosity of the people sitting on that platform and other people here today has done an enormous amount for people who came into magnetic resonance after the first exciting stages.[142]

Steiner: Thank you. May I ask the two neuroradiologists in the audience to defend imaging of the brain?

Professor Ian Isherwood:[143] As some say, hype springs eternal. Can I just make one or two comments on my perception of the negative factor that Brian

[141] The Overhauser effect – the discovery by the American physicist Albert Overhauser in 1953 of how to increase the signal-to-noise ratio by transferring polarization from electrons to nuclei which made it possible to enhance NMR signals for a number of unusual samples. Overhauser A W. (1953) Polarization of nuclei in metals. *Physical Review* **92**: 411–415.

[142] Professor Longmore later wrote: 'I think it is a sad acccident of history that imaging was regarded as less scientific than spectroscopy. The National Heart Unit founded a new branch of medicine – cardiovascular MR. This discipline now has its own society and many thousands of babies with congenital heart disease have been spared dangerous catheterizations. Now coronary artery flow and imaging are revolutionizing the management of coronary disease. Has spectroscopy saved any lives?' Fax to Dr Tilli Tansey, 10 July 1998.

[143] Professor Ian Isherwood (b. 1931) was Professor of Diagnostic Radiology, at the University of Manchester from 1975 to 1993, now Emeritus, and Consultant Neuroradiologist at Manchester Royal Infirmary from 1962 to 1993. He was President of the British Institute of Radiology from 1984 to 1985, the European Association of Radiology from 1989 to 1991 and the British Society of

[Worthington] and others have referred to. I think you have to put this into historical context. The first CT scanner outside the Atkinson Morley's hospital[144] was in Manchester in 1973 and one of the earliest whole-body scanners in 1975. By the time we get to 1981 or 1982 the period we are now speaking about, many people felt that CT had reached a plateau of excellent spatial resolution. The images were excellent. They were understandable, not only by radiologists, but by the clinicians who requested the examination. Now it is correct, as Gordon [Higson] has said, that CT was not so readily available in this country, as it was in the United States, but, nevertheless, CT was seen as a clear imaging view of most of the parts of the body. The MR images which were then available were, of course, very poor by comparison in that context, and you have to recognize that CT was then available in many district hospitals in the United States and beginning to become available in this country too. So we are talking about the direct reference of clinician to general radiologist, and the perception of the piece of X-ray film that was presented to the clinician by a radiologist. He saw it in terms of the old X-rays that he'd been used to. Now, that wasn't so in some departments, and I can go on to my own department. Our interest in CT had been throughout on the quantitative aspects, a feature lost, I have to say, in most radiology departments. In the United States, the majority of CT was, and still is, carried out as an imaging procedure without reference to the quantitative background, often carried out by technicians and simply reviewed by radiologists as pictures. We were concerned to know whether the quantitative aspects would be valuable. That proved to be the difficult thing to demonstrate except in one particular, and that was bone-mineral densitometry which has since led on to a good clinical tool in terms of dual energy and X-ray transmission assessment.

We were aware, in Manchester, following the field, that the opportunities in MR were enormous. As an academic department, we were not interested so much in the pictures as in the quantitative prospects for this particular procedure. And it was on that basis that we approached Waldo Hinshaw, who was a friend of Brian Pullan, then the Head of Medical Biophysics in Manchester. And Waldo, I think, was half way between Massachusetts General Hospital (MGH) and Technicare. Technicare seemed to be the best option for imaging at that time, in the assessment that we could make, and we approached the MRC, this was in early 1982, having had long discussions with Waldo in 1981. In 1982 we put a proposal to the MRC that we would put in a bid, and that it would be for a Technicare instrument and that Waldo Hinshaw might then be part of the team since Brian [Pullan] was trying to persuade him to come to Manchester. It was made quite clear to us by implication that since Lord Weinstock had bought Picker International and put a

Neuroradiologists from 1994 to 1995. He was awarded the Gold Medal of the Royal College of Radiologists in 1995.

[144] See note 100 above.

union flag on it, that Picker would be the preferred option and that Technicare would not be an appropriate move. We took this hint, a very strong hint I have to say, and put in our MRC bid with a Picker instrument on it, and received the grant and continued from there.

Our instrument opened in June 1983. It was, I think, one of the first commercial cryogenic systems after the systems you've heard described. The problem was that it was a 0.26-Tesla system. That was an unusual field strength and it was less than five years, I think, before GE bought the Picker commercial base in Europe except for three sites, the Hammersmith, Cambridge and Manchester.[145] So we were left at that stage as Cambridge was, and less so with the Hammersmith because you had the in-built expertise, with an instrument of unusual field strength, the software of which could not be improved easily, or added to, and no service commitment from GE who'd bought the rest of the commercial base. And we were therefore forced into moving to GE, who had been extremely valuable to us over the previous years in terms of CT development, and that's how we came to have a GE system in the late 1980s. I think those are important issues to record and I think it is also important perhaps to recognize the controversy that existed about low- and high-field strengths at that time. 0.26 was regarded as low, 0.5 was proposed and indeed a great protagonist of 0.5 Tesla was Leon Kauffman in University College London but GE preferred at that stage to go into high-field. That was in the early 1980s, and the reason for that strategy, and I believe it following discussions with them and with Picker, was the concept which had gone before with CT that the bigger the machine, the better the images would be, and this was a perception by the radiologists in the United States. Indeed, much could be done with mid-field and low-field systems and some things could be done that could not be done at high-field in the abdomen as we all well know. GE subsequently changed their views after that historical development of what we have today.

Young: Could I just add one comment on the low- and high-field issue. Of course, the expanding, the hugely expanding area of activity at the moment is actually the electromagnets with fields of 0.2, 0.23 Tesla. It's a complete turn of the circle. Machines which are selling best are all now between 0.2 and 0.3 Tesla. Hitachi Airis and Siemens Open and the Picker Outlook and the Americans still don't understand why.

Steiner: Can we ask Gordon Higson to give the point of view of the DHSS and the Research Councils!

[145] Professor Donald Longmore later wrote: 'There were four centres – including the Royal Brompton National Heart Unit.' Fax to Dr Tilli Tansey, 10 July 1998.

Higson:[146] For those of the audience who don't know, during the ten years or so period that I am going to talk about I was Director of the Scientific and Technical Branch of the Department of Health and had control, more or less, of a budget for the research and development of medical devices. The great triumph of the use of this budget had been in 1969 and the early 1970s when we were contributors to EMI and Godfrey Hounsfield and the development of the CT scanner. So during the 1970s we were really very close to EMI who thought that the medical business was going to be big business for them, and had all sorts of activities going on in their research labs – further development of CT, ultrasound, and many other activities. The emergence of EMI's research lab's interest in MRI came to my attention in 1978 when we had a visit from Dr Ian Young, Dr Hugh Clow and lots of other people. I think quite a team came from EMI. We occupied a conference room in Russell Square and they gave us about half a day on what one could do with nuclear magnetic resonance imaging and this was all done on their Walker machine in the research labs. The object of their visit and their teach-in was, of course, to tease money out of the Department for further developments and they succeeded. We were really very enthusiastic about EMI and certainly, speaking for myself as a former physicist, I'd always wanted to see numbers in these diagnostic tools rather than just pictures. I'd always thought we'd get massive amounts of information out of Hounsfield numbers from CT scanning and it has always been something of a disappointment that it's just an imaging tool. MRI offered this prospect of characterization of tissues rather than just pictures and that was a big attraction I think for the Department at that time. We did conclude a contract with EMI for a two-year programme to develop a clinically suitable imaging machine and that was going to be, as it was, the first really clinically usable machine – in England at any rate, not in Scotland. We actually signed that contract about the end of 1979, by which time the specification had changed quite a bit and the Neptune project[147] to build the cryogenic magnet was of course the most significant feature. And this contract was, I think, for £350 000 over two years. In 1979 it was quite a lot of money.

There were many strands to what was happening at this time. So I'll try and take a strand at a time. I don't think I can do it chronologically, it will be too confusing. The programme was to complete a machine and, really, I think the biggest time factor was getting the magnet to work and install it in Hammersmith in 1980. In fact, it didn't happen until right at the end of 1980 if I am correct, about December. Most of 1980 was occupied for me not with worrying about the date of installation in Hammersmith, but with worrying about what was going to happen to the project, because during 1980 EMI had got themselves into financial difficulties and were bought by Thorn – and became Thorn EMI and the

[146] See biographical note 66 above.

[147] op. cit. note 118 above.

Chairman of Thorn was Peter Laister. I had a number of meetings with Peter Laister at which he told me about how distressed he was with what they had found at EMI, particularly in the medical field. They decided this was not a winner and it wasn't where Thorn was going to make its money and they were going to offload the medical business. Most of the medical business, of course, was EMI's concern and they could do what they wanted with it, but the contract for the development of the Neptune scanner was not just EMI's business. We had written a very carefully worded contract with EMI which not only was aimed at bringing some royalties back if the development was successful, but also kept control over just how that project could be disposed of, and indeed where the work could be carried out in the hands of the Department. So although EMI had to sell it and get money back for it, they could only sell it with the approval of the Secretary of State. I was going to say that, in practice, that meant my approval, but I will tell you that that is not the case. EMI started off to try and sell this project for the best price they could get and they approached all the imaging companies. Prospective purchasers had to make two visits: they had to go to EMI and negotiate the commercial terms, and then they had to come into the Department and try and get the political approval and they all came – Technicare, Pfizer, and others I have now forgotten and GE, that is General Electric of the United States. The front runner, undoubtedly, was GE. They had a lot of money available and they wanted this project. They were doing a lot of research themselves and they were keeping away from the type of imaging development that EMI was doing, because they actually thought they could acquire it. General Electric of the UK, who I will return to when I take the next strand, had not made any bid for this project and I'd had a number of meetings with various companies, and thought I had narrowed it down by this stage to GE. However, Lord Weinstock of GEC went to visit the Secretary of State and arranged that the project should be transferred to GEC. So the Secretary of State *did* give his permission for the transfer of the project and I then just had to make it work, and EMI and GEC had to agree some commercial terms. That was really quite an interesting period.

Then in July 1981 I went with the Secretary of State for the official opening. From then on, I think, the Hammersmith story was one of outstanding clinical success. I do remember Graeme Bydder actually bringing to my office, (he was a very courteous gentleman) the first real pictures, saying this is white matter and this is grey matter and we can distinguish them. That was a good moment.

Let me go on as to why it went to Hammersmith Hospital. Ian [Young], I have to disagree with you. I believe that the right to place this device for its clinical trials, once the Department had agreed to support it, was in the hands of the Department and I remember thinking very seriously about this. We had had some excellent experience with the development of CT. As Godfrey Hounsfield will remember, the initial trials that were done on your little lathe bed mock-up were

done by three clinicians: James Ambrose, Frank Doyle and Louis Kreel. It was, I think, an excellent beginning of the development of CT and I wanted very much to follow the same path as closely as we could. Now all those three clinicians had been really excellent collaborators, but from what I thought of NMR and its future, the obvious man to place this with was Frank Doyle. I can remember going with Ronald Oliver, who was then Senior Medical Officer in the Department, to see Robert Steiner and Frank Doyle at Hammersmith to discuss with them their interest in becoming the clinical collaborators on this project. You were very sceptical, Robert, I have to say. Frank [Doyle], I think, was enthusiastic from the beginning. I think Frank saw the possibilities from that very day, because he probably knew all about them anyway and I think that you [Robert] were very conservative about it, but the machine went into Hammersmith. It started work, got some brilliant successes, and then we had this terrible incident with Frank,[148] and my admiration for you, Robert, for the way you stepped in and took command of the project, is unbounded. It was an absolutely magnificent task that you did. I don't know what happened to your routine clinical work, because I never saw you then do anything but drive NMR and that was absolutely tremendous. And you've just had that continual struggle from then on of keeping the thing going.

Steiner: Well, let me remind you of a point that you made to me Gordon [Higson] at the time. Louis Kreel got a CT scanner from the DHSS, Jamie Ambrose already had the first one for some time, but we at Hammersmith never got a CT scanner from the Department of Health. We had to buy our own, so you said to me, 'Let's make a swap, we will give you the prototype MRI machine instead.' That's partly why we got it, you owed it to us.

Higson: I'll tell you some more about it. In 1978 there was the first request for money from EMI. It was followed very quickly by Peter Mansfield, who came in and also asked for some support. Again, we negotiated support for Peter Mansfield. Bill Moore and Neil Holland then heard about money being dished out from the Department of Health and came and asked for money and we didn't give them any. GEC had not asked for any money at that time. They had a very modest programme, I think, on NMR, but what they did shortly afterwards, and I can't be sure about the date, but probably 1980 or 1981, was to contract to buy an imager which was to be built by Moore and Holland and used by Brian Worthington and what we ended up doing after all these complicated negotiations between GEC and EMI and the Department, was to put in some more money and

[148] The 'terrible incident' refers to Professor Frank Doyle's stroke mentioned earlier.

pay for that machine that GEC had ordered from Moore and Holland to go into your department.

And then other things started to happen. Also in 1979 we got involved with George Radda. So many things started to appear then. David Gadian was doing spectroscopy at the Royal College of Surgeons. There had started to be some general concern about a fragmented UK research effort and I can remember one or two high-level meetings with Sir James Gowans [Secretary of the MRC], and Sir David Phillips when he was Chairman of the Science and Engineering Research Council (SERC).[149] Rex, I don't know whether you were at any of those meetings, trying to get some order into the UK effort, but they ended up with the only funding bodies interested being the MRC and the Department of Health. We came to a sort of *modus operandi* with Jim Gowans that the Department would pay for equipment development, or equipment supply, but the actual support of the clinical teams had to be from the MRC and that was the situation we arrived at with Hammersmith. But that took a bit of managing to say the least. I can't remember the sums of money, but I think that in those early years of the 1980s, the Department was paying more than a million pounds a year, maybe up to a peak of about a million and a half pounds a year, into the various NMR activities, and this was out of an R&D budget of about £4 million. It was an enormous slice of our budget and became almost unmanageable, and it took a lot of talking with the MRC to get them to take on the running of the clinical programme while we tried to get some money back for the next medical device development.

One last anecdote is that sometime very late in my career at the Department, it must have been about 1986 or 1987, I got a call from the Secretary of State's office to say that I was to go to the National Heart Hospital and see Professor Donald Longmore. This was on an instruction from Number 10 and I was to ensure that Professor Longmore got the NMR machine that he wanted! I'd got this call about midday. About 2 o'clock I was in the National Heart Hospital, and we talked and I went back realizing he was a very well connected man. But I had no money and I spent the evening talking to people at the Department of Trade and Industry, lying through my teeth about a loan of some money to buy a machine which in due course would be repaid from Donald's charity or else by the Department of Health, neither of which either of us had the slightest intention of doing. I was leaning on the fact that Number 10 were keenly interested in this and you got an imager, Donald, and you never paid for it and neither did I. The DTI made their sole contribution to MR imaging with your machine.

[149] The responsibilities of the Science and Engineering Research Council (SERC), formerly the Science Research Council, were later split between the Engineering and Physical Sciences Research Council (EPSRC) and the Biotechnology and Biological Sciences Research Council (BBSRC), funded by Government through the DTI and the Office of Science and Technology.

Longmore: We got two more after that!

Steiner: Gordon, many thanks, your talk was most informative.

Professor Tom Treasure:[150] I would just like to say something about 1981 and to see what reminiscences and what memories it brings back. In 1981 I was working in a lab in the United States as a young research fellow and what we were studying was the effect of hypothermic circulatory arrest and it was a real struggle. There was a paper from Boston, Massachusetts, the first author was Norwood, but I don't know who the physicists were on it. They put neonatal rats into their magnets and produced the most spectacular information as far as we were concerned about changes in pH from the phosphate peaks and the loss of the high-energy phosphates and they were clearly able to get, in the magnet, the sort of information that would take us dozens of animals and weeks of work. We were overwhelmed by it.[151] The mood at the time amongst the people I was listening to, was that this was a scientific tool, valuable in biochemistry, that was being hijacked by the American medical market as an imaging tool, because that's where the money was and that's where the resources were being put. That's what I picked up in 1981 from those around me. What do you think?

Young: There was certainly a school of thought that went along with that. There were a number of people you knew who felt you could scratch a high-resolution spectroscopist and obtain that sort of reaction.

Booth: Two questions if I may. The first question is at what stage did patenting come into this. Was patenting a problem as it was with monoclonal antibodies,[152] for example, and were there arguments with the Americans and others about this? That's my first question. The second question is what the MRC was doing about this. Now John Galloway was here before tea, I don't know if he is still here, but he may know what the MRC position was. I remember seeing one of George Radda's first applications which went, I think, to the Systems Board in those days.

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[150] Professor Tom Treasure FRCS (b. 1947) trained in London and the USA, and now holds a personal chair in Cardiothoracic Surgery in the University of London at St George's Hospital.

[151] Norwood W I, Norwood C R, Ingwall J S, Castaneda A R, Fossel E T. (1979) Hypothermic circulatory arrest: 31-phosphorus nuclear magnetic resonance of isolated perfused neonatal rat brain. *Journal of Thoracic and Cardiovascular Surgery* **78**: 823–830.

[152] See Tansey E M, Catterall P P. (eds) (1997) Technology Transfer in Britain: The case of monoclonal antibodies. In *Wellcome Witnesses to Twentieth Century Medicine*. Vol. 1. London: The Wellcome Trust, 1–33.

Higson: I am not sure that I can answer fully although I know something about this. The MRC, of course, had supported the two groups at Nottingham and John Mallard [in Aberdeen] during the 1970s and I think that the MRC support involved them gaining patent rights (inventors will correct me on this). The MRC was bound at that time, to pass all patents to the National Research Development Corporation (NRDC),[153] so there was, in the early 1980s, a lot of squabbling about who owned patents, particularly those in the hands of EMI and then GEC, whether the work had been done before the support started or afterwards or even in the middle of a project, so there was a lot of arguing as to whether patents were owned (a) by the inventors, (b) by NRDC, or (c) by the manufacturers. And my recollection is that there was a deal in which the EMI portfolio was handed over to NRDC, at a cost of course. I think NRDC bought out everybody's so that they had a full portfolio. Does anybody remember this?

Young: Yes, there was certainly discussion. As far as patenting, it was the only thing Ingham used to let us do and we used to retire to the pub every Friday night and all the inventions were made by either Fuller, Smith or Turner. We then put them in under those names to see how far we could get. We usually got quite a long way actually, because the Director wasn't terribly bright about our activities. He lived in another world. The names are those of local breweries. There was a deal with NRDC but I think that Terry Gooding unscrambled it in some disastrous manner, but that would be into the 1980s. There were all sorts of complications and there was a deal that was done, was undone, and was done again – and ended up as a mess.

Mansfield: The first invention on MRI filed by us was in 1974. I was a bit naive, and not terribly street-wise, so our very first paper on imaging just went into the public domain without patent cover.[154] But my original invention of NMR imaging was not done with a grant from the MRC or indeed a grant from anyone. We were between grants at the time. But we had had money previously from the old SRC which left us with some equipment to use. I found out later that we were obliged in those days to actually file patents with the NRDC if we had received money from one of the government-funded agencies, so this is what we did.

For the first several years, before we got involved through Gordon Higson with the Department of Health and with Picker, our patents were filed through the NRDC. Later when we got involved with contracts with the Department of Health, they insisted, weirdly in my view, that we file our patents with the

[153] The National Research Development Corporation (NRDC) was established in 1949, set up under the Development of Inventions Act 1948 as a Corporation by the Board of Trade, to safeguard and commercialize inventions arising principally from publicly funded research. See note 46 above.

[154] op. cit. note 15 above.

Ministry of Defence. So these documents disappeared into a black hole. A couple of important patents eventually surfaced with GEC. The route is confused because we are talking about an era in MRI development when EMI got out of all medical imaging and Picker hadn't, I understand, been created at that point.

Eventually GEC acquired Picker, an ailing CT company in the States, and then transformed it into Picker International. I think that is how it happened. Roger Ordidge, who is in the room, is co-inventor of one of these patents. We were very concerned about their eventual fate. They may have ended up via NRDC with BTG. If they have, it's a very circuitous route. But I think the handling of the patent situation was actually a scandal. That's what I wanted you to say and the Department of Health has to carry some of the blame for it, I am afraid. Sorry, Gordon, but that's how I see it.

Wood: After all this discussion of the history of the business, I wonder if it would interest people to know exactly where we are now. There are, in fact, 10 000 of these units around the world. This is where it has all led. I am glad to say, this country is responsible for the manufacture of about a third of these and, in fact, something that always makes me a little warm, there are 30 000 patients a day who have scans in magnets that we have made in Oxford. The market is increasing overall at about 5 per cent a year and Ian is absolutely right, the low-field end, the cheap end of the market, is increasing most, at something rather more than double the average rate. However, there is an enormous variation in terms of the numbers of MRI units per head of the population around the world. A statistic that is often used is the number of scanners per million of the population, and this varies from Japan which has the most, a figure of just over 18 scanners per million of the population, America is a little bit less, about 16, the European average is just below 4 and the British average is just below 3.

Two things came up in the conversation which I just might comment on. You were talking about whether the magnet that was ordered by command of Number 10 Downing Street, was ever paid for. It makes me wonder if I ought to go back into the books and see whether we were ever paid for it. (**Longmore**: Yes you were!). Secondly, John Mallard talked about a magnet that was sent to Geneva and there's a little anecdote about that which might show that the industrial people making things have problems as well as the medical people. We supplied this magnet to M and D Technology for a clinic in Geneva and I think it went up on something like the fourth floor of a private clinic.

Mallard: It was a late-Victorian building, windows had to be taken out to get it in.

Wood: Anyway it went in. We had tested this magnet. Inevitably, you know, some magnets are better than others and some are worse. This was one of the best magnets we had ever made and we were very proud of it. We sent it to Geneva and no sooner was it put into use, we were told it wasn't working properly. I don't know whether we had it back, or if we went out. I think we had it back in Oxford.

Mallard: I don't think you had it back. You went out to it.

Wood: Time and again we went out. Whenever we went out and operated it, it worked beautifully. Whenever we left Geneva we got complaints that it wasn't working. A fair amount of bad blood developed, I have to say. The people out there said we hadn't made a good instrument and we said that they didn't know how to use it, and so it went on. The key to end the story was, of course, this was a magnet with a vertical field with coils in the horizontal plane. Also unlike a superconductor where any extraneous magnetic fields are shielded from the system, this was a conventional magnet powered by a generator, rectifier and so on. And it turns out that all the trams in Geneva are fed off an enormous ring main and whenever a tram starts up the vertical magnetic field in the whole of Geneva changes by so much that one of these scanners is thrown completely out of focus.

Mallard: But the interesting thing was it was only the return circuit line that affected the magnet, not the out line and a small change in the return circuit by the tram company cured it. Could I just make a comment on the MRI patents please, because I think it is very important? I felt that because all of us were supported by public monies with our salaries, whether we were on grants or not, all our work should be patented through what was then NRDC, so it was something like eight patents in the NRDC portfolio from Aberdeen. I think there are about 14 patents altogether in their portfolio, bringing in something like £10–12 million a year to what is now BTG. The point that I want to make is that I am very worried that NRDC has become a privatized BTG, because I was able to say to all the young research workers, none of whom wanted to patent the work, they all wanted to get it published yesterday for the honour and glory and whatnot. I was able to say, 'Look your salary's coming out of public money, other peoples' income tax, you have got to patent it', and eventually they all agreed and all the patents were done. Nowadays you can't say that, because you are going to make money for a private company, BTG, so you have lost that argument with young people. Now in defence of BTG, and I jump to their defence now, when the whole thing became big financially, all the manufacturers were saying, 'Shucks to you' to BTG: they were paying nothing. BTG had the size and the strength to take International

General Electric to court and I am told they spent £1.2 million on the legal case[155] and they won and eventually all the companies had to sign up to pay royalties themselves. So, again, this business of the Government saying to the universities do the patenting yourself, it's a waste of time, because if the crunch really comes, a university could not take IGE to court and spend £1.2 million.

Isherwood: This is a trivial question, but it has something to do with twentieth-century history. Can I ask John Mallard, is it correct that the term spin-warp was used entirely because Jim is a fan of Star Trek [laughter]?

Mallard: No, I don't think it's true.

Steiner: Ladies and gentlemen, it's six o'clock and we have to stop the discussion. First, I want to thank all of you for coming this afternoon and participating in this rather unusual, exciting and very interesting meeting. It is all due to Chris Booth, who together with his colleagues, organized it, they certainly gave us a great time! Thank you Chris and your colleagues once again, so let me hand over to you.

Booth: Robert, I don't think it's really me you should thank, I merely represent the Group, but thank you for your very kind remarks. I would like very much to join him in thanking you all for your contributions which have really been quite remarkable. A most engaging day we've had and also to thank Robert Steiner, for putting himself on the line, and taking on board what has been at times quite a difficult discussion.

[155] Some of these legal, financial and industrial relationships are described in Blume, op.cit. note 26 above, *passim*.

GLOSSARY*

Chemical shift – Difference in resonant frequency between similar nuclear species bound to different chemical sites in a molecule. Provides information relating to chemical structure. Measured in parts per million (ppm) relative to some standard absorption line.

Coil – Single or multiple loops of wire designed either to produce a **magnetic field** from a current flowing through the wire, or to detect a changing **magnetic field** by a voltage induced in the wire.

Computerized tomography (**CT**) – A technique which revolutionized medical imaging in the 1970s, bringing new insights into the anatomic basis and natural history of many diseases.

Computer of average transients (**CAT**) – A signal averaging device.

dB/dt – Time varying **magnetic field**.

DEFT – Driven equilibrium **Fourier transform**.

Echo-planar imaging (**EPI**) – A high-speed snap-shot imaging technique, characterized by an oscillating readout gradient generating a train of **spin echoes,** encoded along a second gradient axis using either a steady encoding gradient or a sequence of short blips.

Echo time (**TE**) – The time in milliseconds between application of the 90° pulse and echo signal in a **spin-echo** pulse sequence.

Electron paramagnetic resonance (**EPR**) – Sometimes referred to as **electron spin resonance** (**ESR**).

Electron spin resonance (**ESR**) – The resonance phenomena associated with unpaired electrons, for example in ion radicals. It was discovered by the Russian scientist Zavoyskii in 1944. The first commercial spectrometers were produced by Varian Associates in the late 1950s.

Fourier transform (**FT**) – Mathematical technique developed by the French mathematician Jean-Baptiste Fourier (1768–1830) for sorting out frequencies present in a complex waveform. In NMR, Fourier transform of the **FID** yields the absorption spectrum.

Free induction decay (**FID**) – Signal from a magnetically polarized sample following a short **RF** pulse.

Frequency – The number of cycles per second of the electromagnetic radiation. The units are cps or **Hertz** (**Hz**).

Gauss (**G**) – The **magnetic field** of an **MR** scanner is measured in units called **Tesla** (**T**). An *older* unit of measurement, **Gauss** (**G**) is sometimes also used, with **1 T**=10^4 **G**. One gauss is the measured field strength at 1 cm from a straight wire carrying a current of 5 amp.

Gigahertz (**GHz**) – Unit of **frequency** measurement, equal to 10^9 **Hz**.

Gradient – In **NMR** imaging, **magnetic field** gradients are required to provide a distribution of Larmor frequencies over the sample, thereby rendering the signal spatially dependent. Measured for example in **Tesla** per metre (Tm^{-1}).

Gradient coils – Small electromagnets that produce **magnetic field gradients**. These are switched on and off throughout the scan to change the phase and **frequency** of resonating nuclei within the subject.

Hertz – Unit of **frequency** measurement, same as cycle/second (1 **kHz**=10^3 **Hz**, 1 **MHz**=10^6 **Hz**, 1 **GHz**=10^9 **Hz**).

Inversion recovery (**IR**) – Pulse **MRI** technique which begins by inverting the magnetization with a 180° pulse and then, after a time **TI** (**inversion time**), measures the T_1-controlled recovery of the magnetization to equilibrium. This sequence provides an image with twice the **T_1-weighting** discrimination of a **spin echo** sequence with short repetition time and short **echo time**, but at the expense of a longer imaging time.

Kilohertz (**kHz**) – Unit of **frequency** measurement; equal to 10^3 **Hz**.

Low-field – A **magnetic field** from 0.26 **Tesla** to 0.5 **Tesla**.

* We are very grateful to Wilfred Baldeo for his considerable help in compiling this glossary.

Magnetic field – The region of magnetic forces (attraction or repulsion) around a magnet: the stronger the field the stronger the forces.

Magnetic moment – A property possessed by some nuclei as a consequence of their inherent spin and charge.

Magnetic resonance (MR) – Absorption spectroscopy involving transitions between the energy levels corresponding to the different orientations of an (electron or nuclear) **magnetic moment** in a **magnetic field**. See **nuclear magnetic resonance (NMR)**, **magnetic resonance imaging (MRI)**.

Megahertz (MHz) – Unit of **frequency** measurement; equal to 10^6 **Hz**.

NRPB – National Radiological Protection Board set up by the Radiological Protection Act in 1970 as an independent statutory body.

Nuclear magnetic resonance (NMR) imaging (or MRI) – The absorption or emission of electromagnetic energy by nuclei in a static **magnetic field**, after excitation by a suitable **RF magnetic field**. The peak **resonance frequency** is proportional to the applied **magnetic field**.

Planar imaging – Class of **NMR** imaging methods in which information is gathered from spins in the whole of a selected plane simultaneously.

Probe – Collective name for the **RF coils** (and sometimes **gradient coils**) of an **NMR** spectrometer or imaging system.

Quench see **superconducting magnets**.

Radiofrequency (RF) – That part of the electromagnetic spectrum associated with transmission of radio waves. More specifically, electromagnetic radiation in the approximate wavelength band 10^{-1} metres and beyond. (Corresponding frequency band is $\approx 10^9$–10^4 **Hz**). **Resonance frequencies** required in **NMR** experiments fall in this region.

Relaxation – The process by which an atom or molecule in an excited state falls back into its ground state.

Relaxation time – Characteristic **NMR** parameters, of which most frequently mentioned are $\mathbf{T}_1$, $\mathbf{T}_2$. $\mathbf{T}_1$ (**spin-lattice**) is a measure of the time required for the spin system to return to thermal equilibrium with its surroundings (lattice) following perturbation (for example by an **RF** pulse). $\mathbf{T}_2$ (**spin–spin**) is a measure of the decay time of the transverse component of magnetization. $\mathbf{T}_2$ relaxation contributes to the decay of the **NMR** signal (**FID**). The magnitude of $\mathbf{T}_2$ depends on magnetic interactions between nuclear spins.

Resistive magnet – A magnet that uses normal non-**superconducting** material such as copper or aluminium in its coils. The heat generated by the current in the coils has to be removed, usually by circulating water.

Resonance – Response of physical systems to stimulation by vibrations of specific **frequency**. In **NMR**, vibrations are provided by **RF** waves, which interact strongly with the nuclear spin system.

Saturation – Situation in which the rates of upward and downward energy-level transitions induced by radiation are equal so that no net energy is absorbed from the radiation.

Scalar coupling – A coupling interaction which does not depend on direction. In the case of **NMR spectra** it is usually a magnetic interaction transmitted through the electrons of chemical bonds which is unaffected by the tumbling of the molecules in a liquid. It contrasts with dipolar coupling, a magnetic interaction transmitted through space between magnetic nuclei which may be in the same molecule or in different molecules; dipolar coupling is averaged to zero by random molecular motion occurring at a high enough frequency.

Shim coil – Small electromagnets that are activated to correct for irregularities in the main **magnetic field**.

Shimming – The optimization of **magnetic field** homogeneity in an **NMR** spectrometer by adjusting currents through the **shim coils**.

Signal-to-noise ratio – The ratio between the amplitude of the recorded signal and background noise, which distorts that signal. The signal-to-noise ratio (and hence image quality) may be improved by taking more averages of the signal, by using longer sampling times, and by sampling larger volumes.

Spectrum – The display of absorption peaks that are plotted as a function of their resonant **frequency**.

Spin – The intrinsic property of an electron or nucleus which determines the **magnetic moment**, described classically as a rotation of the nucleus about its axis.

Spin echo – A phenomenon brought about by the action of a 90° RF pulse followed by another 90° or 180° RF pulse characterized in that the **free induction decay** (**FID**) signal process is reversed to produce signal growth reminiscent of the echo signal or target return signal seen in early radar equipment which follows an initial transient **RF** pulse.

Spin multiplet(s) – Nuclear resonances with a particular **chemical shift** which are split into a number of **multiplets** by **scalar coupling** to other nuclei in the same molecule. This coupling is often loosely referred to as **spin–spin coupling**.

Spin–spin coupling – In **NMR** spectroscopy this refers to magnetic coupling between nuclear spins; it is usually used loosely to refer to **scalar coupling** between spins in the same molecule which give rise to **spin multiplets**.

Spin-warp imaging – A position-dependent phase twist (or 'warp') is applied on the magnetization, achieved by incrementally stepping the amplitude of a phase-encoding gradient prior to signal read out.

Steady-state free precession (**SSFP or SFP**) – Method of **NMR** excitation in which strings of **RF** pulses are applied regularly and rapidly, with interpulse spacings short as compared with $\mathbf{T}_1$ and $\mathbf{T}_2$.

Superconducting magnet – A solenoid, with no iron core, wound from a special conductor, which below a certain temperature has zero electrical resistance. **Superconducting magnets** are used in **NMR** spectrometers to generate high field strengths. Solenoid magnets are immersed in liquid helium at 4K at which temperature the niobium alloy windings lose all electrical resistance and become **superconducting**'. The established **magnetic field** is maintained as long as it is kept unperturbed and fed with liquid helium and liquid nitrogen. Disturbance can cause the windings to become 'resistive' again where upon the stored electrical energy is transferred thermally to the surrounding bath of liquid helium, which then evaporates rapidly in what is called a 'magnet **quench**'.

$\mathbf{T}_1$ – Spin-lattice or longitudinal relaxation time.

$\mathbf{T}_1$-weighted image – An image generated by a pulse sequence that does not allow the magnetization of the tissues of interest to attain their equilibrium values. Contrast in the image is determined by the differential $\mathbf{T}_1$ values of the tissues, with short $\mathbf{T}_1$ tissues, such as fat, appearing bright.

$\mathbf{T}_2$ – **Spin–spin** or transverse relaxation time.

$\mathbf{T}_2$-weighted image – An image generated by a pulse sequence with a long **TR** and long **echo time TE**, so that only those tissues with a sufficiently long $\mathbf{T}_2$ value will still have any remaining transverse magnetization to contribute to the **spin-echo** signal. When the **TE** value is extended beyond 100 msec, the image obtained is referred to as a heavily . This type of image gives improved demonstration of brain lesions, tumour, and oedema, because of their longer $\mathbf{T}_2$ values relative to normal brain.

Tesla (**T**) – Unit of **magnetic field** strength named after the American Engineer Nikola Tesla (1856–1943). 1 **Tesla** = 10^4 **gauss**.

RESEARCH IN GENERAL PRACTICE

The transcript of a Witness Seminar held at the Wellcome Institute for the History of Medicine, London, on 11 February 1997

Edited by L A Reynolds and E M Tansey

Several topics were discussed during the Seminar, chaired by Dr Ian Tait. These included the emergence of research within general practice, both epidemiological studies by general practitioners, and research by practitioners, sociologists and others into the nature of general practice and the doctor–patient relationship. Research in single-practitioner, single practices and multipractice units was discussed, as were the creation and development of the Royal College of General Practitioners, especially the work of its Research Committee and Research Units, and the beginning of University departments of General Practice. The impact of the MRC treatment trial of mild hypertension on general practice research, and the development of the General Practice Research Framework were also considered.

RESEARCH IN GENERAL PRACTICE

Participants

Sir Christopher Booth
Dr Ann Cartwright
Dr Donald Crombie
Professor Sir Michael Drury
Professor Paul Freeling
Professor David Hannay
Dr Julian Tudor Hart
Dr Keith Hodgkin
Dr John Horder
Professor Margot Jefferys
Dr Clifford Kay
Dr Stephen Lock
Dr Irvine Loudon
Professor Marshall Marinker
Professor Thomas Meade
Professor David Metcalfe
Dr Bill Miall
Professor David Morrell
Professor Sir Stanley Peart
Dr Mark Perry
Dr Ian Tait (Chair)
Dr David Tyrrell
Dr W O Williams

Others present at the meeting and apologies: Dr John Ford, Dr Wilfred G Harding, Dr Brian Hurwitz, Professor Anne-Louise Kinmonth, Mrs Joan Mant, Dr Andrew Morrice, Dr Paul Thompson, Professor Nick Bosanquet, Mr Pat Brennan, Dr John Eversley, Professor Godfrey Fowler, Professor D Pereira Gray, Dr Paul Hodgkin, Dr Edgar Hope-Simpson, Professor John Howie, Professor Brian Jarman,. Mr John Kendall, Dr Ekke Kuenssberg, Professor D C A Mant, Dr Geoffrey Marsh, Dr Ian McWhinney, Dr Nigel Oswald, Professor Stuart Pocock, Professor Ian Richardson, Professor Martin Roland, Dr Chris Salisbury, Professor Nigel Stott, Dr Margaret Thorogood, Dr Madge Vickers, Dr C A H Watts, Professor David Wilkin.

Dr Ian Tait:[1] Welcome to this seminar on research in general practice. I may have my anxieties about handling the contents of this seminar, but no anxieties at all about the quality of our witnesses. The success of these Witness Seminars is entirely dependent on the quality of the witnesses. So thank you very much for being here and for responding so generously to our invitation.

A Witness Seminar is in essence, a form of oral history. It gathers together people who have been involved in interesting endeavours in the history of medicine in the twentieth century and records the proceedings. We are not expecting to reach any tidy answers or conclusions at the end of the afternoon. We want the raw material on which other people will be able to work, so the recording of our proceedings is all important.

We are all equal witnesses, the proceedings will be extremely informal and it is important that we hear what it was really like for you, your feelings about it all, as well as the facts. The view from the kitchen rather than the drawing room, as it were. So far as the organization of the afternoon is concerned, there will be opening speakers for each subject, who will set our discussion going. Free discussion between participants is encouraged; interruptions are allowable.

The area of interest must be confined to your own experience, namely the second half of the twentieth century. In the first half, research in medicine was dominated by the hospital and the laboratory. Very little happened outside it. There were prophetic voices, like Sir James Mackenzie,[2] who recognized the tremendous importance and potential for research in general practice, but general practice was not really ready for him. Nearly all general practitioners were engulfed in their day-to-day practice, and they simply didn't think that research was

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[1] Dr Ian Tait FRCGP (b. 1926) was in general practice in Aldeburgh, Suffolk from 1959 to 1990 and active in the development of vocational training for general practice. His MD thesis (1975) on the development and function of medical history taking in clinical practice stimulated his interest in the history of medicine, which he has continued since his retirement. He is a member of the History of Twentieth Century Medicine Group at the Wellcome Institute for the History of Medicine. See Tait I, Graham-Jones S. (1998) General practice: its patients, and the public. In Loudon I, Horder J, Webster C. (eds) *General Practice under the National Health Service, 1948–1997*. London: Clarendon Press.

[2] Sir James Mackenzie FRCP, FRS (1853–1925) was in general practice in Burnley from 1879 to 1907 before moving to London. He became Physician to the West End Hospital for Nervous Diseases and was appointed lecturer in cardiac research to the London Hospital in 1911. He opened the St Andrews Institute for Clinical Research in October 1919 to study the beginnings of disease. See Mair A. (1973) *Sir James Mackenzie, MD 1853–1925, General Practitioner.* Edinburgh: Churchill Livingstone. See note 68 below on St Andrews Institute.

something that they were supposed to do. There were, of course, splendid exceptions and we all remember William Pickles of Aysgarth and Wensleydale. He published his *Epidemiology in Country Practice* in 1939.[3] It was such an exceptional event that he became an international figure. Christopher Booth, who grew up in that practice, remembers that the most popular doctor was not actually Will Pickles but his partner, who was more often there. It raises the issue of the tension between patient care and research which must be close to the thoughts of many of you.

No discipline can make a claim to an intellectual territory of its own without also doing research into it. This thought was very much in the minds of the remarkable group of doctors who served on the Foundation Council of the College of General Practice when it was formed in 1952. One of the first things that the Council did was to create a research committee. It was rather an extraordinary committee. It had five general practitioners, all of whom had their MDs! Not only did they start this research committee, but they advocated that every one of the 22 faculties of the College, that were spread throughout the British Isles, should have a research subcommittee. These were extremely ambitious plans and many people thought them unrealistic. Unrealistic or not, they were a clear demonstration of the determination of the College to reintroduce into general practice a culture of research, and that must be where our story begins today.

I would like to take our first two subjects together, because they overlap so much – that is the Research Committee of the Royal College of General Practitioners in the early years, and second, research undertaken by individual general practitioners. John Horder will lead us into the first, and Donald Crombie will look at some of the individuals who were doing research in general practice at that time. So let us start. May I ask John Horder to kick off for us.

Dr John Horder:[4] The first thing I want to say is how lovely it is to see here so many people I have worked with. I think I have actually worked closely with more than half the people in the room. But, if you know me, you'll wonder why I am here, realizing that I haven't done much research work or indeed been much involved in the research side of the College. For that reason I am going to ask Donald Crombie, who's been very much more involved, to help me with my subject. Nevertheless, I was involved in it relatively early, so I want to start from

[3] Dr William Pickles (1885–1969) was the first President of the College of General Practitioners from 1953 to 1956. See Pickles W N. (1939) *Epidemiology in Country Practice*. Bristol: John Wright and Sons Ltd. Republished by the Royal College of General Practitioners in 1972 and 1984.

[4] Dr John Horder FRCP, FRCPE, FRCGP, FRCPsych (b. 1919) was in general practice in Camden Town, London, from 1951 to 1981. He was Assistant Secretary to the Research Committee at the College of General Practitioners from 1954 to 1956 and its President from 1979 to 1982. He was the first Chairman of the National Centre for the Advancement of Interprofessional Education in 1987, now its President.

what was called the Steering Committee – in 1952. I have been collecting documents for 50 years, so here is a copy of the Steering Committee's report.[5] It must be quite a rare document now. There's one paragraph I'd like to read. It's the first one about research:

> 'From many letters which have been received by the Steering Committee and from publications and correspondence which have appeared in the medical journals, it is clear that there is a reawakening of interest in research work by doctors in general practice and in the possibilities of applying modern principles of scientific investigation into the problems of general practitioners. That important advances in medical knowledge can be made by general practitioners has been demonstrated beyond doubt by men such as Jenner, Withering, Thracker, Budd, Mackenzie, Pickles. [And, being a Londoner, I would add Parkinson.]
>
> 'But much of the field in which these men carried out their exploratory work still remains uncultivated since a great proportion of the conditions met by family doctors never reaches the hospitals in which present day medical research tends to be concentrated.'

After the first sentence there was a reference to two documents. When I looked them up, I was amazed to find that one of them was written by me. I had completely forgotten that I had written something in the *London Hospital Gazette* in 1952.[6]

In what I wrote in that journal (which used to have a lovely cover by Rex Whistler, but has died long since) there was a bit about research which could be relevant this afternoon – about why so little research had been done by general practitioners in the past. There seemed to me at that time to be three reasons. One was that common problems were simply not recognized as needing research, just as we did not recognize the need to educate people about common problems. It all had to be about complicated problems because that was what we had known in our training. The second reason was that general practice did not attract many research-minded people. The third was that they were relatively isolated, much more so, of course, at that time. I did say at that point that this was something soon to be corrected, because I must have known then that the College was about to start. That was in 1952.

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[5] College of General Practitioners, General Practice Steering Committee. (1952) A College of General Practitioners. *British Medical Journal* **ii**: 1321–1328. The text also appeared as a supplement to *The Practitioner* in January 1953.

[6] Horder J. (1952) The opinions of Sir James Mackenzie. *The London Hospital Gazette* **55**: 138–142.

My own involvement in the Research Committee was very brief – it was from October 1954 until 1956, when I was appointed as Medical Secretary, to help John Hunt who had been the main person to have founded the College.[7]

I think the reason that I was asked to join the Research Committee – although Donald will know better – was because my wife and I had done a survey of morbidity in our practice which had included a diagram relating the illnesses looked after by patients themselves, the illnesses seen by general practitioners and the illnesses seen in hospitals.[8] Later that bit of work was picked up by Professor Kerr White in America and developed in a far more systematic way, because he was a proper epidemiologist. It appeared again in the *Bulletin of the New York Academy of Medicine* last August.[9] When we did that very amateur morbidity survey, we of course imagined that we were doing it for the first time, but nothing is totally new. We had in fact got most of our ideas from the Wartime Social Survey,[10] a remarkable bit of work which had involved visiting a large number of homes and enquiring about illnesses, however minor. That was what we also did. But little did I know that Arthur Watts had done the same thing in 1948; Dr McGregor, in Scotland, had done it in 1950; and John Fry in 1951.[11] I have just heard, from Donald Crombie, that Robin Pinsent had done it in 1949.[12] So it is rather important to find out what has gone on already, before imagining that one has had a unique idea.

My memory of the Research Committee by that time consisted of Robin Pinsent as Chairman,[13] Donald Crombie as Secretary, Ian Watson as Vice chairman, myself as Assistant Secretary, A R Laurence, Arthur Watts (who is now

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[7] Dr John Hunt FRCP, FRCS, FRCGP (Lord Hunt of Fawley from 1973) (1905–1987), was in general practice in Sloane Street, London, from 1937 to 1979. He was a founder of the College of General Practitioners in November 1952, serving as Honorary Secretary of the College for 15 years from 1952 and as its President from 1967 to 1970.

[8] Horder J, Horder E. (1954) Illness in general practice. *Practitioner* **173**: 177–187.

[9] White Kerr L, Williams T F, Greenberg B G. (1961) The ecology of medical care. *New England Journal of Medicine* **265**: 885–892. Classic paper reprinted in the *Bulletin of the New York Academy of Medicine* 1996 **73**: 187–205, with discussion 206–212.

[10] Logan W P D, Brooke Eileen M. (1957) *The Survey of Sickness 1943 to 1952*. London: HMSO. The Ministry of Information directed the Wartime Social Survey, enquiring on various topics among a sample of the general population, quarterly from 1941. The health question wanted by the General Register Office for their morbidity index was included from February 1945 until March 1952, covered those aged 16 and over, and asked about any illness or ailment during the previous three months. Scotland was excluded from the sample.

[11] See Watts C A H, Watts B M. (1952) *Psychiatry in General Practice*. London: J & A Churchill. McGregor R M. (1950) Work of a family doctor. *Edinburgh Medical Journal* **57**: 433–453. Fry J. (1952) A year of general practice: a study in morbidity. *British Medical Journal* **ii**: 249–252.

[12] Pinsent R J F H. (1950) The future of general practice. *Lancet* **i**: 917–918.

[13] Dr Robert [Robin] Pinsent FRCGP (d. 1987) was in general practice partnership with Laurie Pike in Birmingham from 1946. He was a member of the Steering Committee which formed the College of General Practitioners in 1952 and a member of the Foundation Council as well as the College's research adviser until his retirement in 1978. He was a central figure in the College's research leading to the three national morbidity studies and the *Research Newsletter*; and was joint founder with Donald Crombie of the College's Birmingham Research Unit in 1961.

90) and R M S McConaghey, who started the *Research Newsletter* (of which I have the first five numbers in this envelope) which later developed into the College *Journal*.[14] We met at the Imperial Hotel in Russell Square, London – a building with a remarkably ornate façade which has now been replaced. There was a constant flow of letters between four or five or us, virtually everyday, most of it in the blue typescript of Mrs Rawlinson, Robin Pinsent's amazing secretary. That literature piled up as typed copies in Pinsent's house and later formed the first contribution to the College archives. Vast numbers of big brown envelopes were gradually cleared out of his house.

Robin himself was a visionary. He was a practitioner right in the middle of Birmingham with a difficult district and a population which changed rapidly and became increasingly difficult. He was an enthusiast and an incredible worker. He wrote one of the earliest text books of general practice, now forgotten but there is a copy in the College library.[15] I had a great admiration for him and think now that his contribution has been underestimated.

During the time I was so briefly involved, the *Newsletter*s show that our concerns were with the first collective College study, which was about the complications of measles, with setting up the epidemic observation unit and with what we used to call 'A survey of the nation's health'.[16] This was in fact the beginning of the first national morbidity survey. I am sure Donald [Crombie] will say something about that, because it was his particular baby, with Dr Logan in the Registrar General's Office.[17] There were some study groups, of which I remember one, run by John Fry, about chest diseases. John Fry seemed to move in and out of the committee, but he was always an important figure because of the research he was doing in his own practice.[18]

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[14] The *Research Newsletter* originally appeared as an occasional supplement to *The Practitioner* from January 1953, and was published by the College from October 1954 to February 1958 when it became the *Journal of the College of General Practitioners* (*Royal College* from May 1967). A less formal circular, *Between Ourselves*, took the *Newsletter*'s place. See Buckley E G. (1990) New decade: new title. *British Journal of General Practice* **40**: 1.

[15] Pinsent R J F H. (1953) *An Approach to General Practice*. Edinburgh: E & S Livingstone Ltd.

[16] College of General Practitioners, Study Group. (1956) The complications of measles. Pt. I. Supplement to *Research Newsletter* No. 11. New Series **3**. *idem* (1957) The complications of measles. Pt. II. *Research Newsletter* **4**: 51-68.

[17] Dr William Philip Dowie Logan FRCP (b. 1914) was in general practice in Barking, Essex, for a year before moving to the General Register Office in 1948. He was Chief Medical Statistician from 1951 until 1960. He also advised the Ministry of Health on statistics, was Head of the WHO Centre for Classification of Diseases and a member of the WHO panel on health statistics. From 1961 to 1974 he was Director of the Division of Health Statistics at the World Health Organization.

[18] Dr John Fry FRCS, FRCGP (1922–1994) was in general practice in Beckenham, Kent, from 1947 to 1991, single-handed to 1960. He was a founder member of the Royal College of General Practitioners and a member of its council for over 30 years. He helped set up the *Journal of Postgraduate General Practice – Update* in 1968; was a consultant in general practice to the British Army from 1968 to 1987; and a member of several committees of the Medical Research Council.

I left that job as Assistant Secretary, as I have said, to become Medical Secretary of the College, but that was for me a disastrous appointment and I became ill. On recovery I became the College Archivist and became the recipient of Robin Pinsent's brown envelopes. That is where I will break off, hoping that Donald will fill in the story.

Dr Donald Crombie:[19] The trouble is I think my difficulty is that I could go on until midnight and have to ration myself, so I have stuck to the title, single practice research.

Tait: We will have a chance to come back to multiple practice research. You'll have to come in again.

Crombie: Since we are reminiscing, starting with Mackenzie, I've actually shared a patient with Mackenzie. I had a patient who was his patient, who had a primary complex when she was 12 and she became my patient when she was 92, so I have this link!

We've talked about research, but I like to term my work as 'organized curiosity', I think that really gets closer to what we are all engaged in. It was actually first used by Matthew Arnold, who was a literary critic and not in medicine at all or in science. And I'd like to start too by paying a tribute to the late John Fry. I could say all sorts of things about Robin Pinsent too, but John [Horder] has covered a lot of the very early ground there. I think John [Fry] was the foremost exponent of the possibilities of organized curiosity by one practitioner in his own practice with his own patients and that's a fairly restrictive format that. I place him with William Withering – you go back 200 years for William, who had an influence outside medicine in that he was probably the real centre of the Lunar Society which was the intellectual powerhouse for the industrial revolution.[20] He wasn't strictly a general practitioner, but I have another contact there in that my old practice, which is over 100 years old, actually is in the geographic centre of where Withering had his practice and his old house, which is now a golf club house, is about 400 yards from where I live. So I have these two personal contacts with the past.

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[19] Dr Donald L Crombie (b. 1922) was in general practice in Birmingham from 1946 to 1992. With Robin Pinsent, he established the first RCGP research unit, the Records and Statistics Unit, which was supported and housed by the Birmingham Regional Hospital Board. This later became the Research Advisory Service when Crombie's practice built new premises, with Crombie as director. See College of General Practitioners. (1963) The Records and Statistics Unit: Research Committee of Council. *Journal of the College of General Practitioners* **6**: 204–216.

[20] See for example, Aronson J K. (1985) *An Account of the Foxglove and its Medical Uses 1785–1985*. London: Oxford University Press. Schofield R E. (1963) *The Lunar Society of Birmingham*. London: Oxford University Press.

The central problem for single general practice research is that there isn't very much of it whatever we say. I could suggest, however, that we do something about this, but probably that had better come out in discussion. Let me just go into the problems, and I think the main restriction can be summed up in numbers, as can the main mitigating factor, which is time. The one thing we have is time and plenty of it, and in a population of 2000 patients, even 10 000 if you have a group practice, events have to occur frequently enough to support rigorously argued conclusions and the numbers problem in any case is compounded by increased population mobility. These are the basic things that get in the way of the single-handed chap. Luckily, we've a long working life and that does compensate for a lot of things. Also, as John [Horder] was pointing out, general practice flows over into so many other categories – sociology, biochemistry and so on – so it's a team. Most research has to be a team or involve a larger number of general practitioners. There are subjects that are open to research that escape these nets of numbers and time. There are the less serious problems which also occur frequently, and I have mentioned John Fry but he also of course included things like chronic bronchitis, which in themselves are some of the more serious things that afflict us. There are the studies of explosive situations, such as epidemics, when the unexpected are never recorded. I think the study of Bornholm disease by WO Williams (who's here today), who got himself called Bornholm Williams, is a classic.[21] For success in this sort of situation, because I think this is also crucial, you have to have a mind that's already prepared to discern and then exploit such a situation, a mind already equipped with the basic recording and data-processing skills. I think this is perhaps where we have a weakness in the way we approach the whole problem of the individual general practitioner.

The other area that is open to us is the search for previously unsuspected links between less common serious morbidity, but also serious morbidity, and familial and other possible causal relationships and I think it is in this category that we have the greatest opportunities for the future. Once again I am coming back to South Wales and I highlight the multiple and interrelated studies done by Julian Tudor Hart in his practice in, it sounds a paradox but it's rural industrial Wales, over a working lifetime, as probably our best example. There's also somebody else, like some of the names that John [Horder] mentioned that have been forgotten. Maurice Stone who, working on the aetiology of coronary atheroma and almost

[21] Bornholm disease, also known as epidemic myalgia or 'devil's grippe', is an acute infective disease due to Coxsackie group B viruses. It was named after the island of Bornholm in the Baltic where several epidemics were described by Dr Ejnar Sylvest. See Sylvest E. (1933) *Den Bornholmske Syge: Myalgia epidemica*. København: Levin and Munksgaards Forlag. W N Pickles referred to Sylvest' work (op. cit. note 3, 93–96) as well as describing the first outbreak in Britain in the College's 1954 *Annual Report*. See also Williams W O. (1958) A clinical and epidemiological study of Bornholm disease. MD thesis, Welsh National School of Medicine (now University of Wales College of Medicine), June 1958.

got there but died young.[22] His work wasn't abandoned, it was picked up by the MRC in a much more extended fashion. I think his was a great loss.

I have been concerned so far with the natural history of disease and there's all the more recent influence, I know this isn't going back very far, but some of the people in this room have been concerned with it, that's the influence of the personalities and socioeconomic background of patients on the incidence of complaints, if not actual clinical problems. And we could have a go at that for the rest of the afternoon. I just personally think that this field's been muddied a bit by the primary emphasis on the combined effects of personalities and socioeconomic factors rather than their possible separate association with clinical problems. There's also the ways for improving quality of doctor–patient communication, doctor empathy with the patient, and patient satisfaction as well as understanding. Well, horses for courses. What sort of general practitioner do we want? These are all areas where the seeds were there even 50 years ago and they have taken an awful long time to show themselves above the surface and we are really into modern times then. There was also one non-British practitioner I would mention and that's Robert Braun of Lower Austria.[23] Like myself, his interest began in the 1950s with the obvious enormous range of inter-doctor variability, but particularly in their basic perception of illness and therefore also formal diagnosis. This was quantitatively obvious in the results of the first national morbidity survey in 1954[24] and he [Robert Braun] came across to this country, stayed with Robin Pinsent and I, and spent quite a lot of time delving into that first big study involving a large number of doctors. His [Braun's] reaction at the time and through his whole lifetime since then to diagnostic variability, took the form of evolving standardized definitions for all the problems and his work, based entirely on a lifetime's experience in a remote country practice is almost unknown in this country, but it has had an enormous influence on academic primary care thinking in France in the last decade and his approach is paralleled in this country, not in research, but by our own Royal College of General Practitioners' approach to clinical auditing. The philosophy of both approaches is based on a search for an idealistic best-buy. In the case of auditing, this is hopefully a benchmark for highest quality.

We could talk about that as a problem rather than as an obvious research area, but I mention him because it is not only in this country that this thinking has gone on. One has to say, since we are making the point, that Canada produced some

[22] Dr Maurice Stone (d. 1988) was in general practice in Leigh, Lancashire. The Leigh Clinical Unit was incorporated as a College research unit in 1978. He was one of the first to identify fibrinogen as a major risk factor of ischaemic heart disease. See Stone M C, Thorp J M. (1985) Plasma fibrinogen – a major coronary risk factor. *Journal of the Royal College of General Practitioners* **35**: 565–569.

[23] See Braun Robert N. (1957) *Die gezielte Diagnostik in der Praxis.* Stuttgart: Friedrich Karl Schattauer Verlag.

[24] First National Morbidity Survey (1954–56). See General Register Office. (1958–1962) *Morbidity Statistics from General Practice,* 3 vols, Studies on Medical and Population Subjects no. 14. London: HMSO.

early thinking, and America very little from what we would call general practice, and I personally think that we have only scratched the surface of this whole area. To me the most central feature here is the variability of general practitioners in everything they do, but particularly in their perception of illness, because this perception of illness lies at the primary centre of any kind of logical model of clinical management. The point I am really making through all this is that as we move down the list of research areas, unique to primary care and only approachable from general practice, we move ever further away from the participation of individuals working on their own in their own practice and involving only their own patients. On the other hand, their involvement is mandatory. I could give you two lists. I have got various lists of ways of approaching this and what I think we should be doing about it. It will come out in discussion if we are interested in it, but I think this is the place where the College of General Practitioners itself should be central and it still isn't. I mean central in the way that the College has been central to undergraduate education and to auditing. There is this need for a central research advisory contribution and it will come out in discussion if there is an interest in it.

Perhaps I will end where I began, because if you go back to Robin Pinsent, Clifford Kay, who is here too, and a large number of people present here all started with some primary study of their own in their practice related to a problem which was their own individual problem. My own was an MD thesis along the lines of Clifford Kay's. It was the interface between primary care and general practice in the very early 1950s. And yet, very rapidly, we all moved into something else. We have all got involved in studies involving much larger numbers of general practitioners and so on. The very earliest studies, very interestingly, in themselves exhausted a field. They were practically all studies of morbidity in general practice, which when you knew nothing, saying what there was in one practice covered an enormous field and was worth saying. But in a very short time, by the time of the first national morbidity survey, that sort of possibility was, if not exhausted, had certainly been covered in the way that individual practitioners were going to contribute.

So may I end on that point? I know it sounds pessimistic, but I do believe if the College was used in the way it is used for educational purposes, as a clearing house, as a place where they could provide an interface, that prepared general practitioners in the way that they have to be prepared to be able to tackle problems when they appear, to organize peer groups about individual interest areas, to do what is only done at the moment by research clubs and little research groups, which is done by university departments, but university departments tend to be concerned with local problems, to have perhaps one big centre of interest, rather than the multiplicity and also to be interested only in those general practitioners, quite rightly, which are in their own environment. So, ending on that point, but

without going into some of the greater detail, as a partial solution to the problem of the single-handed general practitioner.

Tait: Thank you, Donald, very much. Well the subject is now open. Perhaps it would be useful to look back at that period when the Research Committee of the Council [of the College of General Practitioners] was encouraging various kinds of research. Often those were morbidity studies by individuals, and I wondered if some of the people who were carrying out that kind of research could comment.

Dr Keith Hodgkin:[25] One of the reasons why we found research in general practice so hard, was that we were trained in hospital that a good clinician's diagnosis is always correct. We were encouraged to delay making any diagnosis until *after* we had received the results of our special investigations. If the student or general practitioner wishes to learn about his own 'diagnostic process' he/she must record the *suspected* diagnoses which have caused him to ask for a special investigation or consultant's opinion. Analysis of the record later then shows when and how the GPs thinking must be amended. Thus with my partner Aubrey Colling (whose idea it was) we started recording *suspected* as well as *certain* diagnoses. It was a simple process – one or two question marks against a diagnosis of anaemia showed why and when we had ordered a blood test or chest X-ray. Thus when we analysed our 20 cases of cerebral tumour we found that for the first weeks of care we had diagnosed every single case as being due to a tension state. We had delayed even considering the correct diagnosis for six to eight weeks. Such analysis of suspected diagnoses demonstrated clearly that we would learn more from analysing our mistakes and uncertainties than from counting our successes. In a similar way we learnt that the release of pressure over an inflamed appendix was a better indicator of acute inflammation than that of direct pressure.

I think perhaps we are still too reluctant to improve our diagnosis in general practice by analysing our mistakes and dilemmas. This applies especially to large epidemiological surveys where outside criteria are often imposed on the GPs who collect the index cases.

Dr Julian Tudor Hart:[26] I would like to say something about what you asked for, Ian – what was it like? what data was the GP recording? It was horrible, because

[25] Dr Keith Hodgkin (b. 1918) was in general practice in Redcar from 1949 to 1973. He was Professor and Chairman of Family Practice at the Memorial University of Newfoundland, Canada, from 1973 to 1979.

[26] Dr Julian Tudor Hart (b. 1927) was in general practice in Glyncorrwg in the Afan Valley in South Wales from 1961 to 1988. See Mullan F. (1995) Interview with Julian Tudor Hart, February 1995. Primary Care Oral History Project, 1995–1998. Modern Manuscripts Collection, National Library of Medicine, Bethesda, MD. Dr Tudor Hart's practice records or microfiches of the records where

you were given these multi-centre procrustean beds and you'd got to fit these real people with real problems into the beds you'd been offered. They weren't completely procrustean, because you were allowed I think to say that the patient had got up to, perhaps, five problems. Practically all my patients really had more than one problem, so I had to interpret what do the directors of this research really want us to say, what are they after? I rationed myself to giving most people only one problem (which they didn't have, they had three or four), one problem which I was prepared to deal with in the seven or eight minutes perhaps that I had available. Even then, I realized that I was scoring many people with two or three independent problems, that I was becoming idiosyncratic, appearing way off the map in aggregates of all the participating practices. This was indeed the case and I think my observations were dismissed accordingly. But believe me even this didn't in any way reflect the real complexity of the problems my patients had. I think the problem was that we were labeling, not measuring. We were counting labels and so a lot of that material, Logan and Cushion[27] and so on, I think is of great historical interest, but not of much biological interest. Let me illustrate: if in some chapter in the Old Testament there had been a battle between the Hebrews and the Philistines and we'd had some evidence about the two armies, that the Philistines had such and such a number of giants and such and such a number of dwarfs and ditto for the Hebrew army, this really wouldn't tell us very much, except that one army was bigger than the other. But if we were told the number of cubits you needed to be to be classed as a dwarf or a giant, or the mean cubitage of the two armies, then we would actually have data of permanent biological value. Similarly, if in the national morbidity surveys one after another we'd been asked to record blood pressures, the actual pressures, with all the errors involved in measurement rather than the number of hypertensives, hypotensives, and other kinds of tensives, we would actually have useful historical data. But we are still, I think, churning out morbidity data that are based on labels. We are probably doing it even worse now than before, because we now have computer programs that are not designed to answer our questions, but to answer the questions of pharmaceutical companies who want to market their wares, which just want to associate drugs with diagnostic labels. So we are going to have historical data about diagnostic labels which we already know are mostly rubbish. If only we could get to measuring not just counting.

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patients are still living, from 1965 to 1992 can be consulted at the Contemporary Medical Archives Centre, Wellcome Institute for the History of Medicine Library, CMAC/GP/13.

[27] This survey of disease in the general community was designed by the College of General Practitioners and the General Register Office using information on the number of patients affected and the number of medical consultations involved in each episode of sickness from 171 doctors in 106 practices from May 1955 to April 1956. See Logan W P D, Cushion A A. (1958) Vol. 1 for general details. Logan W P D. (1960) Vol. 2 for occupational statistics. Research Committee of the Council of the College of General Practitioners. (1962) Vol. 3, *Disease in General Practice*, for a collection of essays on the results. op. cit. note 24 above.

Tait: Julian, do you think you could tell us how you started? I am always fascinated by the loners. What really got them going amongst all the other people in the valleys in Wales.

Tudor Hart: Well, I started in completely the opposite way than has been suggested. I kept seeing people with coronary disease who were not supposed to have it according to the folk lore that was being taught in teaching hospitals and was reflected in journals. Your image of a typical person with a coronary was descended from your image of a typical person with hypertension. It was a hard-pressed businessman, worrying terribly about his future, because he might lose one or two million pounds. These were not the people who were getting coronaries. I was seeing coronaries in people in their late thirties and early forties, really horrific events, pump failures in otherwise perfectly good people and they seemed to be happening all the time in a population which was mainly heavy manual and poor. So I found that there was no data available for valley populations, because this was not a geographical category. I wrote to the Registrar General, that lovely South African whose name I have forgotten already [Abe Adelstein[28]] who wrote a lovely letter back again which, if I had it somewhere we should frame and give to the College [RCGP], about how GPs were helping people like him. They were really moved by anything that they got from mere GPs. And he wrote back, made available free, which would never happen to you now, a whole lot of stuff which cost him quite a lot to produce, raw data from the Registrar General's material. I got stuff for all the valleys, for all the Vale of Glamorgan, the whole of Gwent and so on, and I just went through all these things and found that there was a dramatic difference in the age-standardized death rates for coronary disease between the valleys and the Vale of Glamorgan, that the people who lived in the easy-going affluent areas were not getting it and the people in the valleys were getting it and ditto with strokes. So I found very early on what Michael Marmot and loads of other people have confirmed over and over again, which is the social class gradient for coronary disease and stroke.[29] Nobody else noticed that, because I published it in the College *Journal* and on the whole people of that ilk didn't read the College *Journal*, but it had an enormous effect on me because I thought, 'Oh Jesus, you can actually find something out, you can discover something.'[30] I thought it was a big thing to discover and it gave me enormous confidence to go on, even though I

[28] A M Adelstein (d. 1992) was chief medical statistican for England and Wales. He arrived in England in 1961 from South Africa, having been director of research and medical statistics of the South African Railways. See Marmot M. (1992) Obituary: A M Adelstein. *Lancet* **340**: 1463.

[29] Professor Michael Gideon Marmot (b. 1945) is Director of the International Centre for Health and Society at University College London Medical School. See Marmot M G, Elliott P, Rose G A. (1992) *Coronary Heart Disease Epidemiology: From aetiology to public health*. Oxford: Oxford University Press.

[30] Hart J T. (1970) Distribution of mortality from coronary heart disease in South Wales. *Journal of the Royal College of General Practitioners* **19**: 258–268.

think in fact if actually the output is rather trivial and you have only contributed half a brick and all that stuff, at least you don't think that when you are doing it. I think you need an enormous amount of energy and commitment even to produce half a brick and if somebody tells you right from the beginning that that's all you are ever going to produce, you won't take that much trouble.

Finally, as you asked me to contribute again, I wish we would use the word intelligence more about this question of research, because then we would realize – I mean the army uses intelligence because it hasn't got any, except, hopefully, in the Intelligence Corps, if it didn't have that it would be a completely blind beast blundering about killing people, without any aim or purpose, and hopefully the Intelligence Corps gives it some sort of sense of direction. Now that's rather, I think, like medicine. If you don't know what the hell is going on in your practice, what on earth are you doing, with these terribly powerful and dangerous weapons, which if they impair people by 1 per cent in their reaction time on the motorway or something like that and if you give that to enough millions of people, we are killing people on quite a big scale and I think that has happened. How can you have all that weaponry and not have an intelligence system in your practice – in one practice? How can there be such a thing as a practice with no research? Who's going to tell you what's happening? Nobody. You have got to find out yourself what's happening. You do it with very crude methods, like 10 per cent random samples got out by a trainee or by your receptionist, from which you can see most of the big things that are happening in your practice, or not happening. It's usually the things that are not happening – the diabetics that you haven't seen for two years and so on that are important. You must have that intelligence system. If you don't have it, then how dare you talk about research? If you do have it, how dare you not move on from this simple primitive intelligence system just for finding what the hell's going on, to start asking some more sophisticated questions? We are wrong to categorize audit as one kind of activity and research as something else, aimed at getting into some constipated journal, as a paper that hardly anybody ever reads. I don't think there are two kinds, one audit and the other research. I think there is one continuous distribution of intelligence.[31]

Tait: Thank you for those vintage remarks, Julian.

[31] See Hart J T. (1992) Opportunities and risks of local population research in general practice. In Gray D J P. (ed.) *Forty Years On: The story of the first forty years of the Royal College of General Practitioners*. London: RCGP. *idem* (1997) Response rates in South Wales 1950–1996: Changing requirements for mass participation in human research. *Non-random Reflections on Health Services Research*. London: BMJ Publishing, 31–57.

Professor David Morrell:[32] I would like to pick up something that Keith [Hokgkin] raised and that was that he blamed his medical education for a lack of curiosity and a feeling that everything was certainty. I'd like to blame my medical education and coincidentally my medical educator is sitting next to me here [Professor Sir Stanley Peart]. He's one of the few medical educators who actually taught me to think. Not many of them did that, but he did. But one of the disservices he made was that he gave me my concept of research and when I went into general practice I really couldn't think beyond this. Now not only did he do that to me as a student, but when I went into the air force I was posted to the Royal Air Force hospital at Ely, my predecessor there had been none other than Stan Peart and the people there used to tell me what a clever guy he was. That he was always doing research. Now I don't know whether it's true or not, but I was told that he used to go round the farmers and get them to send him rabbits and he used to take their kidneys out and play around with them in a variety of ways and this was my concept of research. I decided that I didn't really want to play with rabbits' kidneys and therefore I didn't really feel that research was for me.

If I could now come back to Ian's question of how did I start doing research and this was from sheer desperation, because I went into general practice in 1957 and I found that many of the things that I had been taught just didn't work, particularly the probability of illness in response to symptoms presented in general practice. What I had learnt in hospital was totally irrelevant. And so I became fascinated with actually interpreting the symptoms presented at primary care level in some sort of a way which would help me to make a sensible differential diagnosis. I did bring with me today a little brown book which I used to keep in my surgery and it's got a lot of headings like backache, headache, feeling tired and things like that and I used to write down the patient's name and the diagnosis I had made in response to these symptoms and so I began to get some sort of a picture of what symptoms presenting in primary care really meant, and then was able to compare this with the more traditional books of differential diagnosis. It was this desperation that drove me to start doing my research and from there it sort of grows on you.

Sir Christopher Booth: The Royal College of General Practitioners in 1952, was, if I remember rightly, vigorously opposed by the then President of the Royal College of Physicians, Sir Russell Brain.[33] The extraordinary thing was that you chose for your first President [Dr William Pickles], a research man, a man who had been in research in solitary practice, or virtually solitary practice. There are two

[32] Professor David Morrell (b. 1925) was Professor of General Practice at St Thomas's Hospital Medical School from 1974 to 1993, now Emeritus.

[33] Sir Russell Brain FRS (Lord Brain of Eynsham from 1962) (1895–1966) was President of the Royal College of Physicians, succeeding Lord Moran in 1950, and re-elected annually until 1957.

questions, one is why did you do it and the other is why did you choose a research man as your President and not one of these big time political animals that exist in medicine?

Horder: Well, the College had actually been in mind for a hundred years, as people here know. It was Ian Tait who ferreted out this story. It had been in mind and reached discussion in Parliament several times in the middle of the nineteenth century so it wasn't a new idea. It had been suggested again by the Metropolitan Counties branch of the BMA around 1880 and there were various individuals in the 1940s who had been writing to the journals about the possibility. But it was John Hunt and Fraser Rose who picked it up. Hunt's story is particularly interesting. He'd been a senior lecturer at Bart's on the medical unit and also at the National Hospital, Queen Square. He was obviously set for a teaching hospital job, when, in 1937, he suddenly decided to become a general practitioner in Kensington. I have never completely understood what caused that to happen, but I think the move proved very important historically. He was an exceptionally energetic man, who would start his work at five in the morning. He had a very exacting Kensington private practice, with a number of influential patients who proved to be allies in the formation of the College.[34]

Another important factor was the Collings Report of 1950.[35] This gave a very depressing picture, particularly of practice in the cities. Undoubtedly it was one of the things which stimulated the formation of the College. At the back of these influences there was a situation whereby every other branch of the profession had a very significant amount of postgraduate training, while future general practitioners were not required to have any. They were expected to be fully trained by the end of the undergraduate curriculum, which by this time was very unsuitable for the purpose. It was taught entirely by people who themselves had specialist training and it was inappropriate in several respects. Those are the influences which come most quickly into my mind, but I hope that someone else can answer the second question.[36]

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[34] Horder John P. (ed.) (1992) *The Writings of John Hunt*. London: Royal College of General Practitioners. Biographical introduction by John Horder. See also DJPG [D J Pereira Gray]. (1988) Lord Hunt of Fawley. *British Medical Journal* **296**: 218.

[35] Collings Joseph S. (1950) General practice in England today: a reconnaissance. *Lancet* **i**: 555–585. Collings was interested in the effect of the new National Health Service, and he surveyed 55 English practices run by 104 doctors in 1949. This survey was not widely accepted and two further studies followed: Hadfield S J. (1953) A field survey of GPs, 1951–52. *British Medical Journal* **ii**: 683–706; Taylor S. (1954) *Good General Practice: A report of a survey*. London: Oxford University Press. See also Petchey R. (1995) Collings report on general practice in England in 1950: unrecognized, pioneering piece of British social research? *British Medical Journal* **311**: 40-42.

[36] For an historical perspective of the early years of the College, written by participants, see: Fry J, Hunt J, Pinsent R J F H (eds). (1983) *A History of the Royal College of General Practitioners: The first 25 years*. Lancaster: MT Press Limited.

Crombie: I think part of the answer was given when John [Horder] was saying that almost everybody concerned with the very early formation of the College had an MD. In fact, the great thing was that everybody concerned had already made their mind up that general practice was as capable of being an academic discipline as any other branch of medicine. It's interesting how many of those early workers had carried out quite systematic and in their time rigorous, as rigorous as they could be, analyses of what they were doing as a basis for the next jumping off point. I think it was as simple as that and it also allowed them to pay no attention to politics, except one person. The one person capable of dealing with the politicians and the establishment was John Hunt, on his own and it was quite certain that the College would not have got anywhere when we started without John Hunt. We had all the other ideas and so on, but there was nobody who could forcefully push just where you had to push, to the extent that he was so good that nobody bothered about politics. It was just one of those things you knew John Hunt would deal with.

Tait: He was in fact the politician.

Crombie: Which he always did – he was just a natural, he didn't have to think about it.

Horder: May I just add to the story I was telling? In fact it was all three Royal Colleges which opposed. Thomas Horder [of the Royal College of Physicians] was also strongly opposed but he changed his mind later.[37] The Colleges suggested that the general practitioners should form a joint faculty of the three existing Colleges.[38] That was a difficult moment for John Hunt. He made the difficult decision to refuse and stick out for an independent organization.

Dr Clifford Kay:[39] Can I just add a little bit to why William Pickles was chosen as the first President, as I perceived it – it may be wrong, and it's possible that the questioner has a slight misconception about the role of the President in our College as opposed to the role in other Colleges. The President is not the chief executive of the RCGP, the Chairman of Council is that person and I suspect that William Pickles was chosen particularly because he was non political and they did not want

[37] Thomas Horder, later Lord Horder (1871–1955), was a distant relative of John Horder.

[38] At that time, the three Royal Medical Colleges were the Royal College of Physicians of London; the Royal College of Surgeons; and the Royal College of Obstetricians and Gynaecologists.

[39] Dr Clifford Kay FRCGP (b. 1927) was in general practice in Manchester from 1955 to 1995. He was part-time director of the Royal College of General Practitioners' Manchester Research Unit from 1966 to 1992, and consultant from 1992 to 1997. See Kay C. (1992) Oral contraception and other multi-observer studies. *Forty Years On: The story of the first forty years of the Royal College of General Practitioners*. London: Royal College of General Practitioners, 1992, 284–289.

their President to be a political figure and he was a renowned figure at that time and was seen to be in the tradition of Mackenzie and, as far as I am aware, he was the only one who was in that position at that time.

Crombie: Just in passing, it's interesting that the Dentists have just gone through the same process and they've become a Faculty of the Royal College of Surgeons.

Dr Mark Perry:[40] Was there any support from within the other Royal Colleges? Obviously there was the opposition from the head of the Colleges, but I am conscious of attempts to form a kind of general academic practice in the 1940s, coming from social medicine and I am wondering if anyone was supporting it?

Horder: I don't remember any support from inside the Royal Colleges, except later when Robert Platt, President of the Physicians, became a very strong supporter and actually helped with the organization of the College exam when it started.[41] Indeed he took parts of it himself. It was a complete change, after Russell Brain's strong opposition. Perhaps he too might have changed his mind later. It so happens that I was his house-physician [Brain], but it was the first appointment I held and this was well before the story of the College of General Practitioners started. I never discussed such things with him.

Dr Stephen Lock:[42] I think we ought to put it into context that throughout history, the two older Royal Colleges have opposed pretty well everything, particularly the formation of new colleges. They opposed the formation of the obstetricians and gynaecologists in the 1930s. The physicians said that gynaecology belonged to physicians and the surgeons said that obstetrics belonged to the surgeons. They certainly opposed the College of Pathologists and latterly they've been opposing the College of Paediatrics, which, I am very glad to say, has finally evolved. So I think if we put it into perspective, there would have been something totally wrong with the College of GPs if they hadn't opposed that as well.

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[40] Dr Mark Perry is in general practice in Manchester and, at the time of the seminar, was an MA student in the Wellcome Unit for the History of Medicine, Manchester.

[41] Sir Robert Platt (Lord Platt from 1967) (1900–1978), President of the Royal College of Physicians from 1957 to 1962 having succeeded Sir Russell Brain. He was Professor of Medicine at the University of Manchester from 1945 to 1965, and a member of the Royal Commission on Medical Education from 1965 to 1968. See his autobiography, *Private and Controversial*. London: Cassell, 1972.

[42] Dr Stephen Lock FRCP (b. 1929) was the Editor of the *British Medical Journal* from 1975 to 1991 and is a member of the Steering Committee, History of Twentieth Century Medicine Group, Wellcome Institute for the History of Medicine.

Dr Irvine Loudon:[43] Two things, first the Collings Report,[44] which I am sure was very influential, but what is often overlooked is that it was influential in two ways. It produced these marvellously readable horror stories. I've recently been back through the Collings Report more than once, but it also mentioned the side of general practice that did exist in a minuscule quantity which could be seen as a model for how general practice could develop under the NHS. He mentioned one practitioner who bought a whole lot of equipment for himself and did as much investigation as he could on his own, but his colleagues, to quote Collings thought he was stark raving mad, because he would bankrupt himself by doing so and go out of practice. He also singled out the Highlands and Islands medical service, saying these are some of the finest men I have ever met. Now in the Collings Report, he never actually mentioned that there ought to be a College of General Practitioners, but he did deal with the ways that general practice could develop in terms which would have been sympathetically received by John Hunt and his colleagues at the time it was founded. So the Collings Report is influential for two reasons. It showed the awful side of industrial practice, but also it didn't say, which it might easily have done, general practice ought to be abolished and we ought to have polyclinics and outgoing community services from the hospital. It did say it should be developed along lines of high clinical standards. That's the first thing.

The other thing is about the first attempt in the 1840s.[45] What is astonishing about that attempt to found a college and they actually thought of it as a Royal College from the word go, after all the Royal College of Surgeons in 1800 had 'Royal' attached to it as soon as it was founded, and they wanted it to be the same and they finally got to the stage, after months and months of work, of having the agreed approval of the Royal College of Physicians and the Royal College of Surgeons, but at the final meeting the surgeon,[46] whose name I have forgotten, who was a representative from the Royal College of Surgeons reneged on it and said we cannot accept this and the whole thing collapsed. But it did get an extraordinary distance and although there may have been other mentions of Colleges of General Practitioners, until the 1950s and the immediate period before it was actually formed, there was no serious attempt, but the 1841 one got a very long way and I find it entertaining to try and think if that had been a College of

[43] Dr Irvine Loudon (b. 1924) was in general practice in Wantage, Oxfordshire, from 1952 to 1980 when he became Research Fellow of the Wellcome Unit for the History of Medicine, University of Oxford and a full-time medical historian. op. cit. note 1 above.

[44] Collings Report. op. cit. note 35 above.

[45] College of General Practitioners. (1953) An attempt to found a College of General Practitioners 108 years ago. *First Annual Report*, Appendices I and II. McConaghey R M S. (1972) Proposals to found a Royal College of General Practitioners in the nineteenth century. *Journal of the Royal College of General Practitioners* **22**: 775–788.

[46] Dr Irvine Loudon later wrote: 'My memory was at fault. In fact, the decision not to ratify the previous agreement that such a College [of General Practitioners] should be formed was recorded as a decision of Council of the Royal College of Surgeons rather than any one individual.' Letter to Mrs Lois Reynolds, 20 February 1998.

General Practitioners founded in the 1840s in England and Wales, if not in Scotland, would it have had a substantial effect on the development of general practice? It's anybody's guess. It could have died out, or it could have been hugely influential – we don't know, but what is astonishing is how far it got.

Tait: Thank you. Can I remind us that we are talking about research in general practice, so these are essential foundations for it, but we don't want to get stuck on the growth of the College.

Hodgkin: I am sure that because the Royal Colleges of both Physicians and Surgeons – in general – had such a poor opinion of GPs and general practice, this stimulated some of their more far-sighted senior members to start the MRC Committee for Research in General Practice.[47] We have to thank Sir James Spence, Lord Platt, Max Rosenheim and many others for encouraging GPs to do research in the 1950s and early 1960s when their morale was so low.

Professor Margot Jefferys:[48] I think it is useful to take into account not just the internal politics and perceptions of groups of doctors, but of what was happening on a world scale and the effects of both the political settlement of 1948 [the beginning of the National Health Service] and developments in medical practice on patients' perceptions. General practitioners felt they had been abandoned by their specialist colleagues in the Royal Colleges and by the political establishment. The effect of advances in disease prevention and treatment were attributed by the public to advances made in heroic hospital-based surgery, rather than to environmental measures and pharmaceutical products whose control was largely in the hands of general practitioners. In short, the presentation of the capacity of medicine to save life and improve its quality as based mainly on specialist advance affected not only the public's image of the relative importance of medicine's various branches, but that of members themselves and new entrants to the profession.

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[47] Dr Keith Hodgkin wrote: 'The Committee was the forerunner of the Royal College of General Practitioners' Research Committee and as you can see it contained a number of significant names. This MRC Committee was started by Sir James Spence in 1953, just before he died of lung cancer in 1954. The Committee was disbanded about 1963. The GP members who met four to five times a year were: Sir Robert Platt (Chairman, deceased)[not a GP], Dr G F Abercrombie (deceased), Dr John Fry (deceased), Dr G K Hodgkin, Professor Richard Scott (?deceased), Dr G C Sheldon (deceased), Dr Peter Walford (?deceased), Dr G I Watson (deceased) Dr C A H Watts (deceased) and Dr R E Hope Simpson (Secretary). Sir Richard Doll's wife was, I believe, the first secretary (using her maiden name – Joan Faulkner [not a GP]).' Letter to Dr Tilli Tansey, 24 February 1998. See MRC Committee for Research in General Practice. (1960) Determination of the age/sex structure of general practice populations: A basic requirement for epidemiological research in general practice. A Report to the Medical Research Council. *British Medical Journal* **i**: 1496–1497.

[48] Professor Margot Jefferys (b. 1916) was Professor of Medical Sociology at Bedford College, University of London, from 1968 to 1982, now Emeritus.

Professor Marshall Marinker:[49] I just want to make one brief point. I know we are going on to discuss university departments quite soon and I am terribly interested in this early history of research before university departments, because there were no career motives for any of the people in this room to do the work that they did. They were driven by things like curiosity and conscience. Now I am not saying that that isn't happening today in university departments, but there are different motives and reasons for that, and I would like to see historians looking at that more closely.

Professor David Metcalfe:[50] I started in very much the situation that Margot describes. I was being groomed for stardom as an obstetrician, clambering up professorial units, and being told that you couldn't practise worthwhile medicine in general practice. The more charitable people said that that was because there wasn't time and of course we had no open access to labs or X-rays, and the less charitable ones said it was because we were just lame brains as far as that was concerned. It was Stephen Taylor's book, *Good General Practice*[51], which picked up the good bits out of the Collings Report, plus the College beginning to encourage people to have disease registers and age–sex indexes. I was very much influenced by Bill McKean, who was a very good GP in inner Liverpool at the time and being on a professorial unit we card-indexed absolutely everything so that we could write a series of papers about anything that happened. For the first time I saw that you could do that in general practice and that, in fact, that you could be at the front line as Julian said and you could look critically at what you were doing. So it was not the Colleges and educational institution, but was having insights into a research capability, that took me out of obstetrics and into general practice.

Tait: I think it is very important that you were lucky enough to have an example and once you got that self-esteem then it was easier. I wonder if Dr Williams has something to say from Wales, because he started so much at that time.

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[49] Professor Marshall Marinker (b. 1930) was in general practice in Middlesex and Essex from 1959 to 1973 and Foundation Professor of Community Health (later General Practice) and Head of the Department of Community Health at the University of Leicester from 1974 until 1982; Director of the MSD Foundation from 1982 to 1992 and has been Visiting Professor at the Department of General Practice, United Medical and Dental Schools of Guy's and St Thomas's Hospitals, since 1991. He was a member of the Council of the Royal College of General Practitioners and has served as Chairman of its education division from 1974 to 1989 and of the Committee on Medical Ethics from 1987 to 1989.

[50] Professor David Metcalfe (b. 1930) Professor of General Practice at the University of Manchester from 1978 to 1992, now Emeritus.

[51] Taylor S. (1954) *Good General Practice: A report of a survey*. London: Oxford University Press. Supported by the Nuffield Provincial Hospitals Trust.

Dr W O Williams:[52] I did 45 years' continuous research, in general practice, on 34 different subjects (or diseases) and published over 80 scientific papers. They were all as a result of epidemiological research, and I have learnt something, which I think is very important.

It is important to cultivate inquisitiveness during your daily work. When you are working in general practice, you are working with all types of people of all age groups, of both sexes, and from a whole variety of social class backgrounds. You must develop a habit of looking and taking notice of unusual deviations from the normal. Some may be staring you in the face and you fail to notice them, but if you develop your mind to be curious, you will see things that others miss.

I have brought a graph to show you which illustrates my point.

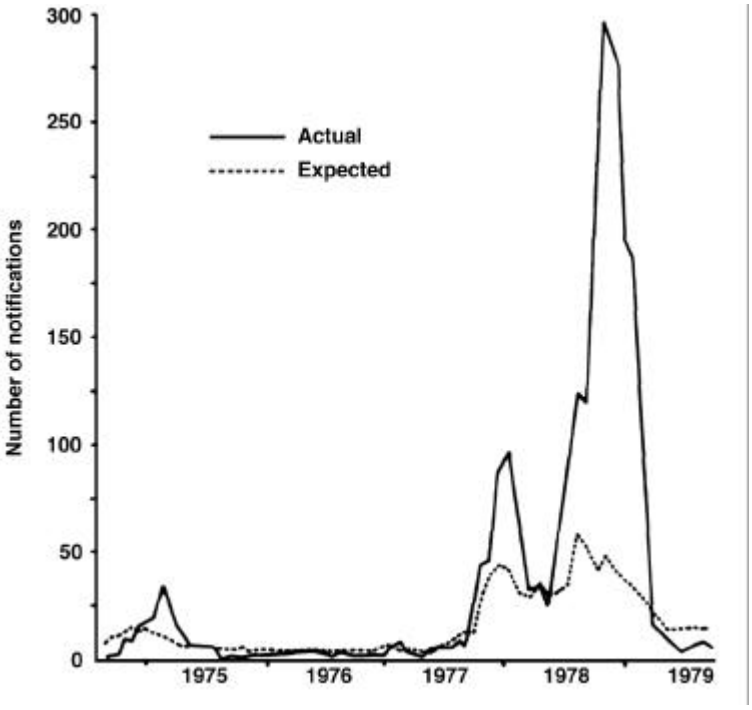

Figure 2. The number of notifications of whooping cough a month in the whole of West Glamorgan for 1974 to 1979. The expected number of notifications shown for West Glamorgan is calculated from the number of notifications for England and Wales and the population ratios between the two areas.[53]

[52] Dr W O Williams, FRCG (b. 1921) was in general practice in Swansea. He was Honorary Director of the Royal College of General Practitioner's Epidemic Observation Unit and the Honorary Director of the College's Swansea Research Unit at University College, Swansea. See Williams W O. (1970) A study of general practitioners' workload in South Wales 1965–66. *Reports from General Practice* no. 12 London: Royal College of General Practitioners. See note 21 above.

[53] Royal College of General Practitioners, Swansea Research Unit. (1981) Effect of a low pertussis vaccination uptake on a large community. *British Medical Journal* **282**: 23–26. Permission to reproduce Figure 2, page 24, has been granted by the BMJ Publishing Group.

Whooping cough epidemics occur in peaks. A peak occurs when the pertussis antibody level of the community has dropped to a critical level. This drop in antibody level after an epidemic takes about four years before the community become vulnerable to another peak again.

The smallest peak occurred in 1975, but something dramatic happened to alter this trend in peaks. A paper in the *British Medical Journal* describing three or four children who were reported to have suffered brain damage as a result of the pertussis vaccine.[54] Newspapers got hold of it and blew it up out of all proportion. I wondered what effect this would have on parents' willingness to have their children vaccinated against pertussis?

Parents understandably became very frightened to allow their children to be vaccinated against whooping cough, so I immediately planned a study on the possible effect this would have on the community.

All the general practitioners in West Glamorgan were included in the study. This resulted in my receiving over 3600 notifications of whooping cough during the epidemic of 1977–1978.

I employed five full-time nurses who had been hospital sisters. All Degree I cases had been identified by cough plates, throat swabs or nasal swabs. Each patient was seen three times at specified intervals. The nurses travelled a total of 29 000 miles and the study was a complete success.

Tudor Hart: Can I ask you a question? Can you either explain, or give me permission to explain, why it was that of all those 34 research subjects you weren't able to develop your own practice population as a research base? I think the reason is very important.

Williams: I have a very good reason for that. There were four doctors in our practice, and I was the only one doing research.

As in all practices with several partners, any patient cannot see the doctor of his or her choice on that day because he may not be available, and the patient is either asked to see another doctor who is available or she or he is given an appointment to see the doctor of his or her choice on the next available time.

It is difficult to do a study, as Julian has done in his single-handed practice, in a practice of four doctors, when only one of them is doing research. Doctors as individuals have different ways of writing notes, and their handwriting is also varied. Notes may differ in style, readability, and also in the quality of the text.

[54] See Anon. (1975) Whooping-cough vaccination. [editorial] *British Medical Journal* **iv**: 186–187, a report of work published by Kulenkampff M, Schwartzman J S, Wilson J. (1974) Neurological complications of pertussis inoculation. *Archives of Disease in Childhood* **49**: 46–49.

The quality of the doctor's notes vary and few notes are typewritten. However good a partner is as a doctor, his handwriting and his notes may be very poor.

As I was the only one of four partners doing research, I confined my studies to the epidemiology of diseases which I myself had encountered. All the research I have done has been as a result of curiosity. Keeping my eyes open in my daily work and research into curious and interesting happenings as I saw them.

Julian mentions Will Pickles. I knew him well and he became a good friend of mine. I remember meeting him for the first time in John Hunt's surgery in Sloane Square and I found that we had a common approach to epidemiological research and we had both completed a study of Bornholm disease.

Tudor Hart: Can I just mention something – that ties up with what W O [Williams] has been talking about, and it's also something that Chris Booth raised. Will Pickles wasn't a popular doctor in the Wensleydale practice. It was his poor partner on the motorbike who was, and as far as I understand, they didn't have very good relations with each other either. And I think this is typical of partnerships, this extraordinary arrangement that we have now and we are still in this antique phase of history when in general practice we are all owning little corner shops, although some of us are moving into supermarkets now, still they are shops. That's not what hospitals are, at least not yet. Now it's very difficult to do research under those circumstances. In fact, it's only the most primitive, the single-handed shopkeepers that can do research easily, and the bigger your practice, the more difficult it is to do research unless you are a university practice, in which case they are salaried, so they are not shopkeepers. Now the relationships between the shopkeeping partners is critical, some of them keep notes of variable quality, some very good, some people don't keep notes at all – don't write anything down. Now that was quite characteristic 20 years ago. There were plenty of GPs who just didn't keep any records. And this extraordinary ownership that you have in general practice, where you own the practice, and you thought you owned the patients and the patients pretended that you did own them, because that was the way to get on with you, all this had a profoundly limiting effect on research. It's a very good reason why research did not develop on a far greater scale in primary care, when after all we'd got enumerated populations, many practices had enumerated populations from 1911 onwards. In fact, even before that in club practice, but there was no research, because we were still locked into shopkeeping.

Tait: Thank you, Julian, and this is a perfect lead into our next session which is the development of university research. Clearly there are limits to what's possible in a partnership in general practice. General practice was losing its brilliant single-handers. They were moving into health centres where partners often made

individual research more difficult. So can we move on to look at general practice research, or research about general practice based on university centres. Professors David Hannay and Sir Michael Drury, both of whom have had extensive experience in the running of departments of general practice, will start the session.

Professor David Hannay:[55] Well, thank you very much for asking me. I was going to give you a crisp thumb-nail sketch of the history of departments of general practice and their research, but I have decided not to for two reasons. First of all, this meeting is more about the recording of personal experience, and secondly, it would be rather presumptuous in front of this distinguished audience that really represents, in many ways, the history of departments of general practice. So I am going to be unashamedly anecdotal. I did my preclinical training, if it could be called that, at Cambridge. It had the advantages of being flexible, so I did a Part I in anthropology as well as natural science. In the natural science tripos one was unencumbered by any considerations of relevance. We were taught anatomy by anatomists, physiology by physiologists, and whether it was any good to you was your problem, not theirs. I did my clinical training at St George's at a time when it was still at Hyde Park Corner, but extending down to Tooting. There was no teaching in general practice. We had two lectures by a retired public health physician, one of which I missed. This was in the 1960s at a time when the first Chair in General Practice had been established in Edinburgh and at that time only eight medical schools in the whole country required all their students to have any experience of general practice. After a variety of junior hospital jobs, mainly in the London area, but ending in Manchester, where I was actually a surgical SHO and teaching anatomy, I became convinced that general practice was really what I wanted to do and was particularly fascinated by walking through the Moss Side area of Manchester and with what was happening in the community.

By a series of coincidences, Glasgow University were looking for someone to teach behavioural science, because the Todd Report had said that behavioural science was a good thing.[56] They weren't quite sure what it was, but they thought it was something that medical students ought to learn about. I found myself in a strange appointment which was linked between a department of social and economic research and a department of I think it was called epidemiology and community medicine. My job was to develop the teaching of behavioural science, both to medical students and the Diploma in Public Health and it was an

[55] Professor David Hannay FRCGP (b. 1939) was Professor of General Practice at the University of Sheffield from 1987 to 1996. He joined the Department of Community Medicine at Glasgow University in 1968 with an assistantship in General Practice and was attached to the Department of Social and Economic Research, becoming senior lecturer and Principal in General Practice with the Greater Glasgow Health Board in 1975.

[56] Royal Commission on Medical Education. (1968) *Report.* Cmnd. 3569. London: HMSO. Named after its chairman, Lord Todd.

interesting juxtaposition for me, having just completed the primary FRCS. I managed to indicate that I would only do this provided I could continue in clinical work, so I was attached to a practice all the time I was there. The research I did was community based, and was really looking at health in the community and, in particular, illness behaviour. I was trying to unpick all those concerns about the iceberg of symptoms on the one hand, and trivia troubling general practitioners on the other. But being attached to a department of social and economic research was a marvellous opportunity to learn about, and be exposed to, other traditions of research. This is one of the themes I would like to draw out, talking about research in university departments. Because I think one of the problems for general practice and general practitioners is that the research was seen so much in terms of quantitative methods which were appropriate to hospital populations. After a time in 1975 a Chair in General Practice in Glasgow was established, and I moved across to that department as the first senior lecturer. There the research I got involved in was of rather a different sort and concerned teaching. Indeed, the first general practice teaching was done in 1972, and I did that with a final year medical student as an optional course. Interestingly, a lot of the pressure for teaching general practice in medicine came from medical students, initially in the 1960s. The research was much more evaluative, using social science methods, and looking at methods developed at McMaster for self-directed, problem-based learning with continuous assessment.[57] Interestingly the research I did on community health was originally for an MD at Cambridge, but they wouldn't accept it because it was considered to be not sufficiently clinical, although I had actually written it up, so it became a PhD at Glasgow. I had two supervisions with a delightful supervisor who came from Aberdeen. I think we met twice at a pub and that was about it. There was an interesting philosophy in the Department of Social and Economic Research, which was run by a remarkable man, an economist called Donald Robertson, who wasn't the slightest bit interested in the baubles of academia in terms of theses and learned papers, he said that what we really want is research that is going to change the situation and the conditions in Glasgow, which in the late 1960s were Dickensian in many areas. He wasn't a bit interested in higher degrees and encouraged his staff to write books, pamphlets, anything which reached the public.

At the same time, we developed a Master's course for general practitioners, trying to teach research methods. After that phase in the 1980s I went to do rural practice in southwest Scotland, and from there moved to the department in Sheffield. I say department, it was in fact a subdepartment. I was the subdepartment, with one part-time secretary and two associate general practitioners with one session a week each. It has since developed into a full department and the

[57] McMaster Medical School developed a course for self-directed, problem-based learning with continuous assessment. See Spaulding W B. (1991) *Revitalizing Medical Education: McMaster Medical School, the early years 1965–1974*. Philadelphia: B C Decker Inc.

emphasis there was first of all developing the undergraduate teaching, but also research, particularly in encouraging academic staff to develop their own research, which I very strongly believe must come from people's own curiosity.

We come onto contract research later perhaps, but I think the whole essence of research is that people must be really fascinated by what is happening and want to answer questions, because without that spark of curiosity then research simply becomes a drudge. So the development of opportunities for general practitioners to develop their own research credentials, particularly in terms of higher degrees, because that is the currency of universities, was a high priority. We also started a Master's course in primary and community care. This was multidisciplinary and one of the things we learnt was that very few GPs were able to come on this because of problems of funding.

From this very brief story, I would like to just draw out two or three threads. Two of them concern departments of general practice. The first is that I think we still don't sufficiently appreciate the extraordinary phenomenon that general practice is the only clinical discipline, possibly in the Western world and certainly in this country, where the undergraduate and postgraduate sides have been traditionally separated. I think that has had a tremendous impact on the lack of development of research. In the 1950s and 1960s pressures were building up for vocational postgraduate training in general practice and it was probably easier to swing this on the educational budget in North America, because you'd get paid, role-playing doctors taking part, whereas in this country it was easier to fund it on the National Health Service. So a totally separate organization was set up, postgraduate advisers, course organizers, trainers, who in many ways have been way ahead in terms of educational development, but had no research background. Later you had university departments set up with *ad hoc* arrangements by their founding fathers. That brings me to the second fundamental problem and that's one of funding. Because the problem for university departments of general practice, and therefore for their research capability, whether teaching or undertaking it, was that there was no proper funding arrangement such as the service increment for teaching which were very large sums of money which went across to teaching hospitals in recognition of the clinical work they were doing. It was developed, I think, from the 1970s resource allocation formula which looked at the difference in costs between district hospitals and teaching hospitals, which is the extra money we need to put into medical schools in order for the teaching hospitals to function. None of that money came to the departments of general practice. They were always chronically underfunded.

There are two other strands about research. The first concerns not departments but researchers, in particular general practitioners, and is the lack of funding and time. Unlike half the medical profession in training, the hospital doctors who often have periods set aside to do research as part of their training. It

simply doesn't happen for general practitioners. And as many of you will know, the arrangements for prolonged study leave are totally inadequate to provide the kind of time and availability for general practitioners, particularly young principals, to learn about research methods and undertake research. This ties in with what Dr Julian Tudor Hart was saying, it's all wrapped up in this problem of partnerships and the structure of general practice.

I think the second thing which has been difficult for general practice research is the need for researchers to be eclectic about methods. So often, I have seen it happen that somebody who is really interested in research goes along to a professor of public health medicine and is told, 'It's not statistical' or, 'You can't do randomized control trials'. We haven't been sufficiently aware, although we are much more now, of the breadth of research traditions, whether from the biomedical, epidemiological, statistical, or social sciences. I think this is changing now, but it has been a tremendous damper on research in general practice.

To end, I would say that for me if there was one key strand, it has been curiosity. I think research should be driven by curiosity. I think we are moving into a quite different management-driven world now where everything has to be purchased or provided, and therefore we have contract research and I think that raises all sorts of other issues for research in general practice.

Tait: Thank you, David, very much. Can I ask Professor Drury to take over from there?

Professor Sir Michael Drury:[58] Thank you very much, Ian. With one eye on the time and an ear on things that have been said already, I am going to speak very briefly, largely anecdotal, as David has been, and try and draw out some of the threads that he has already mentioned, but also one or two new ones. I realize in being so anecdotal, it almost reads like apologia for either not having done more, or not having done better. My background, as a newly-qualified doctor was all surgical and not even in an academic surgical department, so I had no early training or early experience in research whatsoever and most of the chiefs that I worked for weren't the slightest bit interested in doing any research themselves. Having done my time in the army and then going into general practice for quite coincidental reasons, I was, like most new entrants to practice, far too busy making sufficient money to keep the roof over my head, raising a family, helping to develop the practice, etc. to begin to get involved in research. My chance came when I got a

[58] Professor Sir Michael Drury FRCP, FRCGP, FRACGP (b. 1926) was Professor of General Practice, University of Birmingham, now Emeritus. He was Chairman of Practice Organization at the Royal College of General Practitioners from 1966 to 1971; a member of Council from 1971 to 1985; Vice-chairman of Council in 1980; a member of Committee and Research Division from 1983 to 1985 and its President from 1985 to 1988.

clinical assistantship, funnily enough, in surgery, attached to a peripheral surgeon who was interested in research. The first five papers that I published had nothing to do with general practice, but were concerned with the prevention of postoperative deep venous thrombosis and were published in the *Annals of the Royal College of Surgeons of England.* It was only coincidentally that after I had done that I began to look round and think there must be some sort of field outside in general practice, because in a way, by having this appointment it had bought me some time to think and time to get out of the hurly burly of the practice, and I began to see that perhaps there was something else I could do in terms of research in general practice. So that led me to look at the pros and cons, advantages and disadvantages in early discharge after surgery. It was an entirely coincidental thing.

I then began to realize, as others had, and maybe if I had read more and been more alert, I would have got at it more easily, how limited were the resources and the data-collecting systems in my own practice, for doing any research and I ran into the problem which has already been highlighted by W O [Williams] and others. I noticed when Donald Crombie was speaking in the early part of the meeting, he kept making what I regarded as a sort of Freudian slip from moving out of his title from single-practice research into single-handed practice research. There is undoubtedly a difficulty, if you are an individual practitioner in a group of four or five people, who wants to do some research, who has already got a clinical assistant post outside the practice, in trying to do any research inside the practice, because you are resented for doing that by your partners. I think there are a number of people, who would otherwise have got involved in a much earlier stage, who have been stultified by that.

A little later on I got invited to join Tom McKeown[59] at the University of Birmingham in the Department of Social Medicine, and I was curious why he had asked me to join him. I became a lecturer, and I think for a long time an unpaid lecturer, there. It was only after I had been there for about a year, that I realized that he didn't really want me to help him do any research, in fact he rather resented it if I suggested it. What he wanted me to do was to help establish McKeown in the practices around Birmingham. He wanted that desperately – to get a toe-hold into general practice and he wanted somebody who he thought might be able to talk to the other GPs who could persuade them that they really ought to be GP physicians, GP psychiatrists, GP obstetricians, etc. etc. But that stimulated my interest in academic medicine, so when the chance of getting a paid teaching post came up, I jumped at it for the money. I began in a department of medicine, which had a very different idea, and the department of medicine actually did feel that they wanted to involve themselves in teaching and in research and also general practice, as an area in which work could be developed.

[59] McKeown T, Lowe C R. (1966) *An Introduction to Social Medicine*. Oxford: Blackwell.

As a newcomer to academic general practice in the early 1970s I was, however, pretty much aware that the priorities in the medical school were not that we should be turning out high-powered research from this embryonic department. They were two priorities really. One we should quiet down, damp the fires, blow the smoke away, from the GPs outside who were shouting for a presence in the university. So we were a token that they could put up with. Secondly, they wanted us to teach, and use general practice as a teaching area. I think a lot of them didn't want to do it because they thought it was a good teaching area, but because they thought, 'Well let's get some of the teaching off our backs and we can get on with doing the research.' So teaching was undoubtedly the first priority and establishing a network, a core of practices, within which one could teach, was an important part of it.

That brings me to another area which hasn't been mentioned so far, out of which, I think, a number of important things stemmed. There were several different choices one could make when hypothesizing about the direction of academic general practice. One was whether one was a part-timer or a whole-timer. And that battle, and the arguments, raged for a number of years, most people who were whole-timers supported whole-timing, and most people who were part-timers thought part-time was the best thing. I was aware that there was a psychological shift in that, the whole-timers saw themselves as academics who were using general practice, and I think the part-timers saw themselves as general practitioners primarily who had a toe in the academic field.

The other division was between those universities who had a single university practice and those who didn't, those who used a multitude of practices. And I think it was probably easier for the universities that had a university practice to develop a research area within it, than it was for those of us who opted for a multitude of practices. To begin with, as a part-timer, it was very difficult to do research in your own practice. There was a constant tug between continuity of care for your own patients for whom you were responsible, and the fact that you were going back into the university to teach. And to add to that, the imposition of time taken out of the practice by using your own patients for research as well, I think most people in my position felt that it would have been too much. And, secondly, were the other practices that you recruited. You had, in a way, to establish within them the infrastructure to enable them to do some research, so that you could do it jointly. And getting the money for that infrastructure was extraordinarily difficult, very difficult indeed. It was always a regret to me that the links between Donald Crombie and myself in Birmingham were not made stronger, and not formalized. As a piece of historical information, Donald and I, I believe I am correct, Donald, both felt that a much firmer link between the College's research unit in Birmingham and the embryonic, as it was then, academic unit in Birmingham would have paid a lot of dividends. It would have given the College research unit

access to university facilities in a way it hadn't got, and it would have given the embryonic university department access to the research skills which Donald Crombie and his crew had got. But it was opposed by the College. It was supported by the Department of Health, it was supported by the university, and I think it was largely supported by Donald's unit, but it was opposed by the College who saw Donald Crombie's unit, rightly, as one of the jewels in their crown, and they weren't in the business of giving away any part of that jewel to another department and I could respect that, but, in a way, I think it was damaging.

As an embryonic department, trying to get research going, there seemed to me to be two areas one could develop. First, was to get joint research done with other departments, where you could – with the department of psychiatry and my own department, with the department of medicine and my own department – we could begin to develop joint research, because they had an infrastructure. One of the things they had difficulty with was capturing patients, and we had got access to patients that they hadn't got. They'd also got research know-how, statistical access which we hadn't got, so that would have been helpful. Secondly, we moved, initially, very much into the area, the unrespectable area, of drug trials. It may be that it was because that was an easy thing to go into, but the other side of the coin was that I could see, and I believe many other people could see, that clinical drug trials were a very important area, which was being very badly done and to a large extent it was prostituting research, so that anything one could do to attempt to improve the quality and the reliability of those studies on a greater basis would have been an important area to work in. So those were the two areas we began in.

The shift that I have seen happen since then is that our joint research with other departments over the years has shifted until the department of general practice began to take the lead position. It was no longer the department of psychiatry, assisted by the department of general practice, it was the department of general practice, assisted by the other departments. And that gained us considerable credibility in the medical school and outside, and improved the quality of work. The second thing was that, with the gradual increase in resources, we were able to begin to develop our own training programmes, and I think the impact of these, particularly the Master's degree, such as the one that David Morrell pioneered, but which many other medical schools including Birmingham followed, will be great even if its full potential has not been achieved. There are certainly, out there, a lot of younger doctors now who have got a good training in research methods, and given the time, given the opportunities, and heaven knows given a structure, might be able to achieve something in general practice. One of the things that worries me, looking back at my old department, is to see how much it is now finance-driven by the requirements of the university, and I think a lot of the new research is in danger of being distorted by people having to do a certain type of research because

that is the one that pays, rather than the one that they are interested in, or feels needs doing.

Tait: Thank you, Michael, very much indeed. That was most useful.

Professor Paul Freeling:[60] There is one area that seems to have been missed out almost completely, except I think David Hannay mentioned it, and that is the question of research into education. While we were seeking dignity, university departments of general practice and other people who were involved in trying to apply education and teaching experience to teach general practitioners, felt themselves forced into justifying their teaching by proving that it worked, and by stating what it was meant to achieve. Now it may sound strange today but that was a very unusual idea, indeed I am not sure that it sounds strange today. There was a consequence which I have not heard mentioned and that is why I wanted the point made. The consequence was that the methods of research with which GPs became familiar, were methods which were used for conducting research into education. Now these are not totally different from randomized controlled trials, they are not totally different from epidemiology, they differ in type in some being qualitative in their origins and whenever you think about general practitioners and their research in the years between 1952 and 1972, and perhaps further on in the late Pat Byrne's Unit,[61] this whole question of the effect of our trying to make ourselves credible by justifying our teaching, not simply justifying *what* we were teaching, is something which has to be borne in mind.

Metcalfe: I think it is very interesting that many of the departments of general practice started off bedded down in departments of community medicine, now public health medicine. That was very useful in terms of getting our facts regarded and learning quite rigorous research methods. But it was essentially numerate research methods of a very narrow band, and I think we would have to be honest and say that probably in general practice in day-to-day morning surgery the average clinician makes less use of the research done in his discipline, than most other specialists in their disciplines do. And part of the problem of that is whereas the epidemiological type of research produces results which are highly predictive for

[60] Professor Paul Freeling (b. 1928) has been Professor of General Practice from 1986 until his retirement in 1993, now Emeritus, at St George's Hospital Medical School, London, and Head of the Department of General Practice and Primary Care from 1976.

[61] Professor Patrick Byrne FRCGP (d. 1980) was appointed to the first Chair of General Practice in England at the University of Manchester in 1972, in the department which he had joined as part-time Director in the mid 1960s. David Metcalfe succeeded Byrne in 1978. See EVK [E V Kuenssberg]. (1980) Obituary: Patrick Sarsfield Byrne. *Lancet* **i**: 609–610.

populations, they are much less predictive for individuals and essentially general practice is about individuals.

I was delighted to hear David Hannay make the point of the need for much more eclecticism in the methodologies we espouse. I think that we have ignored rigorous methodologies from things like social psychology and social anthropology, which will give us a lot of insight into the everyday stuff that we meet in general practice. The paradox, of course, is that now, under the influence of the Research Assessment Exercise [RAE, 1992 and 1996], university departments are the last places where you can be in any way adventurous. The pioneers who talked earlier on from their own single practice research, could afford to be adventurous, if you made a mess of it the egg was only on your face. In a university department, however, you have got to get the grants, you have got to get the publications, otherwise you score low on the RAE, so far from being eclectic and relevant in dealing with methodology for our own discipline, we are forced along other channels.

Dr David Tyrrell:[62] I notice that Dr Hope-Simpson was going to be here, but as he was unable to come I thought we ought to mention him as a case history of the development of a very interesting general practitioner.[63] He, I think, would put his research inspiration firmly with William Pickles and Wensleydale, and he spent most of his professional career looking at infectious diseases from a clinical point of view. He did work which is published and quoted throughout the world on the epidemiology of chickenpox and shingles.[64] Then he became interested in respiratory infections, acute minor respiratory infections, again from the clinical point of view. He set up a practice in Cirencester but had some problems. He had one partner who helped to keep the practice going, but he didn't have a research staff, so he and his wife spent every evening producing Pickles-style charts, in their living room. They documented every respiratory disease in the practice – it wasn't a

[62] Dr David Tyrrell FRS (b. 1925) was a member of the scientific staff of the MRC Common Cold Unit at Salisbury from 1957 and its Director from 1982 until his retirement in 1990.

[63] Dr R Edgar Hope-Simpson FRCGP (b. 1908) was in general practice from 1932 in Beaminster, Dorset, and in Cirencester from 1945 until his retirement in 1976. He also directed the Epidemiological Research Unit, a constituent laboratory of the Public Health Laboratory Service, supported by an MRC grant and located at his surgery from 1947 to 1960 when a small virological lab was established in it. He and the Unit continued their epidemiological studies until 1996. See Hope-Simpson R E. (1958) The first Gale Memorial Lecture: Opportunities and pitfalls in general practice research. *Journal of the College of General Practitioners* **1**: 225–245. Unable to attend the meeting he wrote later: 'I am increasingly distressed by the near disappearance of this observational research, a sort of natural history of disease...where are the young Keith Hodgkins, Tudor Harts, Ekke von Kuensbergs, W O Williams, Ian Watsons?' Letter to Dr Tilli Tansey and Mrs Lois Reynolds, 22 June 1998. This lengthy letter, describing several of Hope-Simpson's research projects, has been deposited with a large collection of his papers in the Contemporary Medical Archives Centre, Wellcome Institute for the History of Medicine.

[64] Hope-Simpson R E. (1954) Studies on shingles. Is the virus ordinary chickenpox virus? *Lancet* **i**: 1299–1302.

large one, fortunately – over a period of years. These charts were the basis of his deductions about the influence of climate and season on the frequency of clinical respiratory disease. When the academic world caught up with this and we were able to look for viruses, he was then in a position to have a public health laboratory research unit built into the same property as he was using as his practice. It was run by Dr Peter Higgins.[65] They started to document what viruses were coming and going and causing this fascinating range of respiratory disease and some substantial publications resulted. He was not an organizer of teams. If he was here, I think he would say his research was curiosity driven – it came from inside him. Although he's getting very old now, if he were here we would all have been getting a little restless in our seats at the enthusiasm that he is still capable of generating. He asked me for my opinion two weeks ago on a paper on the polymerase chain reaction published by five Russians and which I had never heard of!

Tait: We now have two rather different aspects of research in general practice to look at. We want to look at multi-centre research and collaborative research between different practices, where individual GPs do disciplined recording, but don't have to organize the research.

James Mackenzie saw the great potential value for medical research presented by the general practitioner's role of providing long-term medical care to a stable and defined population. That concept was reinforced by the morbidity surveys initiated by the Royal College of General Practitioners.[66] I would think that the first time many of us in general practice became involved in research was when Clifford Kay started writing to us about the oral contraception study. So could I ask him to get us going on the subject of collaborative research in general practice.

Kay: Well, thank you very much. I have been asked to talk about these collaborative studies, multi-observer studies, but before I start I think I need to bring to everybody's attention, if they don't already know, that a great deal of what has been said today about the Royal College is already published in two books, first of all *A History of the Royal College of General Practitioners: The first 25 years*, of which John Horder was an author and just 15 years later, not surprisingly, *Forty Years On*.[67] There is a great deal of valuable historical information in those, including a chapter on my subject, strangely enough written by me.

We have to look back and realize that as a collaborative body, as a Royal College, it became a natural consequence that it should predominantly try to

[65] See Tansey E M, Reynolds L A. (eds) (1998) *The MRC Common Cold Unit*, this volume.

[66] National Morbidity Surveys. op. cit. note 24 above.

[67] Fry J, Hunt J, Pinsent, R J F H (eds). (1983) *A History of the Royal College of General Practitioners: The first 25 years*. Lancaster: MT Press Limited. Gray D J P (ed.). (1992*) Forty Years On: The story of the first forty years of the Royal College of General Practitioners*. London: Atalink Ltd for the Royal College of General Practitioners.

organize practitioners, its own members, to do research together and one of the major advantages in doing this was to get the larger numbers of clinical cases that were required to produce some sort of confident results.

It's interesting to look back at Mackenzie's own efforts. His major research was based upon simple clinical observation of his own patients in his own practice for very many years and that's the foundation of his reputation. He then went on to be a consultant cardiologist in London and only when he retired from there did he conceive the idea that if he could do so much himself in his own practice, how much better it would be if practices joined together, pooled their resources, and the possibilities of producing dramatically better results seemed to him to be self evident. He set up an institute in St Andrews and got all the local practitioners to contribute information to him – and it failed. It's interesting to know why Mackenzie thought it failed and why others thought it had failed.[68] It failed, I think, for two reasons, first of all he didn't have general practitioners collaborating with him who had the necessary research orientation, never mind research training. But, interestingly, too, when he started to try and put together the results that came in from the various practices he realized that he hadn't got the statistical tools to aggregate the data. In fact, successful collaborative research depended very much on the work of Bradford Hill who came along 15 to 20 years later and without that statistical basis, that sort of research would have been very difficult.[69]

We need to remember the extraordinary advantages that we have in general practice in the United Kingdom which goes back to what I presume can only be an accident of Lloyd George's 1911 National Insurance Act, which determined that patients should be registered with their doctor. We have a defined population, and if they change their doctor, their records should go with them. Finally, and perhaps most importantly, that general practice should have a gatekeeper role to the secondary services. The result of that is that the information collected by general practitioners can reflect not only what they observe themselves in their own practice, but the outcome of their patients' care in the secondary and tertiary care sectors of the health service. These characteristics, of course, persisted in the 1946 National Health Service Act and I am glad to say is being reinforced by the current proposals for the development of general practice as the major part of the health service. Without these conditions we would have had great difficulty in establishing a proper epidemiological basis for combining valid observations from many

[68] The Institute for Clinical Research at St Andrews was established to study the origins of disease with a view to prevention, by recruiting local GPs to observe and record the progress of disease in their patients. The Institute would provide postgraduate training in clinical research methods. Mackenzie gave up the directorship of the unit in 1924 and died the following year. Work continued until 1945. op. cit. note 2 above.

[69] Sir Austin Bradford Hill FRS (1897–1991) was Professor of Medical Statistics at the London School of Hygiene and Tropical Medicine from 1945 until 1961. A series of 17 articles published by him in the *Lancet* in 1937 introduced the medical researcher to the use of statistics (reprinted as *Principles of Medical Statistics.* London : The Lancet, 1937).

practices to produce aggregated data. You only have to look at those countries that haven't got these advantages to realize what an amazing difficulty they have in trying to evaluate information from the general practice base.

One of the very earliest multi-observer studies was conducted by Dr Ian Watson, and he was very substantially supported and helped by Mrs Joan Mant, who's sitting at the back of the room, who was the research infrastructure in herself, not only for Ian Watson, but also for the research committee for the council of the College for many years.[70] Nowadays she'd be called executive director, or something equally grand, but at that time she was Clerk to the Committee, and without her, her coordination and her administration, we wouldn't have got anything done. Her work was there in the background in the development of all the College's research activities. Ian Watson's work became crystallized in the form of an epidemic observation unit. I think that preceded the formation of the Birmingham unit with Donald Crombie and Robin Pinsent, which came very soon afterwards. From that time other units of the college were formed, of which one of course was my own unit in Manchester which was set up specifically to do the oral contraception study.[71] At one time we actually had six research units going, two of of them were derived from Ian Watson's epidemic observation unit. When he became President [of the Royal College of General Practitioners in 1970] he divided the work of the unit between two people, W O Williams in Swansea and Paul Grob in Guildford. At the same time in Scotland, as a parallel development, a research support unit had been set up in Dundee and that was brought into the fold of what was now called the research division [of the College].

Finally the sixth unit came along because Maurice Stone,[72] to whom Donald has already referred, realized that working on his own he was very vulnerable. The years of research, which he had carried out solely in his own practice on ischaemic heart disease and all the factors which were involved in its development, might go astray completely if, unfortunately, anything untoward happened to him. So he asked whether he could become another College research unit and this was accepted. He worked in Leigh in South Lancashire and so the unit was called the RCGP Leigh Clinical Research Unit. The name was important, because all the other units were epidemiological in nature and his was entirely clinical. He did manage to do something very significant in his recognition of fibrinogen as a major factor for the development of ischaemic heart disease. Tragically the very

[70] Dr George Ian Watson (d. 1979) was in general practice at Peaslake, Surrey and a member of the Foundation Council of the [Royal] College of General Practitioners and its President from 1970 to 1972. He founded the College's Epidemic Observation Unit at Guildford in 1953. For discussion on his multipractice clinical study of antibiotics and measles study in 1956, see Watson G I. (1982) *Epidemiology and Research in General Practice*. London: RCGP, 204.

[71] Royal College of General Practitioners (1974) *Oral Contraceptives and Health*. London: Pitman Medical.

[72] See biographical note 22 above.

circumstances which he sought to avoid led to disaster when he found that he had advanced cancer and died very shortly afterwards. It was impossible to find a suitable successor and the unit came to an end. But Maurice had achieved quite a lot by that time.

We have talked briefly about the need for advice from the College centrally to those who are trying to embark on research, and I think it was suggested earlier in the day that perhaps we hadn't done enough in that direction and maybe that is true, you could never do enough. However Robin Pinsent relinquished the Chair of the Research Committee to become Research Adviser to the College, funded by the Nuffield Foundation. Subsequently, the Chairmen of the research committees took upon themselves the job of trying to guide people in the right direction, sometimes giving advice, but more often pointing them to somebody else who was better equipped to give it. That policy has continued. There was a gap for several years, but more recently Geoffrey Rose, who tragically died during his tenure, and now Paul Freeling, have taken on that task.

That advisory function has always been acknowledged by the College as an important part of its remit. It becomes less important, of course, as university departments of general practice were set up around the country with the necessary expertise to provide advice to people locally.

I think that one of the other points that we may have skimmed over was the College's part in developing a language of health. This started with what was called the RCGP classification by Robin Pinsent and Donald Crombie. It was very brief, about 500 terms and it enabled people to allocate a code to certain conditions which they were seeing regularly. This was the research register.[73] That I think was an important initiative by the College. It was taken up on a world-wide scale by the world organization of general practice, called WONCA (World Organization of National Colleges and Academies of Family Medicine/General Practice). They developed an international classification, but that has never had quite the impact which I think it should have had, and has never been adopted much in this country.

The classification was taken into the computer age by being greatly expanded and then distributed on disk in 1984 and 1986, as the College's computerized classification. That really was the background to the present position in which the profession realized that a single standardized language of health was absolutely crucial if you were going to get communication between the different branches of the health service, on a fully standardized basis. In 1988 a working party of the

[73] College of General Practitioners, Records Unit Working Party. (1959) A classification of disease. *Journal of the College of General Practitioners* **2**:140–159. *idem* Records and Statistical Unit. (1963) Disease labels. *Journal of the Royal College of General Practitioners* **6**: 225–232. The Read Codes patient records system was heavily criticized by the Commons public accouts committee, see Hecke D. (1998) MPs attack NHS chiefs over computer records system. *Guardian*, 6 August.

Royal College of General Practitioners and General Medical Services Committee Joint Computer Group advised the Department of Health that the system developed by James Read from Loughborough was probably the system which ought to be adopted as a standard. That happened with quite remarkable rapidity. The Department [of Health] bought his copyright and there is now a major empire in Loughborough called the NHS Centre for Coding and Classification.[74] The Classification has been extended, so that it is recommended across the health service. It is an essential means for communication and will, I think, help to produce population research across all boundaries of the health service.

Tait: Would you like to tell us something personal about the very beginning of your contraception study and what motivated you to do it and who was involved?

Kay: Well, I shall have to go back a little bit further then and tell another story. When the College was founded in 1952 I immediately joined, but being a very junior member of the profession I could only join as an associate. One of the advantages of the College is that it foresaw the necessity to try and disperse power throughout the country. Unlike many of the other colleges, there is a structure which is regionally based and these are called Faculties. I went along to the preliminary meeting of our faculty in Manchester, the North West England Faculty. I think it was sometime in 1953. Looking around me there were a lot of very senior and eminent people and I stammered to somebody, 'What sort of research are you going to do?' and immediately got co-opted to the faculty board and then to the research committee. Before long I was appointed the first Honorary Secretary of the Research Committee and in a matter of weeks a directive came down from John Hunt which said that somebody so junior cannot possibly be an Honorary Secretary, so I was made assistant Honorary Secretary. At one time the Chairman was Patrick Byrne,[75] and I think we should remember Patrick not only for his efforts in educational research, which were very substantial, but his interest in research more generally. He was one of those who suggested in 1964 that I should be co-opted onto the central Research Committee and that's how I got there.

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[74] Dr James Read, a general practitioner in Loughborough, became the first Director of the NHS Centre for Coding and Classification (CCC). See Chisholm J. (1990) The Read clinical classification. *British Medical Journal* **300**: 1092. The Read Codes patient records system was heavily criticised by the House of Commons Public Accounts Committee. See Hencke D. (1998) MPs attack NHS chiefs over computer records system. *Guardian* (6 August 1998).

[75] See biographical note 61 above. See also Byrne P S. (1973) University departments of general practice and the undergraduate teaching of general practice in the United Kingdom in 1972. *Journal of the Royal College of General Practitioners*. **23**(Suppl. 1):1–12.

Later there was this discussion, which everybody knows began with Ekke Kuenssberg[76] who saw this enormous opportunity for observing what was happening to women who were taking the Pill in their millions around the world. I had had an interest in family planning for some time and I wrote to Donald Crombie, who was Chairman of the Research Committee, and said if anything's going to be set up I'd be interested to be involved in the planning. There was a special meeting of the Research Committee in 1966 and, to my astonishment, Donald Crombie turned to me and said, 'Will you be Recorder?' and I perhaps foolishly said yes. Later on he said, 'Do you know what's involved?' and I said yes, again, but I was completely wrong. That's how I got started.

Professor Sir Stanley Peart:[77] I suppose my first acquaintance with general practice was in 1945, when I qualified, and I never did a house surgeon's job, even though I got a primary FRCS, the easy way I have to tell you.[78] I went down to Hayling Island and I used to ride a bicycle, as I couldn't drive a car then, unusual for a medical student, but I couldn't. I used to ride around Hayling Island on this bicycle, doing a locum general practice on my own, because the father of one of my student colleagues had asked me to do it, he wasn't very well and had had to retire. It was the days of general practice when you got half-a-crown on the table when you saw the patient. I don't know how good I was with the patients, but I certainly got quite fit. The reason I went to Hayling Island was actually because my wife-to-be was stationed in Portsmouth.

My next acquaintance with general practice, other than seeing patients for general practitioners, was when, out of the blue, I was asked to take on the Chairmanship of an MRC working party.[79] A question had been asked by Colin Dollery about the treatment of mild hypertension. You may remember, or may not, that the Veterans Administration in the United States had established that the treatment of very severe high blood pressure, basically in hospital patients, was a success. The drugs used were difficult but nevertheless they established quite clearly that it was worth treating. Up to that time, the hard evidence, the statistics that

[76] Dr Ekkehard V Kuenssberg (b. 1913) was in general practice in Edinburgh from 1939. He was President of the Royal College of General Practitioners from 1976 to 1979 and a member of the Subcommittee on Adverse Reactions of the Committee on Safety of Drugs from 1964 to 1971. See Tansey E M, Reynolds L A. (eds) (1997) The Committee on Safety of Drugs. In Tansey E M, Catterall P P, Christie D A, Willhoft S V, Reynolds L A. (eds) *Wellcome Witnesses to Twentieth Century Medicine*. Vol. 1. London: Wellcome Trust.

[77] Professor Sir Stanley Peart FRS, FRCP (b. 1922) was Professor of Medicine, University of London, at St Mary's Hospital Medical School, from 1957 to 1987, now Emeritus.

[78] Sir Stanley Peart wrote: 'It used to be "Anatomy and Physiology" taken after second MB – at the RCS. (No surgery!)' Letter to Dr Tilli Tansey, 16 March 1998.

[79] Sir Stanley Peart chaired the Hypertension Working Party from 1973 to 1985. It supervised the clinical trial which lasted eight years from 1977, involved 17 000 patients in 170 general practices. The controlled single blind study randomly allocated patients to take bendrofluazide or propranolol or placebo tablets.

people had been asking for, didn't really exist. It existed for very, very severe hypertension, but not for anything else. So, out of the blue, came this invitation. And I looked at it, and I thought well, it's not like the thing that I am any good at, but, flattered by the invitation, I took it on. That enabled me to join the Working Party which contained a large number of friends, which was a real boon, because on that committee there was Bill Miall. I'd first come into contact with Bill Miall at St Mary's, we were both at St Mary's, and he'd gone his ways, including Jamaica, and he'd come back and was really basically responsible for the organization of the resultant trial at Northwick Park. There was Geoff Rose, whom I had first known as a registrar at St Mary's.[80] I eventually shared Geoff Rose with the London School of Hygiene and Tropical Medicine, because the then Professor at the London School was an old friend of mine, and Geoff Rose kept me in line because we always used to have a weekly death and discharge meeting, laughingly called audit now, and as I went through my anecdotal medicine he used to say, 'But you realize that if you'd had more numbers and looked at it more critically, you'd have got perhaps a slightly different approach to that particular patient.' I used to accept this reluctantly, but he was right. Geoff Rose and I kept up that long relationship, because we both believed, he very passionately as you know, in the role of clinical epidemiology in practice and its proper relationship to patients, so he always did sessions on the beds on the medical unit with me. I made quite sure that I never had two epidemiologists on the beds and was content as long as one of them was somebody else's. That was a very fruitful occasion and, of course, there was Tom Meade, with whom I have had a very long association indeed, a very pleasant association. And Colin Dollery believed he was looking after the therapeutics of the trial, to his satisfaction at any rate, and so that was how I was launched into a completely new direction for me, into how you ran a Working Party which was to investigate the vast subject of how you should treat mild hypertension in a large enough population.

A number of problems arose and I will before too long ask Bill Miall, who knows far more about it than I do, to speak on this, and we will then go on to the second trial which is nearer to my heart, the treatment of high blood pressure in the elderly. The number of things that we had to consider seemed to me very important, and I have to say at the outset I don't think they could be carried out in this way except that the country had a National Health Service which mattered and a group of doctors who were willing to devote themselves to this sort of large-scale research which was well directed because Bill Miall put in tremendous effort and tremendous mileage in making sure that that trial worked. So the question was:

[80] Dr Geoffrey Arthur Rose FRCP, FRCGP (1926–1993) was lecturer, later senior lecturer in epidemiology at the London School of Hygiene and Tropical Medicine and at St Mary's. He succeeded Donald Reid to the Chair of Epidemiology at the London School of Hygiene and Tropical Medicine in 1977 until his retirement when he became a Research Adviser to the Royal College of General Practitioners.

how you did it? To get a randomized control trial on the scale that was necessary was a very big problem at the outset, because you had to find out what was the prevalence of the condition before you could decide how big a trial you had to run, and that was the first major hurdle. There was a certain guesstimating going on about prevalence and hopefully some of the figures would eventually announce themselves as the trial progressed, and the numbers eventually had to be very large. Then how to do it? How would you organize it? I hope that Bill will very shortly tell us his approach to this problem.

There emerged, and I think that this is a very important aspect to me, the need for nurses attached to the practices who would carry out a great deal of the work. This is a very important aspect of research in general practice. We've become very familiar now with the rising role of nurses in general practices, the College of Nursing has been coming up behind all the time as to what nurses can do. You get used to the fact that anybody can do anything if they are well trained and they do. The research nurses, as they were called, emerged as a very key part of it and I would associate the name of Greta Barnes in the first place, with that development, because the organization of those nurses and the training of those nurses became paramount.[81]

Finally, the collection of data, and the secrecy which you had to adopt to make sure that that data was kept under wraps. I have to tell you that at one stage, one thing which gave me a great headache was the fact that well on into the trial, we got what seemed to be quite a leak, the sort that any government would be proud of, and I had the unsavoury task of trying to track down where this leak was coming from. I suspected one or two people, some of my friends even. I remember Geoff Rose being quite offended when I asked him whether he had let loose, inadvertently, to somebody the results of the trial as they were emerging. But Geoff, being Geoff, of course took it, and needless to say Geoff would not divulge anything. But we did track it down finally. You wouldn't, of course, get a conviction in the O J Simpson trial on that sort of evidence. I think I have given a very sketchy account of what I have learned about the importance of the organization of the trial and the importance of the National Health Service and the nurses and how you collate data. How you make sure that that data is really reliable, that is, quality control in clinical trials on a vast scale, is a very important subject and I am sure that Bill has got a very much more worthwhile contribution to make and I would like to ask Bill Miall to contribute now.

[81] Mrs Greta Barnes, who was a member of the MRC Working Party on Mild to Moderate Hypertension until 1983, was unable to attend the Witness Seminar.

Dr Bill Miall:[82] I think it might be useful if I were to spell out some of the reasons why the MRC treatment trial for mild hypertension was successful and influential in the development of research in general practice. Stan Peart wrote in the *Lancet* that in his opinion the most important result obtained in the trial was its demonstration that given the right conditions, a large group of general practitioners and their patients were willing and able to follow a rather complicated protocol for the screening and follow-up of appropriate patients for a period of five years.[83] In his view this was more important than determining whether or not one should treat hypertension at an earlier stage than was commonly the practice at that time. Perhaps he was right though I did not agree at the time.

But I think there were a series of factors which contributed to the success of that study. Perhaps the main one was that the question we were trying to answer concerned every practice in the country and a lot of GPs wanted to know the answer. We started with the advantage of an important and relevant question. A second factor was that the condition was easily measured, easily defined and very common so that the screening of appropriate adults in an ordinary group practice yielded an average of about 100 mildly hypertensive people suitable for entry into the trial.

The amount of time required was also an important factor in the success of the programme. It was much greater than was needed for the therapeutic trials for hypertension, which at that time were largely being mounted by the pharmaceutical industry. The size of the commitment and help with staff and training that the MRC was able to give acted as a real stimulus to the interest of the GPs concerned.

Another factor was that the trial involved active intervention. This added an element of interest not present in purely observational studies. The MRC was able to help with the programme both financially and in terms of training and provision of facilities. The Department of Health were at first unwilling to encourage the payment of GPs for research on their own patients but we found out that the precedent for payment had already been set by Dr Kay in his oral contraception study and we were able to persuade the Department of Health to allow GPs to get the same rate of payment for sessions with the MRC that they would have got for clinical assistantships in hospitals. A modest rate of payment for the considerable work load we imposed was an essential element of the trial's success.

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[82] Dr William Miall (b. 1917) was Director of the MRC Epidemiology Unit in Jamaica from 1962 to 1970; a Consultant in Epidemiology and member of the scientific staff in the Epidemiology and Medical Care Unit at Northwick Park Hospital, Harrow, from 1971 to 1983. He was Secretary of the Working Party on Mild to Moderate Hypertension from 1973 to 1983.

[83] Peart W S. (1980) Point of View: The pharmaceutical industry: research and responsibility. *Lancet* **ii**: 465–466.

Another very important factor, as mentioned by Stan, was the key role played by nurses. Part-time nurses were recruited specifically for trial work. In most cases the trial was their only commitment to the practice. They were all SRNs, mostly rather well qualified and interesting people, often partners' wives with a real interest in the problem. The trial also recruited an excellent team of training nurses whose job was to ensure that the high standards were maintained. The role of the nurses in the study was crucial. They relieved the partners of much of the load. They came into the scheme and it was much appreciated by the patients and by the doctors. We tried initially, in a pilot trial, to determine what would be the best way of recruiting patients for this trial and we tried industry and we tried various screening organizations, but by far the best was general practice, and the trial finished up with something like 17 000 patients observed for an average of five years and at that stage involved something under 200 practices scattered throughout the country.

These are some of the factors that I believe contributed to the success of that particular study. Another was the spirit of collaboration generated and enhanced by annual conferences to which one doctor and one nurse from each clinic were invited. These lively and enjoyable two-day meetings also helped to unify the group. Those responsible for the running of the trial were convinced that the decision to mount it in the context of general practice was the right one.

Tait: Thank you, Bill, very much. I remember the sense of being actively involved and the sense of enjoyment many doctors had in the companionship that you managed to give them. Doctors and nurses involved would all meet once or twice a year and you really took a lot of trouble to make them feel that they were involved. That was all skillfully done.

Peart: Can I just take it on from there. The next trial on the elderly brought in a slightly different group. The Working Party stayed much the same, except eventually Bill got too elderly even for that. The same problems were there, but we had got a little more used to them by that time. What I want to show is that there has been an evolution within the MRC in its approach to this [kind of project] since then. Bill, among others, used to importune Head Office about the costs of running an annual meeting for the doctors, nurses, and everybody related to the trial. It was a very important and very interesting meeting, because the people running the trial were bombarded with critical enquiries from the people *in* the trial. I commend that sort of meeting to anybody running large-scale trials. At that time, the MRC looked upon us as rather expensive (you have got to remember that a big-scale trial costs millions of pounds), but they supported us. The

outcome of the trial really matters, because you hope it is going to influence clinical practice on a large scale.

Now we are in the evidence-based medicine era, clinical trials will come even more into their own. But they are all expensive, and it takes us right up to current developments, where the MRC regards the NHS practice group [the Framework] as a national asset.[84] That's quite an achievement, isn't it, to become a national asset? This leads me naturally to ask Tom Meade to talk about his view, because of the HRT trial which he's worked so hard to get financed.[85] I hope he gives you some idea of what it has involved, and the scale of the trial, which is going to be one of the most important for women, and probably also indirectly for men. This trial and its organization has built upon this Framework, *the* Framework of general practice within the National Health Service. We thought initially in terms of two or three hundred practices with the hypertension trial; two or three hundred practices scattered over the whole of the United Kingdom. Now we are talking of nearly a thousand practices. So I'll ask Tom if he wouldn't mind commenting.

Professor Tom Meade:[86] I'll bring the recent history of the Framework up to date fairly rapidly, but before I do that from the historical point of view you might be interested to know that Bill [Miall] set up the Framework and ran the trial from a room that was labelled '007' at Northwick Park, so we knew we had to look out, but I don't think he ever actually had to use the ultimate sanction. Two other people here today whom I should mention are Julian Tudor Hart, who has been a member of the Framework and on whose practice we have relied for a very important function indeed and that is testing out proposals which perhaps seem extremely difficult, to the point of being impossible. For example, can you actually put people on aspirin and warfarin at the same time? Can you collect 24-hour samples of urine on a large scale? Can you get people to take salt-free diets and so on? That's been a very important function of Julian's practice in the Framework. The other is Stan [Peart] himself, who has answered part of David Morrell's question, having completed his journey from rabbit kidneys to epidemiology and

[84] The Framework was created for the mild hypertension pilot study in 1973, which led to the full-scale trial from 1977 to 1985. See Medical Research Council Working Party. (1985) MRC trial of treatment of mild hypertension: principal results. *British Medical Journal* **291**: 97–104. Miall W E, Greenberg G. (1987) *Mild Hypertension: Is there pressure to treat? An account of the MRC trial.* Medical Research Council Working Party on Mild to Moderate Hypertension. Cambridge: Cambridge University Press.

[85] Vickers M R, Meade T W, Wilkes H C. (1995) Hormone replacement therapy and cardiovascular disease: The case for a randomized controlled trial. In: *Non-reproductive Actions of Sex Steroids, Ciba Foundation Symposium 191*. Chichester: John Wiley and Sons Ltd.

[86] Professor Thomas Meade FRS, FRCP (b. 1936) has been Director of the MRC Epidemiology and Medical Care Unit since 1970 at Northwick Park Hospital until it moved to the Wolfson Institute of Preventive Medicine in 1992. He is also Honorary Consultant in Epidemiology at Bart's and Northwick Park Hospital, Harrow.

clinical trials, and brought a breadth of experience and advice which very few other people can match.

Now, to bring things up to date, first of all let me say that I would like to reiterate the importance of nurses in this organization. It's actually called the General Practice Research Framework, which perhaps seems to imply the contribution of only the doctors, but the bulk of the work, I should think 85 per cent of any study, is done by nurses, and the importance of recruiting and training them has already been emphasized. We haven't actually found it all that difficult to recruit practices into trials where perhaps the motivation comes mainly from one of the partners. There have obviously been some practices who have not taken part in a study because one or more of the other partners have vetoed it, but they have been few and far between, and I have been very impressed by the extent to which our contact doctors have usually been able to persuade their partners to sink their individual differences, and to come into trials of topics that they may not have been terribly interested in at the beginning and may even have had some reservations about. The way the Framework developed was really largely down to Stan [Peart] and Bill [Miall], who drew the MRC's attention to the high quality of the two hypertension trials and so in 1986 the MRC designated the Framework as a national resource which should be open to anybody whose research could most appropriately be carried out through general practice. It's been used, apart from my own unit for our own research, by other MRC groups, by the Department of Health, the Public Health Laboratory Service and even by one group in the United States who've actually come over here to do their work, because they think that it can only be done through an organization which has all the advantages of British general practice.

The next step after the designation of the Framework as a national resource was the decision of the MRC in 1992 to expand it, and to make it more representative in terms of numbers of practices of different sizes, geographical distribution, deprivation indices, and so on, and it now consists of 900 practices, covering about 11 per cent of the whole of the UK population. Apart from the two hypertension trials, there are at present ten full-scale studies in progress dealing with antithrombotic treatment, with surveys of gastroenteritis following the problem of salmonella in eggs, trials on asthma, the hormone replacement therapy trial, which Stan has referred to, involves probably about 500 of these practices and 18 000 women, and there are pilot studies in progress dealing with back pain, eye disease, preventing hip fractures, atrial fibrillation and so on, so it has got a very wide agenda now. The MRC, on a rough calculation, is likely to put in something in the order of £50 million into the Framework over the next five years, and other organizations are contributing as well. I think it would be wrong to overlook the fact that there have been, in the past, tensions between the MRC and the College [Royal College of General Practitioners] over the MRC's role in primary care

research, but fortunately one of my colleagues at St Bartholomew's and the Royal London School of Medicine and Dentistry is Yvonne Carter, who is the new Chair of the College's Research Committee and we have had some fruitful discussions about joint enterprises.

The final point I would make is that in my view there are not all that many GPs who are interested in becoming fully fledged independent research workers in their own right. I do not think we should overlook the tremendous degree of altruism that is the main motivation for the contribution the GPs make to the Framework's programme which they see as a way of helping to answer important clinical questions. I certainly support, indeed the MRC is taking active steps to encourage, the training and the active involvement of those GPs who do want to become involved in research, but I don't think we should overlook this other, much larger constituency, those that have no great interest in becoming independent research workers, but who want to contribute to research in general practice.

Tait: Thank you very much, Tom. I think that's extremely useful.

Booth: I think it is natural that the speakers have spoken with a certain degree of modesty about their achievements. What I would like to say, as someone with an interest in the history of the MRC, is that if you read the Council Minutes, their reports for the 1920s and 1930s, there were repeated discussions over whether or not you can involve the MRC in research in general practice and over and over again the answer was no. That went on for a very long time. The research in hypertension and the setting up of the Framework was the first time that a national body of research thought big about research in general practice and that is, I think, an achievement for which the speakers deserve a great deal of credit; the MRC too.

Tait: It does look as though they have actually reintroduced an interest in research into general practice and I think the question of getting the practice alongside is terribly important, and also the question of some kind of sensible financial support for the people who are doing the research.

Hannay: Just a very quick comment about general practice as a data source for research. It clearly is important, but in many ways the pendulum has swung too far and there are studies that are intended to take place in general practice, but which fail because general practitioners feel that they are just getting swamped with requests for data. The practice I was in, in the middle of Sheffield, wasn't a very

big one. At one stage we were getting the equivalent of one questionnaire per working day.

Tait: That's a bit different from the kind of research we are talking about.

Hannay: I agree, but what I was trying to emphasize was the pressures of collecting data in general practice are now of quite a different nature, and that will have implications for the kind of very important exercise which the MRC has been involved in.

Kay: I think in fairness to the Medical Research Council, we must record that they also funded the oral contraception study which ante-dated the hypertension study by some years, so the breech had already been made. The question of reimbursing practitioners was always a very difficult one and we managed to persuade them to pay the magnificent sum of £10 a year, not per patient, but per doctor, for everything they did in the oral contraception study. It was a modest sum in 1968. It became a ridiculous sum when they refused to increase it over the following 20 years. So I am not quite sure that we have won that battle.

Tait: Thank you very much. I want to move on because we have two very interesting and important research issues to look at. Research in a rather broader sense than we have looked at before. We have seen that in some cases research took the form of an examination of the nature and incidence of the diseases seen in general practice. But other doctors wanted to explore the nature and use of the doctor–patient relationship in general practice. The name of Michael Balint is closely linked with this research. I hope Marshall Marinker, who was involved in that research will start our discussion. The other area I want us to cover is the way in which medical sociologists and social scientists carried out research in and about general practice. There was a feeling that we needed to understand what was happening to us more clearly and they worked with us very well. Margot Jefferys did a big study with a Kentish Town practice and Ann Cartwright, who is also with us today, carried out two studies in 1964 and 1977, which were very influential. So perhaps we could start with Marshall's memories of Michael Balint and his influence on general practice. The habit of navel gazing as some people have called it.

Marinker:[87] Thank you very much for that charming introduction, Ian, I look forward to doing the same for you one day. At the beginning of the afternoon Keith Hodgkin said that the most important things we had to talk about were our mistakes, our errors, our blind alleys, and since I am going to be a bit autobiographical, you can be sure that that's what I'll be talking about this afternoon. Listening to the last series of presentations, I began to wonder as I have often done in the past if there was a difference between research *in* general practice and research *about* general practice. I think the hypertension studies described by Peart were terribly important, were ones that were *in* general practice and maybe could only have been done because of the nature of general practice. But there are questions about whether it is *about* general practice. So I have to ask, 'What is the nature of general practice' and has research anything to do with it? I am not sure that I know that it has. Someone else this afternoon, I think it was you, Donald [Crombie], said something like, 'No discipline can lay claim to the name without research', and that again made me wonder whether general practice was a discipline. I have certainly spent most of my professional life claiming that it was, writing endlessly about it, and banging on about it to the boredom of everyone else. But later in life I am beginning to think that general practice is a craft. That's a very important word in my lexicon. A craft in which a number of different disciplines can enlighten what we are doing.

I have to confess that one of the things that Stan Peart did, which helped me enormously when I went to Leicester, was to publish an article called 'Death of the professor of medicine'. I very briefly lamented his passing and then laid claim to the title.[88] Unfortunately, John Swales had been appointed [Professor of Medicine] to Leicester the same week that I had, and he wasn't letting go. But I have often felt that if general practice has a root discipline, then it's medicine. It's one that we share, but one we may see differently, see it through different eyes and have different experiences of it.

I want to talk about two different sorts of worlds that I have lived with in my life in medicine: they are in tension, they form a paradox, but somehow general practitioners have to live with it. In many ways for me they are summarized by the two great influences in my professional life. One was Michael Balint[89] who many of you know was a psychoanalyst. The other was Geoff Rose,[90] who was my head of department when I went to St Mary's. He was a clinical epidemiologist and lots of people have paid much respect to Geoff Rose, none more than I. He had a

[87] See biographical note 49 above.

[88] Peart W S. (1970) Death of the professor of medicine. *Lancet* **i**: 401–402.

[89] Dr Michael Balint (1896–1990), psychoanalyst, organized his first Training-cum-Research Seminar in 1950 while at the Tavistock Clinic, London. He moved to the Department of Psychological Medicine at UCH London in 1961. See Balint M. (1957) *The Doctor, his Patient and the Illness* (2nd edn 1964). London: Pitman Medical.

[90] See biographical note 80 above.

feeling for the world of general practice which was really quite remarkable in someone from a different part of medicine. This feeling went far beyond his interest in epidemiology. I have often felt that the whole of my professional life has felt like a battle between the ghosts of Marx and Freud. Or, in my language, the influence of Michael Balint and Julian Tudor Hart. I say that quite seriously, because both are giants of contemporary general practice, and the differences between their approaches remain important.

I am going to give you scraps of autobiography and tell you about my failures. The very first piece of research I ever did was to ask if frequent attenders were the same as, or different from, other patients in the practice. The kindest thing to say about that work was that I was a young very, very inexperienced, single-handed GP in a town that no-one had heard of, and I had what was a quarter-baked, not even a half-baked idea. I brought it to the Royal College of General Practitioners, the College as it then was, of which I was an associate, and the help and support that I got from people like Donald [Crombie], Robin Pinsent, Ekke Kuenssberg, Basil Slater, was astonishing. I hope that the College is still doing that for its young doctors and giving them that kind of support. Within two or three weeks of putting my head above the parapet I spent a day with you [Donald Crombie] and with Robin and your staff, being taught a bit about your methodologies, and a day with Mrs Marcus, who ran the Family Register research in Edinburgh. They said 'Go to see the two Scots who know most about this'. The two Scots were called Kuenssberg and Sklaroff. I met those two Celts. I learned a lot about the anthropological approach they were taking to family registers and so on.

At about the same time I met and been entranced by Michael Balint – and then spent seven years at his seminars. We'll come onto that in a moment. What I want to tell you about now is the paper that I published in the College *Journal* a year or two into this frequent attenders study (which by the way I never completed, because in the end I had looked at so many variables that I renamed the study 'The meaning of life' – and I never found out what the answer was).[91]

For me, the failure of that paper encapsulates what my life as an academic has been about, and what general practice is about. The first half of the paper has statistical tables in it. John Howie[92] doesn't believe I ever published a paper with statistical tables, but I promise you I published two that year. They were not terribly enlightening, but they were looking at differences in the way in which different subsets of my practice population of 4000 appeared to behave. Then suddenly the paper erupts into family genealogies, and stories about these patients and the fact that their illnesses, which didn't seem to have a name, but seemed to

[91] Marinker M. (1967) Studies of contact behaviour in a general practice. 1. An exposition of methods and a consideration of meanings. *Journal of the Royal College of General Practitioners* **14**: 59–66.

[92] Professor John Howie (b. 1937) was a general practitioner in Glasgow from 1966 to 1970 and has been Professor of General Practice at the University of Edinburgh since 1980. He was unable to attend the Witness Seminar.

have a pattern. One of the things that I did – you'll remember this Donald [Crombie] – was to invent a research tool which I never actually published or used. I made something which I called a 'familigram'. It looked remarkably like music manuscript and I think that's why I liked it so much because it didn't have very much to do with technical medicine, with which I was rather disenchanted at the time. What I did was to plot on this 'music manuscript', the attendances of members of the same family, of which I had a very detailed family tree. You can only construct such a register in a small town where everybody knows everybody else. The bars of this music were months and you could then see incredibly interesting runs and patterns, if you chose the right families. What was interesting was that Donald [Crombie] had introduced me to a woman called Ruth Peachie. She was an anthropologist from the States who had invented exactly the same tool. I don't know what she ever did with it after that, but she and I met, thanks to you [Donald], and had a wonderful time talking about what those patterns might mean. It was the tension between the narrative and the numerate, that seemed to me to be at the heart of the nature of general practice.

I want to say a few words now about my life and work with Michael Balint. I first met Balint round about the 1960s, when one of my friends, John Hunt in Clacton, said that there was an interesting course on psychiatry in general practice. Since we all knew we knew little enough about medicine, and even less about psychiatry, it seemed a good idea to go on a course of psychiatry.

This strange man Michael Balint, whose book I tried to read as a medical student and found very difficult, said that I had to have a screening interview. I went to his very, very imposing rooms in Park Square West. I spent an hour with him, with this incredible Hungarian, at the end of which he put an arm on my shoulder and he said, 'Marinker, I think you will really enjoy these seminars of mine. You are, after all, a little bit crazy'. It was only coming down the stairs that I remembered that he was the President of the British Psychoanalytical Society.

His influence on what we call the nature of general practice has been enormous, and it's been carried forward most of all by people who never met him, who never went to Balint's seminars. This happened because his influence got into the actual bone of general practice.

The nature of general practice was described in a book called *The Future General Practitioner*. Four out of the six writers were actually Balintians of one kind or another.[93] Three of us are in this room. The influence of Balint comes out in the book's strength. I think it comes out also, I have to say, in the book's weaknesses as well. Julian Tudor Hart has criticized the Balint approach as being

[93] Royal College of General Practitioners, Working Party. (1972) *The Future General Practitioner: Learning and teaching*. London: British Medical Journal for the RCGP. The Working Party members were: John Horder (chair), Patrick Bryne, Paul Freeling, Conrad Harris, Donald Irvine and Marshall Marinker with Betty Boase as clerk to the committee.

very doctor-centred, ignoring the organic nature of illness, and behavioural context. These are fair criticisms. But Balint was redressing a balance and this was enormously important. First, he taught a whole generation of doctors that it was very important to listen to what their patients were saying, and to listen without interpreting what they were saying, or telling them what they should be saying, or explaining to them better what to think. Simply to listen to what they were saying. That was enormously important. Second he shook us up by questioning the whole of our nosology. There are so many 'givens' in research. For example, the procrustean bed of the morbidity labels that we were forced to use – Julian [Tudor Hart] talked about it before, and I know that Donald [Crombie] actually researched it. When Donald's unit sorted morbidity data by hand, and not by computer, the secretaries at the unit would look at a sheet of returns from any one of us and say, 'That's Marinker's: these are the rubrics he always uses.' The variance between practices was astonishing, not only in the terms of, say, dyspepsia or peptic ulcer, but in the actual international classification of disease (ICD) headings that we were using. These were remarkably different, not because general practitioners were ignorant, but because they didn't have a language to describe what was going on. I believe that language was shaken in part by what Balint did, and in part questioned by the kind of research that we have been hearing about today – research that looked at what's actually going on and not at the labels that we stick on the patients in order to ignore or dismiss those whom did not 'fit'.

I want to talk very briefly about some research that was eventually published as a monograph.[94] For me, it's probably one of the two or three things in my life I was most glad to have been associated with. It all stemmed from Sir Desmond Pond, who one day said to us, 'Why is it you GPs, when you give your terribly interesting cases, always report new cases. You never talk about people who have been with you for the last five or ten years?' Some idiot in the group said, 'Oh that's because it's terribly boring. All you ever do is give them repeat prescriptions', whereupon Balint's ears immediately pricked up and he said, 'This is what we research', and against our better judgment we looked at these patients and began to draw pictures of them in terms of what kind of people they were, what kind of sociological variables they revealed. We found, for example, that most were either single or early secondarily single and so on, and we began to speculate about the models of their behaviour. We found out quite a lot about what was going on.

When we published the results, the book was divided into two sections, like my rather pathetic first paper. The first is called 'Tables', written by the epidemiologists in our group, and Dick Joyce. The second was called 'People', and it told the patients' stories and tried, which I think we did successfully, to build

[94] Marinker M. (1970) Truce. In Balint M, Hunt J, Joyce D, Marinker M, Woodcock J. *Treatment or Diagnosis? A study of repeat prescriptions in general practice*. Mind and medicine monographs, no. 20. London: Tavistock Publications.

models about what was going on, to give a new name to the condition. So that the 'repeat' prescription was seen not as the treatment, but the diagnosis.

I am going to stop there, because what I think was very sad is that, it is almost impossible to call this sort of research a tradition, but it was the beginning of a tradition. It has not continued, and I hope that the new generation of general practitioners will find their own way back to that way of thinking about the nature of general practice. I happen to think that although it is mysterious, and a bit suspect, and enormously sentimental, I still have this notion that it is of the essence of the nature of medicine.

Tait: Thank you, Marshall, very much. I love diseases that don't have a name, but have a pattern, I am sure there's lots of research there. There are lots of people, I am sure, who would like to contribute. We are a bit short of time, but would anybody like to add to Marshall's very enjoyable contribution at this stage?

Hannay: I think that the tradition which Marshall has been referring to is being carried on although only in small pockets and one is the research that is being done into 'heart-sink patients' at the moment. It's looking at the same kind of issues.

Tait: I think the influence goes on and on. The other area that I want us to look at is that of people trained in different disciplines, looking at general practice, saying important things about us, and sharing those findings with us. Nobody has done that better than Margot Jefferys and I would ask her to speak to us.

Jefferys:[95] Flattery won't get you very far these days! I want to give my experience of researching the primary health care situation in the late 1960s and early 1970s, and to start with why we were able to get considerable funding from the Department of Health. I was Professor of Medical Sociology at Bedford College, London, at the time. We had established good working relationships with Max Rosenheim, Professor of Medicine at UCH, which had just appointed a lecturer to its newly formed Unit of Community Medicine; Wilfrid Harding, Medical Officer of Health of the London Borough of Camden, and senior partners of two outstanding group general practices in the Borough. They had recently agreed to vacate their individual premises and become tenants in a purpose-built Local Authority Health Centre which would also contain the latter's community-based services.

The Department of Health and Social Security had by then the capacity to finance research related to its policy development proposals. I was asked to lead a

[95] See biographical note 48 above.

team which would study the effect on the practice groups and their patients of the move to new premises. The report of the research was published in 1983.[96]

The issues we chose to explore reflected a variety of contemporary interests. In the course of the study there were shifts in our targets and focus, some of them forced on us by circumstances beyond our control, others by the research experience itself. Our research team consisted of two full-time social scientists, one 'unorthodox' recent medical graduate with interests in the content and quality of general practice, and a fluctuating number of coders, mainly recent social science graduates. I was involved but also responsible for other research and teaching at the same time. We early realized we needed a coordinator who would maintain records, and keep in regular touch with practice members as well as with research staff.

We recognized too that the research would throw more light on changes which could be attributed mainly to health centre practice if we were able to study two practices in the same neighbourhood which did not enter a Health Centre. At the start, one was single-handed and the other a two-person unit. But because they differed in many ways from the group practices we could not define them strictly as 'controls'.

We used a variety of research methods, to collect and process data, including long, open-ended interviews with all the health-related staff employed in or attached to the practices. Those with doctors were tape recorded. We attended many of the meetings of the groups. We examined and extracted anonymous data from the personal records of samples of patients registered with the practice. Incidentally, we did not secure their consent – it was before the establishment of research ethics committees. The practice members were prepared to accept our guarantee of confidentiality, and to my knowledge it was not abused. We interviewed briefly small samples of attenders at the practice.

With hindsight, it is easy to recognize a number of faults and avoidable mistakes in the research design and execution. These included over-ambitious, unrealistic assumptions about the time needed to handle the data, let alone consider its implications or lessons for policy relating to the future of general practice. Conflicts of authority also occurred. These issues prevented the study from achieving all that we and others had expected from our work.

On the other hand, I feel that the issues on which we concentrated in our published account are likely to be of more enduring value to future historians and interpreters of behaviour in small formal organizational settings, such as community healthcare units, than the more immediate effects of change at the micro-level would have been.

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[96] Jefferys M, Sachs H. (1983) *Rethinking General Practice. Dilemmas in primary care*. London: Tavistock Publications.

What we brought to light were the difficulties facing doctors and other healthcare professions in adapting to a rapidly changing contemporary social order. Older assumptions about the 'proper' relationship of doctors and patients, of doctors and other 'caring' professionals, of different generations, of men and women could no longer be taken for granted. Solutions were not readily to hand. In highlighting the dilemmas, we were able to record the variety of responses of individuals of goodwill and probity involved in situations which they had not expected to face in their professional life times.

Tait: You are almost making a case for another Witness Seminar, and I very much wanted Ann Cartwright to contribute at this stage.

Dr Ann Cartwright:[97] I would like to say that I did studies from a totally different perspective. I started life as a statistician, but then spent some time with Dick Scott[98] up in Edinburgh, so developed a great interest in general practice. As a statistician I wanted to study a properly representative sample, both of the professionals and of the patients involved. So we started our studies with a random sample of people on the electoral register and interviewed them about their experiences and views about general practice and then got them to identify their GP, but it didn't always run smoothly.

We told the GPs included in the studies that we had got their names from patients and at the pilot stage of the first study one of the GPs wrote indignantly to the General Medical Services Committee (GMSC) complaining that we were interviewing his patients without his permission. The GMSC then wrote to me asking what it was all about and requesting a copy of the questionnaire. At that point I talked to Wilf Harding and showed him a copy of the questionnaire. He said 'Oh good gracious me, you are going into the lion's den, asking patients what they think of their GP.' I also consulted my Advisory Committee which included Margot Jefferys, John Horder and John Fry. They agreed that we should not send the GMSC a copy of the questionnaire but should explain what we were doing and that we were anxious to preserve the independence of our research. I also asked the secretary of the GMSC for an appointment and John Horder and John Fry very kindly promised to go with me. Even so I was not looking forward to the meeting. However the GMSC had to cancel it because of some crisis. They subsequently

[97] Dr Ann Cartwright (b. 1925) was Director of the Institute for Social Studies in Medical Care from 1970 to its closure in 1993. Her surveys of healthcare include patients' experience in hospital; contraceptive services for recent parents; life before death; and elderly people: their medicines and their doctors.

[98] Professor Richard Scott (d. 1983), the first professor of general practice in the world, was appointed to the James Mackenzie Chair at the University of Edinburgh in 1963 until his retirement in 1979. See I M R. (1983) R Scott MD, FRCPED, FRCGP, DPH. (Obituary) *British Medical Journal* **287**: 1890.

suggested another date but by then we had completed the fieldwork so we agreed there was no point in meeting. We were able to do this because that study was funded by the United States Public Health Service. That was in 1964. The second study in 1976 was funded by the Department of Health who insisted that we should get the agreement of the GMSC before they funded it.[99]

Tait: I remember your telling me that it wasn't only the doctors who didn't like the questionnaire, it was many of the patients who were uncomfortable about being asked questions about their doctors.

Cartwright: I don't remember that.

Tait: You said it quickly changed.

Cartwright: We got a better response from patients than we did from the doctors.

Tait: Well, Ann, thank you very much. I think we have had a valuable afternoon, but we must stop. I said earlier on, that it would be impossible to make sensible conclusions or summaries of an afternoon like this. I have some important thank yous to say. First, thank you to the Wellcome Trust for hosting us so well, but most of all thank you to our witnesses, the lead speakers and all of you on the floor. We have had fascinating people from all over the place and I have enjoyed it hugely and I hope you have. Thank you all very much.

[99] Cartwright A. (1967) *Patients and Their Doctors: A study of general practice*. London: Routledge & Kegan Paul. Cartwright A, Anderson R. (1981) *General Practice Revisited: A second study of patients and their doctors*. London: Tavistock Publications.

DRUGS IN PSYCHIATRIC PRACTICE

The transcript of a Witness Seminar held at the Wellcome Institute for the History of Medicine, London, on 11 March 1997

Edited by E M Tansey and D A Christie

The scientific development and clinical use of drugs for the treatment of psychiatric disorders over the past forty years were considered by the Seminar, led by Dr David Healy. Basic work on the mechanisms of drug action and the impact of drugs in psychiatric practice, particularly for the treatment of depression, anxiety, obsessive compulsive disorder and schizophrenia, were discussed. The role of the pharmaceutical industry in developing and promoting new drugs, and the role of new drugs in promoting new disease classifications were reviewed at some length. Subjects as diverse as drug standardization and clinical trials, the creation of specialist scientific societies, tensions between clinical and scientific psychopharmacologists, and the importance of international conferences all emerged during the meeting.

DRUGS IN PSYCHIATRIC PRACTICE

Participants

Dr Derek Bangham
Professor George Beaumont
Sir Christopher Booth
Dr Alan Broadhurst
Professor Arthur Crisp
Professor Gerald Curzon
Professor Michael Gelder
Dr Philip Harrison-Read
Dr David Healy (Chair)
Professor Alec Jenner
Dr James Le Fanu
Professor Isaac Marks
Professor Elaine Murphy
Dr Malcolm Pines
Dr Peter Rohde
Professor Merton Sandler
Dr Donald Scott
Professor Hannah Steinberg
Professor Elizabeth Sykes
Dr Ian Tait
Dr Tilli Tansey
Dr Trevor Turner
Professor Joanna Weinberg
Dr David Wheatley

Others present at the meeting and apologies: Dr John Bancroft, Dr James Birley, Professor Philip Bradley, Professor Michael Bury, Dr Gordon Claridge, Dr Alec Coppen, Professor Bill Deakin, Professor Hans Eysenck, Professor Hugh Freeman, Professor Malcolm Lader, Dr Maurice Lipsedge, Dr Gerald Low-Beer, Dr John Marks, Dr C Pare, Professor Roy Porter, Professor Robin Priest, Professor Linford Rees, Professor Sir Martin Roth, Dr Charles Ryecroft,. Professor Gerry Stimson, Dr Ian Stolerman.

Dr Tilli Tansey:[1] David Healy who is our Chairman this afternoon is a psychiatrist at the University of Wales College of Medicine, based in Bangor, with a very keen and active interest in the history of psychiatry. Over to you David.

Dr David Healy:[2] Thank you very much, Tilli. First of all, I would like on my own behalf and I am sure on behalf of all of you, to offer thanks to the Wellcome Trust for having put on this meeting and I would also wish to offer thanks to Tilli Tansey who has been the person who had the idea to have the meeting in this area and whose energies have brought us all here together today. I am quickly going to open things up with a few thoughts and then I am going to hand it over to other speakers we have. There will be the opportunity for all of you to offer your own thoughts.

Briefly, we want to focus during the first half of the afternoon on how things were in the early days, and after tea on how things have gone since. Just to kick-start you off in the area of what might be a good idea, during the last week or two we have had the shock of the new. We have had cloning. Good history, I feel, should introduce us to the shock of the old. Sometimes we actually forget how things were and the historical vignette can bring this home. I have a vignette from Gerald Curzon who is here, who reports as a young researcher working in London, being at a meeting in the early 1960s, possibly one of the few non-medical people at the meeting, he ventured the idea that something to do with dopamine might be wrong in the brain of people with Parkinson's disease.[3] The eminences at the meeting looked at him scornfully and said if he'd ever seen the brain of a person with Parkinson's disease, he would know that this was not a chemical disorder. This opens up the whole idea of how did people see Parkinson's disease before we came to the ideas that we now have. And that's part of our brief here today – to look at how these things were seen before the drugs were introduced. Often the historical vignette can be an extremely powerful way to convey the changing

[1] Dr Tilli Tansey is Convenor of the History of Twentieth Century Medicine Group and Historian of Modern Medical Science at the Wellcome Institute for the History of Medicine.

[2] Dr David Healy (b. 1954) has been Director of the North Wales Department of Psychological Medicine since 1992.

[3] See Curzon G. (1998) *From Neurochemistry to Neuroscience.* Interview in Healy D. (ed.) *The Psychopharmacologists.* Vol. 2. London: Chapman & Hall, 307–324.

moods, the changing shape of the landscape, and if any of you have these vignettes to offer, please feel free to offer them.

Coming from Ireland, where obviously we were always years behind you in the UK and being much younger than all of the other people here at the table, I can still recall the shock of the new agents that we used. The idea that one would interfere with the brain, the soul as it were, was a very disturbing kind of idea. Nowadays, of course, people think using *Prozac* is no problem at all. The only problem with the selective serotonin reuptake inhibitors (SSRIs) that you may be using is trying to coordinate the colour of the capsule with the outfit that you happen to be wearing that day. The shock has gone. But certainly when I entered the field in the late 1970s the shock was still there. Now for some of you here I am sure there never was any shock. The idea of being able to try and get people well always looked like a good thing to do. For others here, there will be the sense that we were doing something extremely new, something extremely powerful, and possibly somewhat disturbing.

Can I move on then to one more thing that I would like you to consider, which is that drugs introduce a certain standardization to psychiatric practice and there's a quote, from Max Hamilton which I think brings home that.[4] They introduced not only a new means to treat people, but a new language. They introduced rating scales, they introduced operational criteria, they introduced the magic bullet ideology and this has gone beyond drug treatment *per se* and now pervades psychotherapy. Cognitive therapy is very much a magic bullet approach therapy I would argue. You have the idea that there is a very specific defect of logic in the brains of people, which is going to be handled by a very specific technique which will prescind from the psychosocial milieu in which the patient actually lives and breathes. This I will argue is a form of psychotherapy that borrows inspiration from the ideologies or the ways of seeing things that drug treatments introduced 20 or 30 years before that. A possibly somewhat provocative thought, but it's one that I throw open to all of you.

The other thing I have here is an NHS Prescription Pad. I prescribe, many others of you in the audience won't. The drug treatments that were introduced were ones that were available on prescription only. This also will introduce a particular kind of bias into the field. It will divide medicine into orthodox and alternative medicines. *Prozac* is perhaps the most used antidepressant in the UK. St John's Wort is the most used in Germany. This is available over the counter. Germans, strangely it seems, want to stay in control of their own lives, in a way perhaps that we don't need to in this country, who knows. But we end up with orthodox medicine and alternative medicines and one of the interesting things is that a great number of people out in the street refuse to buy the disease model that

[4] See Hamilton M E. (1972) Rating scales in depression. In Kilholz P. (ed.) *Depressive Illness, Diagnosis, Assessment and Treatment*. Boare (Hans Huber), 100–108.

you have to prescribe the pills when you prescribe. So these are issues I think that we can look at during the course of the day. For the moment, however, I'd hoped to focus on what things were like during the 1950s and at this point I will hand over first of all to Alan Broadhurst.

Dr Alan Broadhurst:[5] Thank you very much, David. This week is for me an anniversary. No, it is not my birthday, but it is exactly 48 years ago this week, that I started work with Geigy Pharmaceuticals.[6] It was 1949. I came out of the services armed with a previously acquired, and by then barely remembered, modest knowledge of pharmacology and set about finding a job. It was at Geigy that I found one. We were based in a little house at the end of a row of millworkers' cottages in Rhodes, a small town a few miles out of Manchester. I remember the house looked out onto the Calico Printers' Association Mill. It had what we all thought was the tallest chimney in Britain, now sadly felled by Fred Dibner's enterprise.[7]

My brief was to help set up the infant Geigy Pharmaceuticals in the UK, but in fact I soon found myself commuting between Rhodes and Basel, where I spent increasing amounts of time. Basel was, of course, the headquarters of Geigy and the place where most of the basic research was carried out. After a while I became involved in some work which was to have an impact upon the world of psychiatry, namely the discovery and development of imipramine which was arguably the first effective antidepressant drug. I would like to tell you something about that period in my life. One of the problems at such a distance in time inevitably is that one cannot remember details, but both David and Tilli have said that this shouldn't be a long history. It should simply be an overview, so I am just going to try to remember some of the main facts.[8]

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[5] Dr Alan Broadhurst (b. 1926) was Consultant Psychiatrist at West Suffolk Hospital, Bury St Edmunds, from 1970 to 1990 and Consultant Physician at Addenbrooke's Hospital, Cambridge, from 1970 to 1990. He was also Clinical Teacher in Psychopharmacology in the University of Cambridge for many years until 1996. Fellow of the Royal College of Psychiatrists since 1984. Fellow of the Institute of Biology since 1998.

[6] Geigy Pharmaceuticals (now Ciba-Geigy) began in 1859 as a dye company. It was in 1940 that its first pharmaceutical preparation was produced. For further details about Geigy Laboratories and the discovery of imipramine, see Kuhn R. (1970) The imipramine story. In Ayd F J, Blackwell B. (eds) *Discoveries in Biological Psychiatry.* Philadelphia, PA: J B Lippincott Company, 205–217. Broadhurst A. (1996) Before and after imipramine. In Healy D. (ed.) (1996) *The Psychopharmacologists.* Vol. 1. London: Altman, 111-134. See also Healy D. (1997) *The Antidepressant Era*. Cambridge, MA: Harvard University Press, 48–59.

[7] Fred Dibner (b. 1938), a Lancashire steeple-jack, now a television personality, was famous for his felling of redundant tall mill chimneys. His life is described in Haworth D. (1993) *The Fred Dibner Story*. London: BBC Books.

[8] See Tansey E M. (1998) 'They used to call it psychiatry' – Aspects of the development and impact of psychopharmacology. In Gijswijt-Hofstra M, Porter R. (eds) *Cultures of Psychiatry: Postwar British and Dutch mental health care*. Amsterdam: Editions Rodopi B V, 79–102.

About five years before my arrival at Geigy, that is in about 1944, the first antihistamines were discovered.[9] Henri Laborit, a French surgeon, working in Paris, was trying out drugs of this class to reduce surgical shock and to potentiate the action of anaesthetic drugs.[10] He collaborated closely in this work with Charpentier, an organic chemist, from Rhône-Poulenc. As Charpentier produced new antihistamines, and after pharmacological and toxicity screening tests, Laborit used them in his work. In 1947 Charpentier asked Laborit to try out an entirely new type of antihistamine, promethazine, which was a phenothiazine. This was a much more powerful drug in anaesthesia. Given with pethidine, it formed the so-called 'lytic' cocktail.

A couple of years later Laborit was offered another two phenothiazines, promazine and chlorpromazine. These were even more effective within the lytic cocktail and, moreover, they possessed a new property in that they were thermolytic. Thermolysis allows the body to be cooled effectively by inhibiting the action of the thermo-regulatory mechanism. The technique of 'artificial hibernation' was introduced, in which the patient is pre-treated with the thermolytic drug and then packed in ice. After cooling in this way, tissues, including the brain, can be deprived of their blood supply for brief periods without sustaining damage.[11] Using this technique, early cardiac surgery became much safer.

Whilst all this was going on, we at Geigy were also working on antihistamines. We already had one successful antihistamine, halopyramine, on the market, but when we heard of Laborit's work in anaesthesia, we, too, decided to explore a number of antihistamines to see if they had thermolytic action and could be used for cardiac surgery in the same way. We also felt that antihistamines might provide a starting point in the synthesis of compounds of potential value, as sedatives, analgesics, and anti-Parkinsonian agents. The head of our pharmacology department, Professor Domenjoz who, simultaneously, was Professor of Pharmacology at the University of Saarbrücken,[12] decided that there should be a new approach and that a search should be made for novel heterocyclic antihistamines. The phenothiazine nucleus was clearly of much interest. Rhône-Poulenc had produced it, Laborit had developed its use in surgery and in cardiac surgery in particular. Geigy was not very interested in the principle of 'me-too' drugs and Domenjoz felt that we ought not to follow the phenothiazine route.

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[9] The early use of antihistamines is described, for example, in: Walton C H A, Kristjansson-MacDonell J A. (1947) Antihistamine drugs. *Canadian Medical Association Journal* **56**: 162–169.

[10] Laborit H, Huguenard P, Alluaume R. (1952) Un nouveau stabilisateur végétatif (le 4560 RP). *Presse Médicale* **60**: 206–208.

[11] Deschamps A. (1952) Hibernation artificielle en psychiatrie. *Presse Médicale* **43**: 21 June.

[12] Robert Domenjoz (b. 1908) was Head of Pharmacology at the Geigy company in Basel from 1941 to 1958. He was on the staff of the University of Saarbrücken from 1950 and Professor of Pharmacology and Toxicology from 1958 to 1977.

A search for non-phenothiazine tricyclic structures was therefore started. After a while a substance was unearthed, iminodibenzyl. Now iminodibenzyl was not a new drug. It wasn't a drug at all, in fact, at that point. Iminodibenzyl had been discovered in 1898[13] and had been used briefly as an intermediate, in the preparation of Sky Blue, a dye-stuff, but had been abandoned and had long been gathering dust on the shelves. Iminodibenzyl, however, had a tricyclic ring structure, similar in appearance to the phenothiazines, but slightly different and it was an interesting candidate. Domenjoz asked two of Geigy's organic chemists, Schindler and Häfliger, to prepare derivatives of iminodibenzyl. Organic chemists never do things by halves, as some of you will know. Ours produced 42 separate basic alkylated derivatives: they were distinguished only by differences in their side chains. The basic central tricyclic nucleus was not altered.[14]

Pharmacological testing was then undertaken on some of them by Professor Domenjoz and Drs Theobald, Herrmann and Pulver. I was privileged, and most fortunate to be able to work with Dr Pulver, although I should add that I was, at that point, a very junior member of the team. Testing of the derivatives revealed the presence, in varying degrees, of antihistaminic activity, together with sedative, analgesic and spasmolytic properties. We were particularly interested to find that some of the compounds also possessed thermolytic activity. Properties varied according to the constitution of the side chain. Thus analgesic action was markedly increased by the presence of a quaternary carbon atom. A -CO group next to the nitrogen atom on the central ring invested these compounds with significant local anaesthetic activity. Tissue distribution studies were then undertaken in rabbit of a few of the more interesting looking derivatives. No behavioural tests were carried out at this stage. Even if such tests had been available at that time we were not looking for the presence of any behavioural modification. Eventually, after LD_{50} studies in mice, some of the compounds were tested in human volunteers. Inevitably, I found myself recruited into this study – volunteering came with the job!

A few of the derivatives seemed worthy of further investigation. The first, given the code number G 22150 was tested in 1950 and 1951 as a potential hypnotic. This had been the least toxic of all the compounds. Unfortunately, its hypnotic effect in insomniac patients was unreliable and it was abandoned.

Another derivative, G 22355 also looked interesting. It too, had shown low toxicity in animal testing, it was not particularly sedating. It was an antihistamine and it was thermolytic. It looked as if it might be worth investigating further in surgery, where artificial hibernation was to be used. But before this investigation could be undertaken another important discovery had been made in France. For a

[13] Thiele J, Holzinger O. (1899) Properties of o-diaminodibenzyl. *Liebigs Annals of Chemistry* **305**: 96–102.
[14] Schindler W, Häfliger F. (1954) Derivatives of iminodibenzyl. *Helvetica Chemica Acta* **37**: 427.

moment we must switch back to Henri Laborit's use of chlorpromazine in surgery. This phenothiazine was a valuable constituent of the lytic cocktail but with increasing experience of it, Laborit became aware that chlorpromazine possessed an anxiolytic effect, even when given alone. He discussed this with two colleagues, Professors Delay[15] and Deniker[16] at Hôpital Ste Anne, and they and other psychiatrists at Hôpital Val de Grâce[17] tried it out in patients suffering from a variety of psychiatric disorders. It was soon found to have a remarkable and beneficial effect in patients with schizophrenia.[18] So back in Geigy, we decided to try out G 22355, not in anaesthesia but in schizophrenia. We wondered if it might share chlorpromazine's anti-psychotic properties, for of all the iminodibenzyl derivatives we had available, this drug was the directly analogous compound to promazine, with a straight side-chain containing three -CH_2 groups.

In 1954 we asked Dr Roland Kuhn,[19] a psychiatrist at Münsterlingen Hospital on Lake Constance in Switzerland, to try out our new drug in patients with schizophrenia. By this time I was working closely with two colleagues, Drs Paul Schmidlin and Otto Kym, from our clinical pharmacology group and the three of us made many visits to Münsterlingen. Dr Kuhn was quite interested to try G 22355 if it were likely to be of value in his patients with this disorder. His hospital was finding the newly introduced chlorpromazine to be too expensive for them for routine use and the idea of free samples of what might turn out to be a successful substitute for the phenothiazine compound was attractive. Some of the patients were already being treated with chlorpromazine and this was discontinued. Others had not received chlorpromazine at all.

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[15] Professor Jean Delay was full Professor and Head of the Department of Psychiatry, Hôpital Sainte Anne in France. For a description of his life and career see Healy D. (ed.) (1996) *The Psychopharmacologists.* Vol. 1. London: Altman, 2–27. See also Delay J, Deniker P, Harl J M. (1952) Utilisation en thérapeutique psychiatrique d'une phénothiazine d'action centrale elective. *Annales Medico-Psychologiques* **110**: 12–17.

[16] Professor Pierre Deniker was Professor of Neuropsychiatry, Hôpital Sainte Anne in France. For a description of his role in the discovery of chlorpromazine, see Healy D. (1997) *The Antidepressant Era.* Cambridge, MA: Harvard University Press, 45–47.

[17] The Val de Grâce was the Central Military Hospital in Paris; the group of psychiatrists working there at that time were Hamon J, Paraire J and Velluz J. See Hamon J, Paraire J, Velluz J. (1952) Remarques sur l'action du 4560 RP sur l'agitation maniaque. *Annales Medico-Psychologiques* **100**: 331.

[18] Delay J, Deniker P. (1952) 38 cas de psychoses traités par la cure prolongée et continue de 4560 RP. *Rapports et Comptes Rendus: Congrès des médécins aliénistes et neurologistes de France et des pays de langues Françaises* **50**: 503–513. See also NIMH Psychopharmacology Service Center. (1964) Phenothiazine treatment in acute schizophrenia. Effectiveness. *Archives of General Psychiatry* **10**: 246–261. The Lasker Prize often regarded as the forerunner to a Nobel Prize, was given to Laborit and Deniker in 1957 for their discovery of the clinical properties of chlorpromazine. Note, however, that there were many bitter disputes over who actually discovered chlorpromazine, and no Nobel Prize was ever awarded. Claims were made by: Charpentier who synthesized it; Courvoisier who reported the distinctive effects on animal behaviour; Laborit who first noticed distinctive psychotropic effects in man; and Delay and Deniker who outlined its use as an antipsychotic. See also note 32 below.

[19] For a detailed account of the imipramine story, see Kuhn R. (1970) The imipramine story. In Ayd F J, Blackwell B. (eds) *Discoveries in Biological Psychiatry*, ch. 16. Philadelphia, PA: J B Lippincott Company, 205–217.

The clinical trial was completely uncontrolled in modern terms. This meant that any effect of the experimental drug would have to be of a high order to be regarded as significant. In fact, such was the case. The whole team of workers, both staff at the hospital and scientists from Geigy, waited with bated breath. Within a period ranging from three days to three weeks, certain very definite results began to appear. These results were not only fascinating, they were, in some patients, quite alarming. Several previously quiet patients began to deteriorate with increasing agitation. Some developed hypomanic behaviour. One gentleman, in such a state, managed to get hold of a bicycle and rode, in his nightshirt, to a nearby village, singing lustily, much to the alarm of the local inhabitants. This was not really a very good PR exercise for the hospital, and I can't say it endeared the hospital to Geigy either. Of course, not all the schizophrenic patients reacted in this way. Some even improved, especially if there were a major depressive component in their illness. Even so, it was clear that the effect of the drug was not particularly desirable in schizophrenia and that it was producing a very different effect from chlorpromazine.

The clinical trial was discontinued and we all went back to our drawing boards. Much discussion took place within Geigy. Clearly the reaction we had seen in some patients was not due simply to withdrawal of chlorpromazine in people previously treated with it, for similar hypomanic-agitated episodes had occurred in other patients who had not earlier been treated with chlorpromazine. Paul, Otto and I stumbled around considering a variety of unlikely hypotheses and mechanisms. Then basing our thoughts on the most naive scientific reasoning, something which I now look back on with a kind of embarrassment, we wondered that if the flat mood of schizophrenia could be lifted to hypomania by the drug, could not in a similar fashion a depressed mood be elevated also?

Well, I remember a subsequent discussion with Roland Kuhn about this and the look of suspicious disbelief on his face. He was cautious about the trial of G 22355 in depression, but he was persuaded. So in 1956 the drug was tried on a number of patients with depression. It soon became clear that it had a dramatic, and, this time, beneficial effect. By the time the whole series of 40 patients had been treated, we became certain that G 22355 represented a major advance in the treatment of depressive illness. After a delay of about three weeks a significant percentage of patients showed considerable improvement. The drug was given the generic name imipramine [*Tofranil*].[20]

My next task was to organize some properly controlled clinical trials. By this time double-blind studies[21] were just coming in, Max Hamilton[22] had developed

[20] Kuhn R. (1958) The treatment of depressive states with G 22355 (imipramine hydrochloride). *American Journal of Psychiatry* **115**: 459–464.

[21] A 'double-blind study' is where neither the doctor nor the patient knows who receives what treatment.

his rating scales, so that changes in psychiatric symptoms could be more easily quantified. So that it was against this background that studies were set up. The first British study was by Leslie Kiloh, working with Martin Roth; then followed in quick succession studies by Linford Rees, Sylvio Benaim, George Ashcroft, Donald Eccleston and others.[23] One particularly interesting study was by Hilda Abraham. Hilda Abraham was the daughter of Karl Abraham, the distinguished psychoanalyst, and she seemed a very unlikely person to carry out a clinical trial because she was also a psychoanalyst. She, in fact, got in touch with me and said she found it fascinating that a drug could actually pull people out of depressive illness. She asked if she could try it, and with Ismond Rosen, who sadly has just died, designed a beautifully controlled double-blind study.

All the studies confirmed the early findings. For me, it had been a remarkable experience which changed the direction of my career. I went off and became a psychiatrist. Like so many other discoveries in pharmacology, serendipity had played a major role. The antidepressant effect was completely unexpected and discovered entirely by accident. Luck was on my side too, I just happened to be working in the right place at the right time.

Healy: Two quick points before I pass over to Merton Sandler. The interest of companies I think to chase this area can be brought out by the fact that SK&F, who released chlorpromazine over in the US in 1954, in 1955 made $75 million on it. A lot of the other companies said, 'whatever it is, we've got to have one of them', so this perhaps explains something. But as regards the antidepressants this was in the era when you could move a drug, from the time it was first used with people into the clinic with a license, in the course of six to eight weeks. It took two years for Geigy to buy the idea that there might be a market for an antidepressant. When they looked out there at the world outside, where we are now told 100 million people in the world on any one day of the year are depressed, they couldn't see sufficient numbers who were actually depressed, who might be a market for this compound. So something has changed.

Professor Merton Sandler:[24] I want to take you back first to 6 September 1944, when the first V2 fell on London. This is important because quite a lot of V2s fell

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[22] Hamilton played a notable part in the process of clinical trial methodology through the construction of the Hamilton Rating Scale for Depression. See Hamilton M E. (1960) A rating scale for depression. *Journal of Neurology, Neurosurgery, and Psychiatry* **23**: 56–62. See also note 4 above.

[23] For a review, see Rees W L, Healy D. (1997) The place of clinical trials in the development of psychopharmacology. *History of Psychiatry* **8:** 1–20.

[24] Professor Merton Sandler (b. 1926) was Professor of Chemical Pathology at the Royal Postgraduate Medical School, Institute of Obstetrics and Gynaecology, University of London, from 1973 to 1991, Professor Emeritus since 1991. He was a Governor of the British Postgraduate Medical Federation between 1976 and 1978, and of Queen Charlotte's Hospital for Women between 1978 and 1984.

on London later, a lot of damage was done and the Germans nearly won the war; they just stopped in the nick of time. The most recent V2s used as a fuel the really ghastly toxic liquid, hydrazine, and when the war ended there was a tremendous lot of this stuff sloshing around Europe and it could be had for a song. It was caustic, highly toxic, and stuff to avoid. But, of course, it was readily available to any drug company that wanted it. Hoffman La Roche did want it and at Nutley[25] they set up quite an operation.

Let me remind you that at this time, at the beginning of the 1950s, tuberculosis was a scourge and a half. I used to work at the Brompton Hospital at that time and we were doing artificial pneumothoraxes, and artificial pneumoperitoneums, and those ghastly mutilating thoracoplasties, taking away the ribs and collapsing the lungs down. Tuberculosis was the big target of the drug companies at that time. Well, at Nutley, to cut an awfully long story short, using this hydrazine left over from the V2s as a starting point, Hoffman La Roche synthesized isoniazid and iproniazid. Iproniazid was interesting because the orthopods who gave it to patients with bone tuberculosis were convinced that it was rather better than isoniazid for the purpose. Ted Sourkes,[26] whom many of you will know, worked at that time at Merck, Sharpe and Dohme at Rahway, New Jersey. Ted Sourkes is a quiet man who deserves to be rather better known, but made many significant contributions to psychopharmacology. He used to say 'Sourkes works at Mercks'. Ted Sourkes remembers the *New York Times* on Good Friday in 1952, that's why he remembers it because it was Good Friday, and there was this lurid headline, that patients treated with a new drug, iproniazid, were dancing in the wards even though they had holes in their lungs.[27] And this caught the fancy of the world press, including the British press; some of you may remember it from that time. This was thought of by psychiatrists as just a euphoric sort of side-effect of an effective drug that one had to put up with. Indeed, because of this 'adverse reaction', as they thought of it at that time, iproniazid was nearly killed off as a drug because its sister compound isoniazid, worked very well and did

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Amongst other honours and positions he was President of the British Association for Psychopharmacology from 1980 to 1982 and honorary member 1993.

[25] American headquarters, Hoffman La Roche.

[26] Ted Sourkes is a distinguished Canadian neurochemist, whose early published work includes Sourkes T L. (1961) Formation of dopamine *in vivo*: relation to the function of the basal ganglia. *Reviews in Canadian Biology* **51**: 444–456. Sourkes T L, Murphy G F, Rabinovitch A. (1961) Conversion of D1-M-tyrosine to dopamine in the rat. *Nature* **189**: 577–578. Sourkes T L. (1961) Methods of study of pharmacologically active substances and chemical activity of the nervous system. *Methods in Medical Research* **9**: 121–124.

[27] We have been unable to find this announcement. Ted Sourkes wrote: 'Some of us were having lunch in the Merck cafeteria, and the *New York Times* item was mentioned. One person pointed out that by publishing on a semi-holiday the people were going to get maximum news exposure (i.e. little else happening or being reported). There was some discussion about the announcement, and then Morris Solotorovsky, Head of Bacteriology at the Merck Institute and an authority on the tubercle bacillus, said "but they are dancing with holes in their lungs".' Letter to Professor Sandler, 26 March 1998.

not produce this adverse reaction. You must remember that everybody at the time knew about the stimulants amphetamine, cortisol and caffeine; why should the side-effects of this drug iproniazid be qualitatively different from other known stimulants?

A guy called Nate Kline,[28] many of you will have known him, an international wheeler-dealer, a likeable and charismatic fellow, had had his picture on the front cover of *Fortune* magazine as one of the ten best known men in America, not best known *psychiatrists* in America, but best known *men*. He was a flamboyant, buccaneering fellow. He would try anything on his patients, and it was possible to do that in those days. Accordingly he tried iproniazid on a rag bag of patients, you know, funny odd schizophrenics and a few possible depressives from his private practice and somehow distilled a paper from the results. You know where he published it first? In the *Congressional Record*.[29] That was so typical of Nate Kline. There's a Congress Committee on Psychiatry and he told them all about it for maximum publicity. There were three of them, his leg man Loomer, a chap called Saunders, whom he had poached from Ciba-Geigy, and Kline himself. Scientifically they presented it at some regional psychiatric meeting in Syracuse, in Upstate New York, this momentous discovery that iproniazid was useful in depressive illness.[30] Loomer, first author and presenter, was sulking in his tent at the time, because Kline had called a press conference three days before the presentation.[31] The newspapers were pretty full of Kline only, and Loomer and Saunders didn't get a look in. Saunders always claimed that the idea came from him, that he'd put the two parts of the equation together, the monoamine oxidase (MAO) inhibitory ability and the clinical effect of iproniazid and so when Kline was given the Lasker award, the second time in fact he'd won the Lasker award[32] (this is a prestigious one you know, one of the big ones), and when Kline was given the Lasker award for this work, Saunders immediately started a court case, again another long story. Saunders was eventually awarded one-third of that prize. The first time Kline won the Lasker award was for his work in reserpine and schizophrenia. But that's a different matter.

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[28] Nathan Kline (1923–1983) at the time of his involvement with iproniazid was Assistant Clinical Professor of Psychiatry at Columbia University and Director of the Research Facility at Rockland State Hospital in New York.

[29] Loomer H P, Saunders J C, Kline N S. (1957) Iproniazid, an amine-oxidase inhibitor, as an example of a psychic energizer. *Congressional Record* 1382–1390.

[30] The paper was presented at the Regional Research Conference held at Syracuse on 'Research on Affects', in April 1957. Loomer H P, Saunders J C, Kline N S. (1957) A clinical and pharmacodynamic evaluation of iproniazid as a psychic energizer. *Psychiatric Research Reports* no. **8**: 129–141.

[31] A few days before the Syracuse meeting, Kline held a press conference at which he announced the findings. The *New York Times* implied that the work was by Kline alone (7 April 1957, 82), leading to some ill feelings between Loomer and Kline and a subsequent correction in the paper.

[32] The much sought-after Lasker Prize was awarded annually by the Lasker Foundation, set up by Albert and Mary Lasker in 1942 to support research on mental health, birth control, and cancer research. Mary Lasker was a vigorous campaigner for mental health, and she had considerable influence in the NIH and with Congress.

What I wanted to say was that Mike Pare and I came along then. We were the old firm who had somehow got together in the British army, bored out of our minds with nothing to stretch us in a military hospital in Shorncliffe in Folkestone. I had a pathology lab and Mike Pare was a clinician. We set up our own sort of research laboratory. We made so many mistakes, but we stumbled through and, in fact, made a number of rather intriguing observations. We published a paper or two then,[33] but what I want to say is that when Mike came out of the army he went to the Maudsley and I had got involved with carcinoid syndrome at the Brompton and all of a sudden, the indoles seemed to mesh with psychiatry. Mike and I, out of the army, started to work together again.

Mike started a trial at the Maudsley of iproniazid and we were the first ever – it seemed the obvious thing to do – to give intravenous DOPA and intravenous 5-hydroxytryptophan to depressed patients,[34] what the Americans long after called 'precursor load strategy'.

This was six years before Schildkraut came along with the monoamine hypothesis of depression;[35] it seemed obvious to us, even in 1959, that that was the best interpretation of what was happening, so we gave these substances in the lag period before the monoamine oxidase inhibitors started to kick in. They didn't have any effect, because we were using far too small doses, and anyway the material we used was half strength, i.e. D/L: a racemic mixture. It was rather interesting, however, because it gave us an insight into some parallel carcinoid problems, that I happened to be investigating at the time. Poor old John Jepson who several of us here knew well and liked, and who died so tragically early, made a major contribution in this area. He devised a chromatographic system that Gerald [Curzon] and I both used, that we all used in those days.[36] And when we ran a carcinoid urine in the system we found a very large spot of 5-hydroxyindoleacetic acid. When we ran urine from patients who'd been given 5-hydroxytryptophan intravenously, there was a massive chromatographic spot of 5-hydroxytryptamine (5-HT). When later I came to investigate a urine sample from what seemed to be a run-of-the mill carcinoid patient and there was this massive spot of 5-hydroxytryptamine, it seemed obvious that this was a 5-hydroxytryptophan-

[33] Sandler and Pare's initial research was on investigating a new liver function test. Their first published papers related to effects of starvation. See Sandler M, Pare C M B. (1954) Starvation aminoaciduria. *Lancet* **i**: 494–495. *idem* Aminoaciduria in March haemoglobinuria. ibid. 702–704.

[34] Pare C M B, Sandler M. (1959) A clinical and biochemical study of a trial of iproniazid in the treatment of depression. *Journal of Neurology, Neurosurgery and Psychiatry* **22**: 247–251.

[35] Schildkraut J J. (1965) The catecholamine hypothesis of affective disorders: a review of supporting evidence. *American Journal of Psychiatry* **122**: 509–522. As early as the end of the 1950s, it was thought that antidepressants acted on monoamines, although it was still unclear as to whether 5-HT or noradrenaline was the neurotransmitter involved. At the same time a similar proposal was published, see Bunney W, Davis J. (1965) Norepinephrine in depressive reactions. *Archives of General Psychiatry* **13**: 483–494.

[36] See Jepson J B. (1955) Paper chromatography of urinary indoles. *Lancet* **ii**: 1009–1011.

secreting carcinoid tumour and indeed it turned out to be so.[37] And there's a group of carcinoids, something like 5 or 10 per cent of them, that in fact do secrete 5-hydroxytryptophan.

I mentioned this intravenous 5-hydroxytryptophan because of Gaddum (a funny guy Gaddum, I used to be scared to death of him, we all were), and Gaddum had said perhaps it's the 5-HT in our brains that keeps us sane.[38] Well, Mike Pare and I teamed up with a German psychologist called Brengelmann, this wasn't too long after the war, about ten years after the war, and we still felt a bit uneasy about mixing with Germans. Anyway Brengelmann was a bit heel-clicking, but interesting and good at his work. We gave volunteers LSD and then gave the same volunteers LSD after they had previously been treated with 5-hydroxytryptophan. There was some significant attenuation of the effect of the LSD. I think this paper was quite a landmark. It's one of the most neglected papers in the literature.[39] No one ever quotes it and yet it really was a milestone. We could only do five patients, because the sixth was a disaster. The Maudsley registrar who was a volunteer, after getting a shot of LSD, really went round the twist and he was psychotic for six months and more. Those were the days, you know, when you didn't really have to get ethical permission for anything. You are all shaking your respective heads in sorrow, I know. Well, we all did this sort of thing and it seemed all right at the time.

Let me tell you about Gaddum. The last time I saw him he was dying from a carcinoma of the stomach. I suppose this was the early 1960s. I was down at Babraham giving a talk about the things that we had been doing at that time. Gaddum was Director of the place, he looked a bit like Stan Laurel, he'd lost a tremendous amount of weight, Laurel in Hardy's trousers (or is it the other way round?), and he was still working at the bench for 14 hours a day, perfusing goldfish gut with Substance P in minute little chambers. Anyway I gave the seminar, expecting to be torn to shreds by Gaddum but all he wanted to know was why I called it 5-HT. Gaddum said, 'I call it HT'. I explained to him that there is a 6-HT and a 5,6-di-HT, but he didn't seem to be convinced.

Healy: It was an era, as you say, when people could give anything almost to anyone and to just take curiosity here, methylene blue is the dye from which the phenothiazine nucleus came and it was first produced in 1875. As early as 1898

[37] Curzon G. (1955) A rapid chromatographic test for high urinary excretion of 5-hydroxy-indole-acetic acid and 5-hydroxytryptamine. *Lancet* **i**: 1361–1362.

[38] See Feldberg W. (1967) John Henry Gaddum 1900–1965. *Biographical Memoirs of Fellows of the Royal Society* **13**: 57-77. Gaddum J H. (1953) Antagonism between lysergic acid diethylamide and 5-hydroxytryptamine. *Journal of Physiology* **121**: 15P.

[39] Brengelmann J C, Pare C M B, Sandler M. (1958) Alleviation of the psychological effects of LSD in man by 5-hydroxytryptophan. *Journal of Mental Science* **104**: 1237–1244.

you can find literature on its use to treat nervous problems,[40] for which it seemed to work and the person who actually produced the article said, 'I know loads of other people using this as well.' So there seems to be this thing we have which is if something new appears there's a group of us who are prepared to say, 'well let's try it'. Has all that changed, because you can't now try things in quite the same easy way as people once did? That's perhaps an issue to throw open for later on. Gerald can I bring you in at this point?

Professor Gerald Curzon:[41] I remember that 5-hydroxytryptophan-secreting tumour very well, because I also had some of the urine in 1955 and I was really very peeved when Merton wrote a paper on it,[42] as I didn't spot exactly what kind of tumour it was but he did. I guess I am here more as a witness, than as a participant, because I am not a psychiatrist. I got involved in this area in 1953 when I came to the National Hospital in Queen Square as a research assistant to Dick Pratt, a psychiatrist in Eliot Slater's department. I'd recently done a PhD in biochemistry at Leeds and I knew nothing about psychiatry, except that I felt respectful towards Freud and I was impressed by Jung, although not for any particularly scientific reason. Now Dick was an early biological psychiatrist. He was a physical methods man, and it came as quite a shock to me to learn from him that he didn't hold psychoanalysis in much esteem. This got me into a lot of heated dinner table discussions, because in the 1950s, and in fact afterwards, one of the signs of enlightenment out in the lay world was a kind of religious faith in psychoanalysis.

When Dick interviewed me for the research assistantship, he showed me the chemical structure of LSD and he said, 'How do you think this causes hallucinations?' I'd never heard of LSD. It was a few months before Aldous Huxley's book, *The Doors of Perception*, publicized the hallucinogens[43] to the general public and years before LSD became a street drug. But I had heard of serotonin (5-HT), because it was marginally relevant to my PhD thesis and if you wrote a PhD thesis like mine, that didn't have any results in it, you dragged anything that was marginally relevant into the introduction. So I said, 'Well, it reminds me of this new thing in the blood called serotonin.' And Dick said, 'Is there any of it in the brain?' and I replied, 'Well, not as far as I know'; which wasn't too far out at that time. I wasn't aware that Twarog and Page had only just

[40] For example, in the mid-1890s Paul Ehrlich (who shared the Nobel Prize in Physiology or Medicine in 1908 for his work on immunity) conducted studies of the nervous system that involved testing the effect of methylene blue on neuralgia and on malaria.

[41] Professor Gerald Curzon (b. 1928) was Professor of Neurochemistry at the Institute of Neurology, University of London, from 1976 to 1993, now Emeritus.

[42] Sandler M, Snow P J D. (1958) An atypical carcinoid tumour secreting 5-hydroxytryptophan. *Lancet* **i**: 137–139.

[43] Huxley A. (1954) *The Doors of Perception*. London: Chatto and Windus.

detected it in the brain.[44] Also a month or two after my interview, Gaddum reported that LSD blocks the action of serotonin on smooth muscle.[45] However, I was offered the job and Dick told me to read a book that had just come out called *Prospects in Psychiatric Research*.[46] This had derived from a Mental Health Research Fund Symposium in 1952 and when I was asked to speak here I thought it would be interesting to see how it had stood up to the passage of time. One session at the meeting was called 'Ignorances in biochemistry, endocrinology and pharmacology'.[47] Ignorances in biochemistry didn't even get a whole session of its own; only a third of a session. Reading it 44 years on, reminded me of the ideas that had provoked Dick Pratt to set up the project I was to work on. At the symposium, Derek Richter suggested that some psychoses might well be clearly defined inborn errors of metabolism, and he put forward phenylketonuria as a kind of model. He was also enthusiastic about the relatively new technique of paper chromatography as a powerful research tool, as indeed it was at that time.[48] I remember Sir Charles Dent, Dr Dent as he then was, who was a pioneer of its application of paper chromatography to medicine, saying to me, 'With paper chromatography at your disposal, the world would be at your feet.'

Another big influence on Dick Pratt was Eliot Slater. He was a psychiatric geneticist, among other things. These influences all came together in our research project, which was to look at differences between schizophrenic and normal urine by paper chromatography.[49] This was called 'looking for the spot' and the hope was that it was going to reveal the hypothesized biochemical genetic defect in schizophrenia. We were then going to determine whether giving schizophrenics LSD or mescaline would increase the excretion of the spot. Not something that would easily have got passed the Ethics Committees nowadays, but then it was

[44] Twarog B M, Page I H. (1953) Serotonin content of some mammalian tissues and urine and a method of its determination. *American Journal of Physiology* **175**: 157–161. Twarog B M. (1988) Serotonin: history of a discovery. *Comparative Biochemistry and Physiology* **91C**: 21–24.

[45] op. cit. note 38 above. Gaddum J H. (1954) Drugs antagonistic to 5-hydroxytryptamine. In *Ciba Foundation Symposium on Hypertension: Humoral and neurogenic factors*. Boston, MA: Little, Brown, 75–77.

[46] Tanner J M. (ed.) (1953) *Prospects in Psychiatric Research. The Proceedings of the Oxford Conference of the Mental Health Research Fund*. Oxford: Blackwell Scientific Publications.

[47] op. cit. note 46 above, 109–155.

[48] Paper chromatography (a technique for separating the components of complex mixtures) had just been developed as a research tool, for which Archer J P Martin shared the 1952 Nobel Prize for Chemistry with his co-worker, Richard Synge. See James L K. (ed.) (1993) Archer John Porter Martin. In *Nobel Laureates in Chemistry 1901–1992*. American Chemical Society and the Chemical Heritage Foundation, 352–355. *idem* Richard Laurence Millington Synge. ibid. 356–358. Gordon H. (1996) Richard Laurence Millington Synge FRS 1914–1994. *Biographical Memoirs of Fellows of the Royal Society* **42**: 455–479. Martin A J P, Synge R L M. (1941) A new form of chromatography employing two liquid phases: 1. A theory of chromatography, 2. Application to the micro-determination of the higher monoamino acids in proteins. *Biochemical Journal* **35**: 1358–1368. Martin A J P. (1964) The development of partition chromatography. In *Nobel Lectures: Chemistry, 1942–1962*. Amsterdam: Elsevier, 359–371. See also notes 36 and 37 above.

[49] Curzon G. (1958) Urinary excretion of indoles in schizophrenia. *Confinia Neurologica* **18**: 211–216.

perfectly easy to do this kind of thing. In fact, I was going to take some mescaline myself, and go down to the National Gallery and see what the pictures looked like, but my wife was against it. Also a paper came out in the *Journal of Mental Science* about some pretty horrific mescaline and LSD hallucinations, so I never touched mescaline.[50]

It all seemed quite exciting doing this kind of work at the time, but I guess that one of my greatest bits of scientific good fortune was, unlike some people in the 1950s, I never found the spot. I did learn something about gut bacterial metabolism, about drug metabolism, about metabolism of dietary constituents. Looking back, the biochemical techniques at our disposal were very powerful compared to what had been available only a few years before, but they were very limited as tools for the study of psychiatric illness. However, something one might ask is, how much of present research in biological psychiatry is still really looking for the spot, but with more advanced technologies?

So, coming back to the Mental Health Research Symposium. In it Max Reiss mentioned acetylcholine, he mentioned noradrenaline in passing, which Marthe Vogt had recently detected in the brain[51] and he speculated that there might be other important brain amines. Desmond Pond, who was an EEG expert, made probably the most interesting contribution, both positively and negatively. He said, and I am actually quoting him, 'Treatment by biochemical means must always be of the shot-gun type'.[52] Well, I guess many of us would still incline more to that point of view than to Huxley's statement that mescaline opens the doors of perception.[53] Huxley, a kind of general polymath but no pharmacologist, said that anyway mescaline was less toxic than any other substance in the pharmacological repertoire; which was very confident of him. Still, I don't think many people would go as far in the other direction as Pond, who also said, 'The only possible biochemical treatment would be the transfusion of normal blood into abnormal persons'.[54] He also said something that was more prescient, 'That most mental disorders probably involve biochemical variations from the norm, rather than something as sharply defined as phenylketonuria'. Most biological psychiatrists would now agree with this. Another prescient remark was made by Martin Roth who was probably the youngest person there. He said that the physiology of adrenocorticotrophic hormone (ACTH) and cortisone might become an important growing point for psychiatric research. This, in fact, did occur, especially with respect to depressive illness and there has been a lot of mileage in this kind of

[50] Sandison R A. (1954) Psychological aspects of the LSD treatment of the neuroses. *Journal of Mental Science* **100**: 508–515.

[51] Vogt M. (1954) The concentration of sympathin in different parts of the central nervous system under normal conditions and after the administration of drugs. *Journal of Physiology* **123**: 451–481.

[52] op. cit. note 46 above, 152.

[53] op. cit. note 43 above.

[54] op. cit. note 46 above, 152.

idea. What else from *Prospects in Psychiatric Research*?[55] One participant said, 'First we must complete the map of the central nervous system, the anatomical map, the chemical map, the functional map'.[56] Forty-four years later we are still getting there. One more thing, I thought I would look at the index [of *Prospects in Psychiatric Research*] to see what key words were not there as this may indicate the big changes since 1953. Serotonin, dopamine, neurochemistry, neuropharmacology, none of those words were in the index. Something that indicates a difference that already existed between the educated public as a whole and research-orientated psychiatrists, is that the index only contained a passing reference to Freud. There was one reference to Jung but it wasn't to Carl Gustav Jung, it was to a Richard Jung.

Healy: Thank you very much, Gerald. The transfusion of normal blood into a person who had schizophrenia was done by George Simpson and it appeared to be of little use as it turned out.[57] Can I hand over now to Alec Jenner?

Professor Alec Jenner:[58] My excuse for coming is the desire not to drop too quickly into total obscurity in medical history, so I suppose I can do my best. I did have experience of the lunatic asylum before phenothiazine. I lived in a little place near Hanwell Hospital,[59] which is famous, of course, for being the hospital in which John Conolly had worked, and which became St Bernard's in Ealing. My first love was the girl who lived along the road, called Betty, and she one day suddenly became acutely catatonic, and that had a very profound influence, and of course it introduced me to mental hospitals of the 1940s where I began to work as a sort of volunteer. Betty didn't want to have anything more to do with me. The infatuation was probably one way. She smelt, she was dirty, the place was full of urine, the people, who were standing in the corridor, were catatonic. I think what I want to say is that it's fantastic what the difference is, and there have perhaps been greater advances in psychiatry in that sense than perhaps in other branches of medicine. Of course, it was in the late 1950s that I began to work on catatonia and I concluded that the reason why it really disappeared was because I was trying to do

[55] op. cit. note 46 above.

[56] The participant was Professor A Kennedy, Professor of Psychological Medicine at the University of Durham at that time. op. cit. note 46 above, 159.

[57] See Simpson G. (1998) The emergence of clinical psychopharmacology. In Healy D. (ed.) *The Psychopharmacologists.* Vol. 2. London: Chapman & Hall, 285–306.

[58] Professor Alexander Jenner (b. 1927) was the physician in charge of the Medical Research Council Unit for Chemical Pathology of Mental Disorders between 1965 and 1967, and Director of the Medical Research Council Unit for Metabolism in Psychiatry between 1967 and 1982. He was Professor of Psychiatry at the University of Sheffield from 1967 to 1992 and is a Fellow of the Royal College of Psychiatrists (1972) and of the Royal College of Physicians of London (1980).

[59] Hanwell Hospital was the mental hospital which served most of Middlesex at the time.

something with it, working for Gjessing in Norway.[60] But one thing very striking happened with Gjessing's patients, if we moved some of them from one ward to a different sociological position, one of the very classical periodic psychiatric conditions changed. They also changed when they were given phenothiazine. It was the fact that you could do these things two ways that had a very profound effect on my further attitude. Clearly the doctor can concentrate on being enthusiastic for what he likes. He isn't dealing with something so clearly ontological as he might think, even if it's much more convenient to do so with drugs, and often more effectively than it is by the attempt to change the social situation of the patient.

However, if I have any special right to address this group, it's probably less because of what I did about periodic catatonia and the pink spot,[61] (fortunately, we never found it), than the fact that we did the first double-blind controlled clinical trials of the benzodiazepines, and in that sense I have perhaps had a ringside, if not in the ring, view of their use in society. I was a naive young psychiatrist, much before I became a naive old one. I happened to read in the popular press about a lion and tiger trainer. He found that the new compound made available by Roche products in Switzerland was valuable in his work making the tigers and lions easier to train. It struck me immediately that, while we hadn't got lions and tigers in a large Sheffield outpatients department, there were some problems that we could try to treat similarly. I wrote to Roche who actually were thinking of doing trials anyway and they were delighted of course that someone was equally enthusiastic about giving benzodiazepines to people in outpatients.

The psychiatric outpatients in those days at Sheffield involved absolutely crowds of disturbed people to whom little individual time could possibly have been given by a junior doctor. Here then was a chance to do something for them and professionally for ourselves. As I have said, Roche were delighted and in fact, despite the fact that we introduced benzodiazepines, what we got in return was £50 for a flame photometer to study lithium. They did rather better. The criteria we used to evaluate the benzodiazepines were heavily dependent on the patients' preferences in double-blind studies of a, b and c etc. They were actually bottles either of benzodiazepine, barbiturate, or a placebo. Patients knew they were in trials and they simply had to say which they found most helpful. We, and they, seemed to be delighted that they picked more or less consistently, in a statistically significant way, the benzodiazepine. That was when chlordiazepoxide was called methaminodiazepoxide because Roche had missed a chloride radical. It became chlordiazepoxide when they found a very simple chemical error had been made.

[60] Rolv Gjessing (1887–1951), a talented psychiatrist, was the Medical Superintendent of Dikemark Sykehus, the hospital serving most of Norway. During the war he published much of his acclaimed work in the *Zeitschrift für Neurologie und Psychiatrie*.

[61] This refers to the chromatography 'spot' everyone was searching for, indicating abnormal metabolism (see Curzon's contributions earlier in this meeting).

Later on, other benzodiazepines were similarly studied by us and they consistently gave statistically positive results in anxiety states, so we felt delighted that we had found drugs which you could take in very large doses, and we took enormous doses ourselves to see whether they were toxic. They didn't do that much harm. It seemed a wonderful replacement for the barbiturates which were what people were given before. We had no thoughts about them being addictive. In subsequent legal matters I was asked whether if you gave them an addicting substance, were you surprised that they said they liked it? Well at the time however ignorant or naive we were, we were not thinking about addiction at all and we were happy with our little publications[62] and our new flame photometer. We noticed, however, that when we studied the new drugs, we were always studying the same people, however happy they were with the benzodiazepines, most of them were still coming back and were addicted both to our clinic and benzodiazepines and they didn't in one sense seem much better, but they consistently said they wanted the drugs.

In the recent legal preliminaries, I was asked to appear on behalf of Roche, that meant I saw, like many other people had, an enormous number of case histories of plaintiffs who complained about what terrible things had happened to them whilst on the drugs. I doubted, having read more than I wanted to, that any had much of a case. Most of them seemed to pretend that there was nothing wrong with them before they started the drug and that there were major disasters afterwards. They, of course, then lost legal aid and I lost my retirement top-up for my contribution to the Roche products, which was much better than a flame photometer.

I don't know that I want to say a great deal more, as I thought I had to be very brief. Benzodiazepines are interesting and effective in short term. Clearly they are holistically scientifically interesting.[63] I did some good I think by putting people on them, getting them over small patches. I did a great deal more harm aggressively taking people off when I thought that we were doing something legally harmful. I also became far more of a sociologist, even though there were so many more things psychiatry could do. But I think I only want to state our ignorance still of an existential position of what is best to do when and how much time have we got to do it anyway.

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[62] See for example Jenner F A, Kerry R J, Parking D. (1961) A controlled trial of methaminodiazepoxide (chlordiazepoxide, '*Librium*') in the treatment of anxiety in neurotic patients. *Journal of Mental Science* **107**: 575–582. Kerry R J, Jenner F A. (1962) A double blind crossover comparison of diazepam (*Valium*, Ro5–2807) with chlordiazepoxide (*Librium*) in the treatment of neurotic anxiety. *Psychopharmacologia* **3**: 302–306.

[63] For a history on the discovery and use of the benzodiazepines, see Cohen I M. (1970) The benzodiazepines. In Ayd F J, Blackwell B. (eds) *Discoveries in Biological Psychiatry.* Philadelphia, PA: J B Lippincott Company, 130–141. Smith D E, Wesson D R. (eds) (1985) *The Benzodiazepines. Current standards for medical practice*. Lancaster: MTP Press.

Healy: Thank you very much, Alec. Your thoughts prompted a phrase which came to mind. Gerald Klerman,[64] around 1969, coined a phrase 'pharmacological Calvinism', the idea that something you like can't be doing you good. This is perhaps relevant to all this somewhere. Just where, I am not sure, perhaps we could throw it open to the floor at this point and ask people what they think or what they recall.

Professor Elaine Murphy:[65] We are going through an interesting period in old age psychiatry right now, because either later this week or next week, the first drug licensed in this country for the treatment of dementia will be available.[66] This puts us in the same position as psychiatrists were in the late 1940s with imipramine and the new phenothiazines, except this drug probably doesn't work. One of the things that's obvious to me is that it will begin to shift the relationship between the professionals who make a contribution to the service. One of the things which has characterized the development of old age services for people with dementia is that the doctor has a relatively small part to play. Since we have not been able to do anything medically about the cognitive problem of dementia, we have to indulge in what a social worker colleague of Gerald Curzon and I, Erma Gibber, used to refer to as 'culinary psychiatry', where you prescribed a pinch of this and a pinch of that, but nothing much helped. This led to other professionals taking a greater role – far greater importance has been attached to the social management and the psychological management of the families' problems, seeing the problem in context. It has seemed to me that the negative of the miracle of psychiatric drugs, and it has been a miracle, if not as big a miracle as we'd hoped, was the neglect of other aspects which Alec was talking about. I wonder if people who lived through that period can comment on the increasing power that drugs gave to psychiatrists and whether that has been a good or bad thing.

Healy: Could I add in just to that point, the opposite kind of example, from the opposite end of the age spectrum. If we look at perhaps child psychiatry. It has been said that there is no treatment in all of medicine for which the evidence is more compelling than the treatment of hyperactivity, with methylphenidate and that evidence has been there for 10, 20, 30 years, and yet it is still unused. There are child psychiatrists within the UK who will go through their training and say

[64] In 1959, Gerald Klerman coordinated the first trials of chlorpromazine, which were reported in 1964 and established the value of antipsychotics in the management of schizophrenia. Cole J O, Goldberg S C, Klerman G L. (1964) Phenothiazine treatment in acute schizophrenia. *Archives of General Psychiatry* **10**: 246–261.

[65] Professor Elaine Murphy FRCPsych (b. 1947) was Professor of Psychogeriatrics in the Division of Psychiatry at the United Medical and Dental Schools of Guy's and St Thomas's Hospitals, University of London, from 1983 to 1995. Since 1995 she has been Chairman, City and Hackney NHS Trust.

[66] Aricept (*Donezepil*) manufactured by Eisai–Pfizer.

that they haven't ever prescribed a drug and they will claim this as something to be proud of. I am not saying that they oughtn't to be proud of it, but I am just saying you know the issues of how teams relate to the prescriber or what the prescriber can do. It's a hugely complex area. Would anyone like to come in on this theme generally?

Professor Hannah Steinberg:[67] Only to say that as basically an experimental psychologist, I have always been very interested in equating, if one can, drug effects with environmental effects; sometimes one can actually do this and show that by changing the animal's environment, one can get hyperactivity similar to that by giving drugs.[68] And maybe our clinical trials should take into account social improvement as well. Usually one just devises a double-blind clinical trial, and thinks that one has satisfied everything. Well, in practice, life isn't usually like this; real people have other interests than swallowing a pill and feeling different. And I rather agree with Dr Healy's point that that's been the downfall of 'drug people'; the social environment, and the general happiness of people have been too narrowly defined. Maybe we could do more by looking at the whole patient and at the whole situation, particularly in old age, when people are very lonely and social improvements would make a bigger difference nowadays than we expect. It's not something that is a popular view, because it's too difficult to test and probably would cost too much.

Professor Michael Gelder:[69] Will you allow a slightly different point? You have talked about phenothiazines, about imipramine and about the MAOIs, but nobody has mentioned lithium. This surprised me, because if we think of the major changes that came about at that time, that is perhaps one of the greatest. You asked at the beginning whether there were resistances to the introduction of the new drugs. I don't remember them. I was a young, keen, registrar when they were first in use, so perhaps I was interested in the new, however, I don't think there were any great resistances to moving from what was the established practice of

[67] Professor Hannah Steinberg has been Visiting Research Professor, School of Psychology, Middlesex University since 1992. She was Professor of Psychopharmacology at University College London, the first such position in Western Europe and probably in the world, from 1970 to 1992. For further details see Steinberg H. (1996) Bridging the gap: psychology, pharmacology and after. In Healy D. (ed.) *The Psychopharmacologists*. Vol. 1. London: Altman, 215–237. She now works on psychological benefits of physical exercise, exercise addiction and endorphins, see Steinberg H, Sykes E A, Moss T, Lowery S, LeBoutillier N, Dewey A. (1997) Exercise enhances creativity independently of mood. *British Journal of Sports Medicine* **31**: 240–245.

[68] Davies C, Steinberg H. (1984) A biphasic effect of chlordiazepoxide on animal locomotor activity. *Neuroscience Letters* **46**: 347–351.

[69] Professor Michael Gelder (b. 1929) has been W A Handley Professor of Psychiatry, University of Oxford since 1969 and Honorary Consultant Psychiatrist for Oxford Regional Health Authority (later DHA) since 1969.

treating depressive disorders with amphetamine, treating schizophrenia with insulin, and treating both with electroconvulsive therapy (ECT),[70] to treatment with more effective drugs. What surprised me, and it came to me when Dr Broadhurst was talking, was what was new was the idea there were drugs which had delayed effects, which didn't have an effect immediately. I was very impressed that in your trial in Switzerland you were quite prepared to wait three weeks for something to happen. Now I suppose there was the knowledge that when depressive disorders respond to ECT, there's a delay, and that insulin was thought also to work after delay. Nevertheless it must have been something rather new to think of a *drug* that was going to have such a long delay; it has always been one of the puzzles, and still is, of the action of the drug.

Turning again to lithium, there was resistance to the introduction of it for three reasons. First, the original research was so extraordinary and Cade had such an improbable original theory about its action.[71] Secondly, some of the original clinical trials were rather weak, so that when it was introduced, the idea of prevention was quite a hard one for people to swallow. Do you remember that Michael Shepherd wrote a paper called 'Lithium: another therapeutic myth?'[72] He had the sense to put a question mark at the end of the title, but it was a sign, I think, that it was very difficult for people to accept the preventive actions of the drug, partly because of the poor basic research, partly because it was a very simple compound which didn't seem complex enough to have such a profound effect. So that would be my answer to 'were there resistances?' and I do think we have got to talk more about lithium. Also I would like to ask to ask Dr Broadhurst about the willingness to wait three weeks for an effect of imipramine: I am very impressed that you waited that time, before you were ready to say, 'There is no effect'.

Broadhurst: I quite take that point, but I don't think it was because of cleverness on anybody's part. Until then we had lived in a pharmacological culture where most drugs acted fairly quickly. If, for example, you took an analgesic like aspirin for a headache, then you expected it to act within 30 to 45 minutes. If it didn't, you would probably take another tablet. Delayed response to active medication in adequate dose was less common in those days. In the case of the imipramine trial,

[70] Electroconvulsive therapy (ECT) remains the most rapid and effective treatment for severe acute depression; often used in drug-resistant cases.

[71] John Cade was the first to report on lithium's use for acute manic states. Attempting to show the presence of a toxic agent in the urine of manic patients, solubility studies using lithium salts led to the discovery of lithium's role in the control of manic excitement. See Cade J F J. (1949) Lithium salts in the treatment of psychotic excitement. *Medical Journal of Australia* **14**: 349–352. Cade J F J. (1970) The story of lithium. In Ayd F J, Blackwell B. (eds) *Discoveries in Biological Psychiatry.* Philadelphia, PA: J B Lippincott Company, 218–229.

[72] Michael Shepherd FRCPsych (1923–1995) was Emeritus Professor of Epidemiological Psychiatry at the Institute of Psychiatry, University of London. See Blackwell B, Shepherd M. (1968) Prophylactic lithium: another therapeutic myth? An examination of the evidence to date. *Lancet* **i**: 968–971.

we learned of the long delay before clinical effect, almost by default. We, both Geigy and Dr Kuhn, had no idea of the dosage which might be effective. In consequence, the doses had to be increased progressively from fairly small to what we now know are reasonable therapeutic doses. All this took time and during this time the patients' exposure to the drug was continuing. Moreover, because it was a clinical trial, however uncontrolled, there was an initial intention to continue it for a reasonable period, probably a few weeks, unless we ran into difficulties. The real problem, of course, as you said, was not because it took three weeks, but why? Nowadays there are a number of sophisticated theories which try to explain it, but in those far off days we were blessed by the ability to think of something simple, even if it were naive. We knew, even then, from suggestions by Woolley and Shaw,[73] that low levels of 5-HT in the CNS might be associated with depression. We imagined that imipramine was somehow causing a filling up of a 5-HT reservoir to some threshold level, after which clinical effect appeared. This took time – hence the latent period.

Dr Donald Scott:[74] I was clinical neurophysiologist at the London Hospital and am now retired. Professor Desmond Pond was mentioned earlier and he was the person who made me interested in epilepsy, which is how I came to find out about the use of lithium in the nineteenth century.[75] I was reviewing the earlier treatments and I found that Gowers, in his book on epilepsy published in 1885, mentioned Weir Mitchell; he was using lithium bromide rather than other salts for the treatment of epilepsy. I was interested in Weir Mitchell for various reasons and so pursued it somewhat further. He found lithium was useful in patients other than those with epilepsy. In fact, there is quite a literature which I discovered on the use of lithium in the nineteenth century (I realize that today is supposed to be about the twentieth century, but I thought that something from an earlier century was perhaps permissible and quite interesting). Curiously, therapy with lithium seemed to have disappeared by the earlier part of the twentieth century; I cannot understand for what reason. I presume it is probably because the drug can be toxic and blood levels of patients were not readily available at this time. However, it was

[73] Woolley D W, Shaw F. (1954) A biochemical and pharmacological suggestion about certain mental disorders. *Science* **119**: 587–588.

[74] Dr Donald Scott (b. 1930) was Consultant in charge of the EEG Department at the London Hospital from 1967 to 1992 and Senior Registrar at the Maudsley Hospital, London, from 1964 to 1967. Fellow of the Royal College of Physicians London since 1977.

[75] Scott D F. (1992) The first use of lithium? *British Journal of Psychiatry* **160**: 709–710. See also Gowers W R. (1885) *Epilepsy and Other Chronic Convulsive Disorders: The causes, symptoms and treatment*. London: William Wood (reprinted by Dover Publications, New York, 1964). Mitchell S W. (1870) On the use of bromide of lithium. *American Journal of Medical Science* **60**: 443–445.

clearly used, not only in America, in this country, but also in Germany as a treatment for depressive illness.[76]

Professor Arthur Crisp:[77] I have heard amphetamines spoken of rather disparagingly but when I first came into psychiatry we prescribed *Drinamyl*, a mixture of dexamphetamine and amylobarbitone sodium, and in my hands, perhaps because I was a young registrar, it was jolly good. Then along came the tricyclic antidepressants and the clinical response to these was more ambiguous and variable. I was sad that we lost the ability to judiciously prescribe *Drinamyl*. This step deprived us of the opportunity to help many patients as well as to explore the mind more within the clinical setting. The second point: somebody again raised the issue of tuberculosis as a paradigm for the power of the magic bullet. This question of whether there was an ultimate magic bullet for tuberculosis is, I understand, still controversial. There are still people who will tell you that the improved situation regarding tuberculosis is as much a function of concurrent cultural and nutritional changes in our society. Now, I entered psychiatry just before it seemed to be that the form of some mental illnesses changed quite profoundly. I don't think that was only a function of more vigorous treatment. I think it was also related to profound sociocultural changes. In the 1950s, one saw very severe involutional melancholia and agitated depressions, which were not just a product of them having been left untreated. They could arise abruptly. Alec Jenner has just talked about how Gjessing's catatonic syndrome disappeared the moment he tried to get a handle on it. One continues to see much less acute catatonia these days. I think we have to be rather wary when evaluating the impact of our medication against this changing background.

Dr Malcolm Pines:[78] I am probably the only psychoanalyst in this room. I did my psychoanalytic training while I was at the Maudsley, which was from 1952 to 1955, but before that I did a locum at a private mental hospital, since disappeared, called Camberwell House, not far from the Maudsley. All I had to do was to walk through the wards once a day and sign the books and try and clear my clothes of the smell of paraldehyde, because when I got into psychiatry, and probably there

[76] Johnson F N. (1984) *The History of Lithium Therapy*. London: MacMillan. Felber W. (1987) Lithium prevention of depression 100 years ago – an ingenious misconception. *Fortschritte der Neurologie-Psychiatrie* 55: 141–144 [in German].

[77] Professor Arthur Hamilton Crisp (b. 1930) was Professor of Psychiatry, University of London, at St George's Hospital Medical School from 1967 to 1995, now Emeritus, and Dean of the Faculty of Medicine, University of London, from 1976 to 1980.

[78] Dr Malcolm Pines (b. 1925) was Honorary Consultant and Senior Lecturer in Psychotherapy, St George's Hospital, London from 1969 to 1974, Consultant in Psychotherapy at the Maudsley Hospital from 1974 to 1979 and at the Tavistock Clinic from 1979 to 1987. Fellow of the Royal College of Psychiatrists since 1972 and President of the International Association of Group Psychotherapists from 1980 to 1984.

are some people of my generation here, before the new drugs came in, that was all we had. We had intramuscular paraldehyde, chloral [hydrate], we had the barbiturates, we had modified and deep insulin, ECT, and that on the whole was our repertoire. What a relief it was when chlorpromazine came in, the level of agitation went down in the wards, and the tremendous difference it made to the social system that violence wasn't something that you had to be afraid of or try and control, it increased the morale, it brought a great change into psychiatry. It was the same with lithium. At the Maudsley my first consultant was Brian Ackner, who was one of the people who did the control trial to show up the insulin myth that later on got written up by other people[79] and that was a tremendous relief again that the deep insulin unit was closed. Though, of course, we need to remember that William Sargant[80] went on using it and used prolonged narcolepsy and narcosis when he gave up the National Health Service and he moved to the Priory. I wonder if there isn't anybody here from the Thomas's group who will remember the tremendous combinations of MAOIs (monoamine oxidase inhibitors) and the tricyclic antidepressant that he was trying out, combined with anything else. He was one of these people like Nathan Kline, you know, try it and see if it works. And added to that that you had to believe in it. It wasn't just a question of giving it. There's a famous story of William Sargant going to Belmont one time and they produced somebody who'd been treated with ECT and said, 'Well Dr Sargant, you see ECT doesn't help in these prolonged depressions' and he said, 'Ah, but it's been given by someone who doesn't believe in it'.

Steinberg: It was always said that 'in Dr Sargant's hands' the drug cocktail worked, and that his hands seemed to be extremely important.

Professor George Beaumont:[81] I just wanted to say something in connection with what Arthur Crisp said because I can recall the first job I did in psychiatry in 1959, as a house officer in a hospital in Manchester, the Withington Hospital, and I was working for someone who was quite well known in our part of the world, called Howard Kitching. We were fairly well developed in the sense that we had this very vigorous District General Hospital (DGH) – I suppose one would call it now – based unit, but apart from prescribing quite a lot of Mist Nux Vom, and

[79] Brian Ackner (1918–1966) was Consultant at the Bethlem Royal and Maudsley Hospitals and the Postgraduate Medical School, Hammersmith Hospital. See Ackner B, Harris A, Oldham A J. (1957) Insulin treatment of schizophrenia. *Lancet* **i**: 607–611. Bourne H. (1953) The insulin myth. ibid. **ii**: 964–968. Puller Strecker H, Davies R, Gibson J, Charatan F B, Sandison R, Sargant W, Hunter R A, Rees W L, Mayer-Gross W. (1953) The insulin myth. ibid. **ii**: 1047–1048, 1094–1095, 1151–1152.

[80] William Sargant gives a detailed account of psychological medicine at that time in his book, Sargant W. (1967) *The Unquiet Mind*. London: Heinemann.

[81] Professor George Beaumont (b. 1932) has been a Pharmaceutical physician since 1966. Fellow of the Royal College of Psychiatrists since 1984.

Mist Gent Alk, I remember repeatedly writing prescriptions for *Drinamyl*. This mixture of amphetamine and amylobarbitone was very widely used, and I don't recall really, although one's memory fades for these things, having major problems. It was doled out in massive amounts to our patients who had what, in those days, was called mixed anxiety depression. We seem to have lost that concept somewhere in our classificatory systems until relatively recently. But that was the condition for which it was prescribed. It was at that time in 1959, in fact, when imipramine arrived. I remember how excited we were when it came, but I also remember that after our experience with *Drinamyl* we found it extremely difficult to use and very often our patients would go back to their *Drinamyl*, rather than persevere with the new drug *Tofranil*.[82]

The other thing I wanted to say was that after I left that post, I went into general practice, from 1960 to 1966. In preparation for this meeting I had a look at some of the records, because I have always kept very careful records of all the patients that I have seen in general practice. We only had about four psychiatric diagnoses. Again we had mixed anxiety depression, which seemed to cover most of the patients we saw; the odd endogenous depression; the odd pure anxiety state; and the odd insomniac. But mixed anxiety depression was the thing we saw most of, and looking at what we prescribed, I am surprised to see that in our particular practice, anyway, the most popular prescription was something called *Parstelin*. We got by pretty well with *Parstelin*, we didn't have a lot of problems for about six years with it, until 1966, when Blackwell described the 'cheese reaction'.[83] It's interesting how that particular report on a limited number of patients completely transformed the prescribing of the drug. I did in fact, before Blackwell reported it, see a cheese reaction. Actually I didn't know it was a cheese reaction when I saw it, because Blackwell hadn't told us what it was, but we did have a patient who clearly had the reaction, but on the other hand I have to say that we went for six years with relatively little trouble using *Parstelin*, until that report came out.

Two other very quick points to make from that observation and that is, historically, it's interesting how we were so enamoured of combination products, because most of the things that we then used, mind you we had 'combination diagnoses' in those days, were combination products, *Parstelin* being a good example.

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[82] op. cit. note 20 above.

[83] Barry Blackwell, a psychiatric trainee at the Maudsley at the time, noticed the connection between a number of patients who had been taking a monoamine oxidase inhibitor and symptoms such as headache and hypertension after eating cheese (termed the 'cheese reaction' – the reaction of tyramine in cheese with a monoamine oxidase inhibitor causing unwanted side-effects, e.g. headache, hypertension). See Mayer J. (1968) Cheese and monoamine oxidase inhibitors. *Postgraduate Medicine* **44**: 185–186. Blackwell B, Marley E. (1969) Monoamine oxidase inhibition and intolerance to foodstuffs. *Bibliotheca Nutritio et Dieta* **11**: 96–110.

The other very quick comment to say is that when imipramine did come, one of the things that was a major problem was to educate general practitioners, when it was released on the general practitioner market, to actually recognize depression. I think one factor which comes into the history of psychiatry is the important role of the pharmaceutical industry in education, because every time you introduce a new product, the first thing you have to do before you can sell the product is to teach people to recognize the condition for which it is going to be used. We have seen that so often. In fact, I have recently been engaged in an educational programme for social phobia which has given me a great feeling of *déja vu*, because now we are supposed to have drugs for social phobia, but before we can get anyone to prescribe them we have to teach the general practitioners what social phobia is. That is the kind of phenomenon that has gone right through the history of psychopharmacology.

Healy: On that point, are we creating mental illness that wasn't there before? Clearly in one sense, we aren't. You can always argue that people were out there, we just didn't recognize that they had nervous problems, but if you look back at the records, while we had these large old bins with two or three thousand people in them, the rates of admission into the bins up till 1945 or thereabouts were on the average of 200 per million per year, now they are on the average 3000 per million per year at least, and they are only the people brought into DGH units. We bring an awful lot more people into hospital than we ever used to do and that's not taking into account all the people that GPs treat and have been taught to recognize the illnesses that they were supposedly missing before. Are we doing people a favour here, I'm not sure?

Dr Philip Harrison-Read:[84] I am a psychiatrist and formerly a pharmacologist. We have heard about the bold enthusiasm of the early psychopharmacologists, some of whom are here today. Despite the reluctance of jobbing psychiatrists and GPs to use some of the new drugs in the early days, we have also heard about the apparent ease with which these compounds were given to patients or to volunteers who took part in clinical studies. However, ever since I have been in psychiatry, I have been struck by the reluctance of many patients to take medications, and very recently, a report by the Royal Pharmaceutical Society has highlighted this.[85] There may well be a very deeply ingrained resistance on the part of all patients to take medications prescribed to them, but this particularly seems to apply to people with psychiatric

[84] Dr Philip Harrison-Read (b. 1947) has been Consultant in Psychiatry at the Central Middlesex and Shenley Hospitals since 1991, Honorary Senior Lecturer at Imperial College School of Medicine since 1997, and member of the Royal College of Psychiatrists since 1985. He was formerly Lecturer in Pharmacology at the Medical College of St Bartholomew's Hospital from 1976 to 1982.

[85] Royal Pharmaceutical Society of Great Britain. (1997) *From Compliance to Concordance: Towards shared goals in medicine taking*. London: Royal Pharmaceutical Society.

disorders. As a result, psychiatrists like myself tend to become very preoccupied with persuading people to take the drugs that we know are effective. This may distract us from many of the other things that we should be doing in trying to help our patients. What has happened over the years I think, is that in our enthusiasm for drug treatment, we may have lost some of the other therapeutic skills that are necessary for dealing with mental health problems, and which have tended to give us an advantage over our medical colleagues in other non-psychiatric disciplines. In the area where I work, most of the patients I deal with are noncompliant with treatment and do not wish to take prescribed medicines. In order to cope with this problem, medicines must be offered as part of a package of care, some of which is seen as desirable by patients. A more multidisciplinary approach is called for, not only to get patients to buy the idea that medicines are helpful, but also to convince all the other people, professional and non-professional, with whom we are in partnership in offering mental health services. At a meeting of this sort, where we are enthusing about extraordinary advances in neuroscience, pharmacology and therapeutics, we must not forget that the recipients of these so-called wonder drugs are often, if not always, reluctant, at least in my experience. I think we cannot ignore this if we and our patients are going to get more out of old and new psychiatric drugs in the future.

Dr David Wheatley:[86] I suppose I might describe myself as a latter-day psychiatrist, since for a long time I was in general practice, but I was very involved in doing clinical trials of many of the early psychotropic drugs under the auspices of research grants from the National Institute of Mental Health (NIMH)[87] in the States and I was interested in George Beaumont's, and other people's, reaction concerning *Drinamyl*. One of the first studies that I did under those research grants, was to compare *Drinamyl* to its separate components, the amphetamine and the barbiturate. Nothing was done, I think, double blind in those days, and this was in this mixed anxiety and depression condition, so that one chose patients who had predominant anxiety symptoms and patients who had predominant depressive symptoms. Now I can't for the life of me remember what the result of that was, but the crux of the matter was that *Drinamyl* was very useful for the general practitioner who wasn't really quite sure whether his patient was depressed or anxious. He just saw a patient who had both types of symptom, and considered what was the best thing to treat them with, *Drinamyl*, and it did work as George

[86] Dr David Wheatley (b. 1929) has been Consultant Psychiatrist at the Royal Masonic Hospital, London, since 1990 and Fellow of the Royal College of Psychiatrists since 1982. He was President of the International Society for the Investigation of Stress, from 1988 to 1992 and Honorary Medical Associate, Maudsley Hospital, London, in charge of the stress clinic from 1985 to 1992.

[87] The National Institute of Mental Health (NIMH) is part of the Alcohol, Drug Abuse, and Mental Health Administration and one of the separate institutes of the National Institutes of Health (NIH), one of the world's foremost biomedical research centres, and the Federal focal point for biomedical research in the US.

[Beaumont] and others have said, it worked extremely well. I don't remember there were any problems of dependence and I suspect that that was because it was being properly used, in therapeutic dosage, under the supervision of a medically qualified individual. There was no question of enormous overdoses which is really what has given it its bad name and that's the problem. Give a dog a bad name and it persists. Look at thalidomide, a supreme example. Why could we not have gone on using thalidomide in men and elderly people, where it might have been very useful? But no, it had to be banned[88] and it's the same thing with amphetamines. Amphetamines were wonderful because they are an instant antidepressant. They improved moods straight away, as soon as you gave them. There was no lag period. Now why on earth should we not go on using amphetamines in the early stages of treating depression, whilst we allow our antidepressant effect to build up and then just tail them off, but we can't, because they have a bad name and none of us, I think, would dare to do it for fear of litigation. So this is something that I have seen change, and I think it is to the detriment of medical practice, that the introduction of rules and regulations, which, in a sense, are interfering with what is the basic principle in medical practice, that is the ultimate criterion of what works and what doesn't, the doctor–patient interface.

Professor Isaac Marks:[89] Can I take up David Wheatley's point about the over-banning of compounds? One is reminded that marijuana was regarded as sufficiently useful to be in the *United States Pharmacopoeia* until roughly 1934 when it was taken off and how difficult it is to use for nausea in chemotherapy today. So we do seem to have swings of the pendulum to an excessive degree.

Another point, a different one, is the way we were allowed to experiment with drugs without any ethical approval, without any thoughts of randomized controlled trials (RCT).[90] I was introduced to psychiatry in 1958 in Henry Walton's unit in Cape Town and we tried LSD with a few patients in those days, without thinking at all about doing randomized controlled trials.

I want to pick up also a point about patients' reluctance to take medication and one of the reasons for this that we might underestimate is the amount of side-effects that we don't actually look for. In the 1980s my unit ran two RCTs with clomipramine in quick succession. In the first RCT we looked for sexual side-effects of clomipramine and could find almost none. Then one of the research

[88] See Tansey E M, Reynolds L A. (eds) (1997) The Committee on Safety of Drugs. In *Wellcome Witnesses to Twentieth Century Medicine*. Vol. 1. London: The Wellcome Trust, 103–133.

[89] Professor Isaac Marks FRCPsych (b. 1935) has been Professor of Experimental Psychopathology at the Institute of Psychiatry and Honorary Consultant Psychiatrist at the Bethlem and Maudsley Hospital Trust, London, since 1978. Author of 12 books and 370 scientific papers including many on drug/behaviour therapy controlled trials.

[90] Randomized controlled trials (RCT) are studies which are run in different experimental groups with a prior randomization of the subjects or items to be compared in order to exclude bias of any sort.

workers, Dr Willie Monteiro, spotted that perhaps it was the way we were asking for side-effects that led us to ignore them and many of our patients were very reluctant to take clomipramine. The questions were then asked with more precision in our second randomized trial and lo-and-behold we then picked up a 93 per cent anorgasmia rate in our sexually active patients. So some of our patients' reluctance can be ascribed perhaps to hidden side-effects we are not aware of.

Dr Peter Rohde:[91] Somebody was asking for a person who had worked with Dr William Sargant to explain his secret. Well, I did from 1958 to 1960, and the answer was enthusiasm – unqualified, unscientific enthusiasm – and it was very infectious. During the time when I was there, more undergraduates joined psychiatry at St Thomas' than anywhere else. He had an extraordinary ability to get people to work for him because of this enthusiasm. At the time I was there as an SHO, and later a Registrar, Jim Birley, who was later to be Dean at the Maudsley, and Peter Gautiere-Smith, who was later the Dean at the National Hospital, Queen Square, were both working in the Department of Psychiatry. This enthusiasm had a great bearing on the effect of medicines. Because the whole place was enthusiastic, patients felt something was being done and the drugs appeared to work, not just for Dr Sargant but also for his junior doctors. The problems came later when you started to ask yourself the question as to what was going on. Certainly I found it difficult to go back there, having been away for some time, called up by the Army. Dr William Sargant could not tolerate the double-blind study and when I was involved in one of the first depot-injection double-blind studies in this country, William Sargant wrote a letter to *The Times,* criticizing the study as inhumane.[92] As I was the member of the team who had worked with him, I replied in print. Whenever he met me after this, he would shake his head and say, 'You wouldn't do it to your wife, Rohde, you wouldn't do it to your wife'. As a matter of fact, I would have encouraged my wife to be in that study, if, as the patient's husband, it had been properly explained to me. I think the enthusiasm issue also has a bearing on patient compliance and that if one goes back to the 1950s, patients would be given a great persuasion job, as were GPs, that drugs were the answer to all sorts of things when, as has been pointed out, they were not. But as the phenothiazines, the antidepressants and then the benzodiazepines came in,

[91] Dr Peter Rohde (b. 1933) has been a Consultant since 1970 and an Honorary Emeritus Consultant, Riverside Health Authority, London, since 1988. Fellow of the Royal College of Psychiatrists since 1983.

[92] Hirsch S R, Gaind R, Rohde P D, Stevens B C, Wing J K. (1973) Outpatient maintenance of chronic schizophrenic patients with long-acting fluphenazine: double blind placebo trial. *British Medical Journal* **i**: 633–637. Sargant W. (1975) Should patients be 'tortured' in the name of progress? [Letter] *The Times*, August 29. Rohde P D. (1975) Testing psychiatric drugs. [Letter] ibid. September 5. William Sargant also wrote a personal letter to Peter Rohde on 24 September 1975 criticising his double-blind sample study, which is in the Sargant papers, held in the Contemporary Medical Archives Centre, Wellcome Institute for the History of Medicine Library, CMAC/PP/WWS/A13.

general practitioners started to prescribe. Sargant was at the head of the trend, telling the GPs to prescribe. But of course patients were not stupid and I think that what then happened was a swing against drugs and psychiatry because other issues had been overlooked and the side-effects of drugs had been ignored.

I would touch on two other issues that have been raised. I understand all the wistful sadness for amphetamines but I was working in the emergency clinic at the Maudsley Hospital when amphetamines were effectively banned. There were – and I continue to see occasionally – people who were undoubtedly addicted to these drugs and who got side-effects from them. Some had psychoses while they were taking them and I think this is an issue.

The final point I would comment on is the question which Elaine Murphy raises about the position of the doctor in the team. May I give you Sargant's answer? I remember discussing the issue with him and he said that the Consultants had displaced Medical Superintendents when the NHS started because the Honoraries saw themselves as the top of the pile and said, 'We are not going to be bossed about by a salaried Medical Superintendent'. Once the Medical Superintendent had been displaced from running the hospital by other Consultants, a process of liberation was started which went on to Salmon and then onto Seebohm,[93] with the nurses and the social workers and later everybody emancipating themselves from medical influence. There has been a battle going on, a territorial battle, between those in the health service which is there for the reading if you look at it in those terms. When a colleague was appointed to my hospital at St Mary Abbot's in 1981, he came in with multidisciplinary ideas and the first thing he did when he became Clinical Tutor was to lay on a series of seminars about multidisciplinary psychiatry. Sitting back and listening to these, it was clear that every single discipline was making a play to extend its territory and I think this is one of the things that has been going on in psychiatry in the last two decades.

Steinberg: I am absolutely delighted that *Drinamyl* is still remembered. When we showed that in the laboratory it had bigger effects than any dose of either of the constituent drugs separately, we didn't quite believe it ourselves.[94] I went back to the clinical literature which was very sparse before Dr Wheatley arrived, but it was quite clear that people had definite ideas of how these combinations would work. They would either work as a weak amphetamine, or like a weak barbiturate. In other words, they used the opposite kind of drug to weaken the main effect of the

[93] Thomas W. Salmon (1876–1927) was a recognized leader in psychiatry in 1917. See Braceland F J. (1981) *The Salmon Committee on Psychiatry and Mental Hygiene*. New York: New York Academy of Medicine. Frederic, Lord Seebohm (1909–1990) was the Chairman of the committee which reported in 1968. See *Report of the Committee on Local Authority and Allied Personal Social Services.* Cmnd 3703. London: Her Majesty's Stationery Office, 1968.

[94] Rushton R, Steinberg H. (1963) Mutual potentiation of amphetamine and amylobarbitone measured by activity in rats. *British Journal of Pharmacology* **21**: 295–305.

other one. Or, thirdly the combination would produce a special effect, and the special effect was an improvement of mood and people's feelings about themselves. It was this, I think, that made these combinations so useful, and as far as I know they did not lead to addiction. There were lots of housewives and others, who took one tablet a day for years and were perfectly controlled.

Healy: Can we clarify, Hannah, what was 'mother's little helper'? Was it *Drinamyl*?

Steinberg: It could have been – it was a bit before my time.

Murphy: *Drinamyl* was 'purple hearts'.[95]

Steinberg: Yes. In the USA it was called something else, *Dexamyl*, I believe. Purple Hearts were a military decoration. I was invited to go to Smith, Kline & French (SK&F) in Philadelphia to explain what we had found and I used the name 'purple hearts', not realizing this, and everybody looked rather glum. But this business of combinations of drugs illustrates quite an important point: for a while there was an edict against using combinations, because pharmacologists were looking for 'pure' effects, and practitioners were anyhow not always happy with the idea of fixed ratio combinations. It has now been realized again that many so-called psychiatric states are in fact mixed, and 'mixed anxiety and depression' is again being recognized even though some drug companies may not like it. Elizabeth Sykes and I found that one of the newer drugs, buspirone, acts in this sort of intermediate way in the screening tests that we used.[96] So I think, and other people are beginning to think so too, that there is a great future in combining drugs, provided that you know what you are doing. We have developed mathematical models, which is quite easy now with computers, to actually predict effects of different ratios and different doses of pairs of combined drugs. And one more thing: when I was at Smith, Kline & French in Philadelphia I was determined to find out how these *Drinamyl* mixtures had started because that wasn't recorded in the literature. The mixture consisted of one part of dexamphetamine to 6.5 of amylobarbitone. That was the ratio for man and

[95] Oblong mauve pills, known colloquially as 'purple hearts', were a combination of dexamphetamine and amylobarbitone, the original 'pep pills' which were used extensively by women on weight reduction diets. Their availability was restricted in 1964. See *ABC of Drug Addiction*. Bristol: John Wright, 1970, 17. Glatt M. (1967) The purple heart craze. In *The Drug Scene in Great Britain*, ch. 4. London: Edward Arnold, 43. See also Dickins D, Lader M H, Steinberg H. (1965) Differential effects of two amphetamine–barbiturate mixtures in man. *British Journal of Pharmacology* **24**: 14–23.

[96] Steinberg H, Sykes E A, Davies C. (1989) Buspirone: evidence of mixed anxiolytic/antidepressant profile. *European College of Neuropsychopharmacology Congress*, Gothenburg, Abstracts.

that worked best with our rodents as well.[97] And so, when I gave my lecture, I particularly asked whether anybody could please enlighten me. Apparently, what had happened was that the Chairman of Smith, Kline & French one day wanted to have a good effect and he thought that amylobarbitone alone was too depressing, and would make him sleepy, while the amphetamine alone would make him too excited and jittery, and so he took the smallest marketed dose of amylobarbitone which in those days was half a grain (32.5 mg) and the smallest marketed dose of dexamphetamine which was 5 mg. He put the two together in that particular ratio of 1:6.5 and that's the one that was then marketed, and probably made a fortune for them.

Healy: There's nothing like personal experience in all this, but just on that point, there is an issue here where the Food and Drug Administration (FDA)[98] and the Committee on Safety of Medicines (CSM)[99] begin to come into the picture. Under current arrangements the FDA will only license drug combinations in exceptional circumstances,[100] so that's relevant to why perhaps we don't have these things anymore. One of the things the FDA came in with in 1962 was the fact that these drugs were available on prescription only. There's no natural reason why these drugs have to be prescription only and if you ask me, clearly side-effects are one issue why people won't actually comply with treatment, but another issue has to be the quality of the relationship with the prescriber. This is where the issues of enthusiasm and things like that begin to come in as well.

Professor Joanna Weinberg:[101] As you can hear I am from the US and I am also not a psychiatrist, or a psychologist. But my question has to do with the issue of the elderly which was raised before and this is a somewhat different respect. In the US at least and I am not sure about the UK, but I think it is also true, we have the situation of many, many older people in care, in nursing homes, completely drugged or sedated to a point where they are easy to deal with etc. In a way this is a situation very similar that you were all describing, of the pre-psychotropic drug era.

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[97] Steinberg H. (1990) Epilogue: rodent behaviour tests and antidepressant activity. In Leonard B, Spencer P. (eds) *Antidepressants: 30 years on*. London: CNS Publishers, 508-516.

[98] The Food and Drug Administration (FDA) of the USA (founded in 1938) is the premier drug regulatory organization in the world, inspecting and licensing the manufacture of foods, cosmetics, pesticides as well as human and veterinary medicines.

[99] The Committee on Safety of Medicines (CSM) was created by the Medicines Act 1968 with similar functions to the preceding Committee on Safety of Drugs, which operated from January 1964 to September 1971, when the new Committee started. Along with the Committee on Veterinary Products, it advises the Licensing Authority. See note 88 above.

[100] For example the fenfluramine–phentermine combination was allowed until recently. Graham D J, Green L. (1997) Further cases of valvular heart disease associated with fenfluramine-phentermine [Letter]. *New England Journal of Medicine* **337**: 635.

[101] Professor Joanna Weinberg is Associate Adjunct Professor at UC San Francisco, California, in the Department of Social and Behavioural Sciences and the Institute for Health and Ageing.

My question is why is it that we are so slow, in both countries, in developing ways, to care for the elderly; those with Alzheimer's or with other forms of dementia, or with depression or other psychological disorders that make them anxious? But these drugs just haven't been used very much for the elderly, or tested very much in older people. Can anyone say anything about that or add anything to that point?

Healy: I can quickly comment. This comes back to the regulatory requirements which are simply that a drug has to be shown to work. They don't have to be shown to work in the elderly, or in children. The industry naturally enough will go for the simplest and easiest group of people in which to show how the pill works, and the elderly aren't the simplest, easiest group of people.

Dr Derek Bangham:[102] I am not a psychiatrist or an analyst, but I have been concerned with drug controls for a long time. Since 1964 there has been the Committee on the Safety of Drugs and then the Committee on Safety of Medicines to look after you and do something to filter these drugs.[103] Before that there was little official assessment of toxicity made apart from biological substances covered by the Therapeutic Substances Act. I would be very interested to know what sort of tests the pharmaceutical industry undertook between the stage when they identified something as having an effect in a tissue bath, and giving it to man. Could industry tell us something about the early toxicity tests please?

Sandler: When iproniazid was synthesized in the laboratory in 1952, it was into man and being used for treatment within six weeks.[104]

Broadhurst: With imipramine we carried out LD_{50} tests in mice and in one other species, which I think was dog, at that time. Behavioural tests, of course, were not available because they hadn't really been discovered, as far as I know. But so far as other pharmacological testing, a fairly large range of pharmacological tests, the sort of things we might be doing today and then after that human pharmacology on volunteers. It wasn't bad really, by today's standards, I would say.

Bangham: Was it really that simple?

[102] Dr Derek Bangham (b. 1924) was Head of the Division of Biological Standards at the NIMR from 1961 to 1972. He was later Head of the Hormones Division of the National Institute for Biological Standards and Control (NIBSC), from 1972 to 1987.
[103] See notes 88 and 99 above.
[104] op. cit. notes 27, 29–30, 34 above.

Broadhurst: It was, yes. It depended where you were, I think.

Dr Ian Tait:[105] When I was first in practice, in the early 1960s, I remember we had a popular treatment for mild or moderate emotional disorders which was known as 'the green medicine'. This was a mixture of hyoscine and phenobarbitone in peppermint water. Long after the early antidepressants became available the green medicine was often used as a first treatment. It very often worked. The pressure to prescribe antidepressants really came from the hospital. Patients referred to psychiatric departments would nearly always return with new drugs to take — often a newer antidepressant that we hadn't previously used. Doctors went along with this but patients were not always happy. I certainly remember patients coming back and asking if they could go back on the old green medicine again, known and trusted and without significant side-effects. I don't think that we were ever quite sure about the place of powerful psychiatric drugs. I became, of course, convinced that there were times when they were essential. I remember an obsessional master carpenter who became profoundly depressed. He responded very well to treatment with a tricyclic antidepressant, but decided to stop taking the drug when he felt better. I was called to see him as an emergency a short time later. He was crouched on the floor in a corner of a living room apparently incapable of movement or speech. His condition responded dramatically when his treatment was resumed. That kind of experience made me totally convinced that there were absolute indications for the use of antidepressant drugs, but I don't think we have ever solved the question of how extensive that use should be.

Dr James Le Fanu:[106] I am in general practice. I too have a second-hand William Sargant story from Henry Rollin. He describes the registrar attending the viva in the Diploma of Psychological Medicine, and Sargant says to him, 'You have a rather unusual situation here, you have a patient with schizophrenia, he's had two leukotomies and he's still not quite well, what would you do now?' and the candidate replies, 'Give him another one', and Sargant says, 'Well done, that's the right answer'.

I wanted to raise another question, and it arises in part from what has just been said. Of course, we have this extraordinary experience of patients who respond with extreme sensitivity to medication. Not only that, I certainly find my psychotic patients have quite profound insight about how it keeps them normal, despite this anti-drug sentiment that's much been expressed. But my question is

[105] Dr Ian Tait (b. 1926) was in general practice in Aldeburgh, Sussex, from 1959 to 1990 and was active in the development of vocational training for general practice. See Reynolds L A, Tansey E M. (eds) (1998) *Research in General Practice*, this volume.

[106] Dr James Le Fanu (b. 1950) is in general practice in London. He writes a weekly medical column for the *Sunday Telegraph* and *Daily Telegraph*.

really a philosophical one, and I would be interested to know what your views are on it. One can see that throughout the 1950s, 1960s and 1970s, the way in which these drugs worked obviously had a profound effect of how one conceived of mental illness, that it must in some sense be some sort of biochemical abnormality. One has all these various hypotheses being put forward, such as the amine hypothesis, and the dopamine hypothesis,[107] and yet we are now in this extraordinary situation in the mid-1990s where we don't really understand what the biochemical basis of mental illness is. It has proved to be an extraordinarily elusive thing, that you have these drugs that work, but that one doesn't really understand how it is that they work. And I would be interested, as a sort of philosophical concept, how would the speakers on the platform today conceive of mental illness, what is it?

Jenner: I think that 'mental illness' are the words we use for people who have undesirable behaviour or experiences for which we don't consider they are to blame, and then we try to explain that sociologically, psychologically, and perhaps neurophysiologically, and then we have to see how far we have got in doing so. But I think I can't help it if you want to be philosophical, using Wittgenstein's view, don't tell me what the word means, tell me how people use it, it might help a little bit.

Le Fanu: The point is that one did have quite a good concept, throughout the 1960s and 1970s, when everybody was coming up with all these hypotheses that there was an underlying chemical abnormality, which was somehow or other being fixed by these drugs.

Curzon: I wouldn't really say things have changed very much. I don't think the biochemical concepts are 100 per cent defined, and they are not tremendously different to the ideas of the 1950s and 1960s, that there was too much of this, or too little of that. I think what's happened since that time has been that we have realized how many different kinds of receptor each kind of psychotropic drug can act on, all the different serotonin receptors, all the different dopamine receptors, and that nearly all the drugs used in psychiatric treatment either increase the release of a transmitter, or decrease its release, which alters its availability to a whole host of different sites with different consequences. I guess that the next generation of drugs used in psychiatry are not going to be things like the SSRIs or

[107] Carlsson A, Lindquist M. (1963) Effect of chlorpromazine or haloperidol on the formation of 3-methoxytyramine and normetanephrine in mouse brain. *Acta Pharmacologica Toxicologica* **20**: 140–144, a proposal that blockade of dopamine receptors was responsible for the clinical effects of antipsychotic drugs.

amphetamines, but will act on selective transmitter receptor types, rather than release the transmitter to any receptor that's around. Would you say so, Merton?

Sandler: I disagree. I'd say that the things you are talking about could easily be epiphenomena, you know sort of peripheral things, that accompany the main thing which we hadn't put a finger on. But it's not a question that we are ready to answer at all. I think our approach should be functional. I think we should ask the sort of questions,'Why did the three major breakthroughs in drug treatment all occur in the 1950s?', and then nothing since then? No one has asked this yet. A few slight things like obsessive compulsive disorder (OCD)[108] treatment, OK that's very good, but the main things occurred in the 1950s and then nothing. Was it the fact that we were beasts, and we imposed on our patients any old rubbish that came along from the laboratory bench or what? Why did that happen? It was a strange thing.[109]

Jenner: Was lithium used in the 1950s?

Healy: Lithium was introduced in the late 1940s, early 1950s.[110]

Harrison-Read: I would suggest that one of the factors which helped the early pioneers in psychopharmacology to better understand drug actions, was their willingness to take the new psychotropics themselves. Although of course this might not give any direct information about the experience of mental illness, I think it was important in throwing light on how the drugs might exert a therapeutic effect. I believe there were some quite important insights obtained in this way. I remember hearing Mogens Schou talking about the subjective effects of taking lithium, and I believe he published some of this work.[111] I think this is an interesting approach in connection with recognizing certain side-effects of drugs, for example, the sexual dysfunction with clomipramine that and other SSRI antidepressants that was referred to by Professor Marks. If the investigators using

[108] Obsessive compulsive disorder (OCD) is a neurosis characterized by obsessions (recurrent thoughts) and compulsive rituals (e.g. repeated handwashing).

[109] Professor Curzon wrote: 'Epiphenomena? The neuroendocrine evidence of a 5-HT defect in depression and the evidence that SSRIs act by increasing 5-HT indicate a higher status than that. Of course, there are probably other important things going on of which we are unaware.' Letter to Dr Daphne Christie, 31 March 1998.

[110] A brief account of the early use of lithium is given in Kline N S. (1968) Lithium comes into its own. *American Journal of Psychiatry* **125**: 150–152. See also notes 71–72, 75–76 above.

[111] For reviews, see Schou M. (1968) Lithium in psychiatry – a review. In Efron D H, Cole J O, Levine J, Wittenborn J R. (eds) *Psychopharmacology: A review of progress, 1957–1967*, Public Health Service Publication 1836. Washington: Government Printing Office, 701–718. Schou M. (1997) Forty years of lithium treatment. *Archives of General Psychiatry* **54**: 9–23.

clomipramine had themselves sampled the drug, I think that they would have soon become very aware of this side-effect which occurs with a high incidence and yet is not usually mentioned by patients, presumably out of embarrassment. When I have suggested to colleagues the possibility of themselves taking the drugs they prescribe in order to better understand the adverse effects on patients, I have encountered great reluctance to say the least. There seems to be a profound reluctance on the part of doctors in general 'to have a taste of their own medicine', which strikes me as being unreasonable if we are trying to convince our patients that they are on the whole a good thing. Personally, I have sampled many of the substances I prescribe to psychiatric patients. I was brought up in Professor Steinberg's laboratory where there was a tradition of psychopharmacological research in human volunteers. I still think that it is useful for psychopharmacologists to have had personal experience of at least some of the drugs that they are prescribing to patients, partly to get a better understanding of the mental illnesses that they are treating, but even more importantly, to better understand what patients have to put up with in taking these drugs. I wonder if the panel have any views on this?

Healy: It raises an issue which we hope to pick up after the tea break perhaps. There are whole areas of research that haven't happened and one of the areas is to do with the use of some of these drugs for the treatment of sexual indications. Part of the reason there that these things haven't happened is because the socio-cultural milieu hasn't been interested to have them happen, or else the industry hasn't been able to push the indication. But there's a point there, which is that the drugs which were produced during the 1950s, the ones that you have heard referred to, weren't all the ones that were produced. A whole range of other compounds were also produced and are sitting there on shelves, just as the ones that we have heard about during the 1950s were there on shelves to begin with, and there's a hunch from an awful lot of people in the field that an awful lot of other things are there which could be done. But until the industry gets the feel that there's a market large enough to bear development, these things don't happen. Alan would you like to come in on that?

Broadhurst: That's the truth and vast numbers of these things are just sitting around. Take the case of imipramine – there were 42 derivatives of iminodibenzyl and we were actually not looking for an antidepressant. I mean, just think of that. We were looking for an antihistamine that had thermolytic and other properties. All those things are abandoned, all the others. They are still there. Nobody has looked at them from an antidepressant point of view. There is a vast range of things that still could be done, but, as you say, it's economics.

Another kind of example is sodium valproate, a drug which was first produced in 1962. The psychotropic effects of it were clear from 1974, they had actually been reported.[112] It's only now this year, and in the last two or three years that we have had the large-scale clinical trials to show that it might have a useful psychotropic effect in stabilizing mood disorders.[113] But the reasons those trials are actually now happening is because the industry only found a way to make a patent on a particular form of it a few years ago. So it was there on the shelves for 20 or 30 years and nothing happened.

Beaumont:. First of all the comment about us not taking the stuff ourselves. That's not exactly true, because I have to tell you, and I am going to say something about this later on, that the whole of the clinical pharmacology for the submission on clomipramine was me and a couple of colleagues down the corridor from where I worked. All the pharmacokinetics in the submission was done on me, so we did actually take these drugs ourselves. It's not quite true that we didn't take them.

What I wanted to say in relation to an earlier comment was that I think it is very significant that the major advances, which at the moment we are talking about, were all made before the advent of the conventional clinical trial and one now has to ask oneself whether the conventional clinical trial has been to our advantage or to our disadvantage. Thinking about what James Le Fanu said, two requisites of a good clinical trial, are first, syndromal definition and sensitive means of measuring change, and what seems to have happened as a result of that is that we have had to invent classificatory systems to fit something for which we want to give the drug, and we have to invent rating scales to measure what we think are the symptoms of the illness. By now we have forgotten about all the original complaints, and the illnesses now fit the definitions which our committees have devised and our rating scales measure only the symptoms we choose to measure.

Pines: I want to take off the shelf a powerful drug that hasn't yet been mentioned, which is the doctor, because throughout the 1950s, with the rise of psychopharmacology, we also had the rise of Michael Balint's work with GPs.[114] The drug is the doctor, and we have had all the investigations of the placebo effect which I think are of increasing interest nowadays with psychoimmuno-neurology and the ideas of how the human relationship or the social environment have

[112] Lambert P A, Carraz G, Borselli S. (1975) Dipropylacetamide in the treatment of manic depressive illness. *Encephale* **1**: 25–31.

[113] Post R M, Ketter T A, Denicoff K, Pazzaglia P J, Leverich G S, Marangell L B, Callahan A M, George M S, Frye M A. (1996) The place of anticonvulsant therapy in bipolar illness. *Psychopharmacology* **128**: 115–129.

[114] Dr Michael Balint (1896–1990) was a psychoanalyst, whose work includes Balint M. (1957) *The Doctor, his Patient and the Illness* (2nd edn 1964). London: Pitman Medical. See Reynolds L A, Tansey E M. (eds) (1998) *Research in General Practice*, this volume.

profound effects upon the function of the central nervous system (CNS) or of the whole person. I was thinking of the green medicine which you [Tait] spoke about, which patients preferred, because it is the doctor who gives the medicine, it's him, they take him, his influence, his charisma, his relationship in. My father was a single-handed GP in the East End. All he used to dole out were bottles of medicine and bottles of fascinating looking tablets of all different colours. When I was a medical student I asked him what they were and he said, well they were all aspirins of different colours. Take one green, one blue, one yellow and with his forceful personality it was very effective. So you shouldn't forget the doctor in all this.

Healy: Unfortunately we were going to have four initial speakers for this next part of the meeting as well, but Gordon Claridge[115] couldn't come. We only heard this about three or four hours ago, so I thought I would quickly say a few words just to introduce an issue that he was actually going to talk about, which has been picked up earlier. It is the various different agents we've had, drugs like LSD, have been or ought to have been, wonderful tools to probe the workings of the mind, to find out how cognitive functions are put together. They haven't been. The pharmaceutical industry recently has helped create a whole new branch of science, pharmaco-epidemiology. Now this is a useful branch of science to have. It's a particularly useful branch of science for the industry to have. There's nothing wrong with the industry supporting this area of science, and all of us who actually are prescribers of medicines here. Our views are shaped by the fact that we prescribe and earn our living from prescribing. So there are interests that are at stake. One of the interests, arguably, that hasn't been well catered for, is this whole area of the use of the drugs to probe the workings of the mind, and this is an issue that Gordon Claridge was going to pick up on. The industry haven't supported this. They do one-phase trials to look at what the impact is on the heart, or the respiratory system. They could easily at the same time have a look at what the impact on cognitive function is – they don't. It's an area of research that is played down. So what we have had are fields opening up, but equally there are holes in the field, there are holes in the knowledge that we have and you have to ask why there are these holes. This theme is going to be picked up by George Beaumont, who is going to look at a whole new area that is beginning to open up. Recently it is quite clear that the SSRIs have useful effects on sexual functioning. One of the drug companies has gone out and done some research and has found that one-third of men have premature ejaculation problems. This is a company who have not been known for their unwillingness to sell their drugs for a wide range of indications,

[115] Gordon Claridge began his research career with Hans Eysenck, renowned for his theories of personality and predictions as to the likely effects of psychotropic drugs on personality. Claridge subsequently proposed a theory of schizophrenia as a nervous type – a forerunner of the modern schizotypy concept. See Claridge G. (1972) The schizophrenias as nervous types. *British Journal of Psychiatry* **121**: 1–17.

but this is an indication that they haven't sold their drug for. The whole area, until quite recently, has been taboo. There's the shock of the new here as well, which perhaps echoes the shock of the old which I mentioned earlier. There are a whole load of people who will say we shouldn't be doing this kind of thing. This raises the point that things can only happen when the cultural milieu in which they could happen is ready for them and George Beaumont is going to pick up on just this issue.

Beaumont: Thank you very much, David. Not at the beginning am I going to pick it up, because I just want to say a few general words about how I became involved in this area, because in a sense there is a certain amount of continuity between what Alan Broadhurst has told you and what I am going to tell you. We both worked for the same company. There was a gap between us of about six years, and I would just like to mention that that gap was filled, by somebody who unfortunately is not here, Cyril Maxwell and who subsequently stayed with the company for quite some time. I would like to mention Cyril because he was the sort of link between Alan Broadhurst and myself, and had he been alive, I am sure he would have been able to make a major contribution to this kind of discussion. Now you heard from Alan that there were something like 42 analogues of imipramine which were synthesized by the Geigy pharmaceutical company in about 1958. I joined the company in 1966 and at the time we already had marketed two antidepressants, we had imipramine (*Tofranil*) and we had desipramine (*Pertofran*). One of the analogues which had been developed in the 1958 series, was clomipramine, and I was given the task of evaluating this compound.

Now why did we have clomipramine? Well, I suppose the theory was, just how much validity can be attached to it I don't know, that chlorpromazine was much more potent than promazine. Halogenation of the side chain had something to do with potency and therefore if you chlorinated imipramine, for want of a better description, then you might produce a far more potent antidepressant. That was part of the thinking that lay behind the development of what is now called clomipramine, but in my day was called chlorimipramine. As I have said we already had two antidepressants. We had imipramine well established in the market. The company had also introduced desipramine with the idea really that here was a compound which had a somewhat different profile than the original imipramine, that it might be non-sedating, and might be drive-stimulating, and incidentally, we haven't talked at all in this discussion about the early ideas of the differentiation between stimulating drive and elevating mood and that's a whole subject in itself. And, of course, there was the hope with desipramine originally that it might be faster in its onset of action. This is a familiar story that has been reproduced

continually right until the present time with the newest antidepressants, about the speed of onset of action problem.

So here we were sitting with two antidepressants, imipramine and desipramine, and I was given the job of trying to see what we could do with chlorimipramine, the third antidepressant in the Geigy series. I had to really look around to see what I could find that might possibly differentiate chlorimipramine from the other antidepressants, and in doing that I had a pretty careful look at the existing literature. As we have already heard in discussion today, in those days, not so much now because you wouldn't be able to do it for regulatory reasons, whenever a new compound was introduced there was always a group of people who would take the attitude, 'let's try it on everything'. So whenever you got a new compound, it was tried on every condition which psychiatrists were treating, and for that matter, I suppose, in other branches of medicine. So what I found when I looked in the literature was that there were four papers written in 1967 and 1968, which referred to the use of chlorimipramine in a few patients who had an obsessive compulsive disorder (OCD).[116] This attracted my attention. Here were reports that this condition might be treatable, although in those days it was regarded very much as a bizarre rarity. But nevertheless it just seemed to me that perhaps here was something, here was a hook perhaps on which one could hang one's hat as it were, with regard to identifying something slightly different in the profile of this antidepressant which was third in line in the company's list. One of the papers I picked up particularly, was Lopez-Ibor's work.[117] So I took a group of psychiatrists out to Madrid and we met Lopez-Ibor and asked to see the patients being treated and shown around his clinic. To cut a long story short, this excited their interest and so we were able to launch a programme of clinical trials in obsessive compulsive disorder. Well, I think we all know the outcome of that, that as a result of that programme, chlorimipramine did become established eventually as the gold-standard, if you like, for the drug treatment of obsessive compulsive disorder. It's interesting that one of the contributory factors to getting chlorimipramine acknowledged as a treatment for OCD, which is another thing which we haven't talked about today, and that is the influence of the licensing situation with regard to the registration of new drugs.

When we started with chlorimipramine, in fact, there was virtually no regulatory machinery in this country. And then as our evaluation of the compound proceeded, we had a voluntary system, The Dunlop Committee.[118] It was not until

[116] In 1967, Jean Guyotat claimed that clomipramine might be of some use in obsessive compulsive disorder. Guyotat J, Favre-Tissot M, Marie-Gardine M. (1968) A clinical trial with a new antidepressant G34586. *Congress du Psychiatrie du Neurologie, Dijon 1967*. Paris: Masson.

[117] Cordoba E F, Lopez-Ibor J J. (1967) Monochlorimipramine in psychiatric patients resistant to other forms of treatment. *Actas Luso-Españolas de Neurologia y Psiquiatria* **26**: 119–147 [in Spanish].

[118] op. cit. note 88 and 99 above. The Dunlop Committee issued a report on psychotropic drugs in 1967, see Committee on Safety of Drugs. (1967) Psychotropic Drugs. *Adverse Reaction Series* no. 6. London: HMSO.

1971 that we got a formal system with the Medicines Act, and of course that took a couple of years before it was fully enacted. So you have to look back at some of these early days of the compounds that you have been talking about and which we have singled out as the major advances in psychiatry. All of these came about in the previous climate as far as registration was concerned.

What happened with chlorimipramine was simply this. As far as registering the drug was concerned, having been the physician in charge of the clinical evaluation programme, I was told to write a submission, I wrote every word of it. I think it was about 2000 pages long, right through from the basic chemistry to the side-effect evaluation. I wrote every word myself, locked myself in an office in Geigy Pharmaceuticals for three months and sent it to the Dunlop Committee. I thought I might as well throw in the reports about OCD while I'm at it, so I did and lo-and-behold, and somewhat to our surprise, we got that indication licensed. I don't think we would have got it licensed in the present climate, but certainly we did then. What was interesting was that we had probably got about just as good evidence with phobic states as we had with OCD, but for some reason, I don't know why, we didn't pursue the phobia indication. It is very interesting now to have a sort of *déja vu* feeling about what's going on out there now with some of the new compounds which are now being licensed, for example, for the treatment of social phobia. We had a lot of experience, nearly 30 years ago, of the efficacy of the compound in phobic disorders.

It is also very interesting to note that because we had so little knowledge of the epidemiology of conditions like social phobia, I think it was Marks's and Gelder's work in 1966 which coined the term.[119] We had to invent concepts like diffuse phobic anxiety disorder to find subjects we could recruit for clinical trials.

It is interesting now to read what is going on in the social phobia area. What we called diffuse phobic anxiety 30 years ago was really the generalized form of social phobia. So it's interesting that we were in that area, but we didn't capitalize on it. But I do want to stress the importance of the regulatory process in this historic development of drugs, because I think it is something that we shall have to consider very much. I looked back on the train coming down this morning to some of Archie Todrick's work and I was very interested to see that way back in the 1950s and 1960s, Archie Todrick described chlorimipramine as a selective potentiator of 5-HT.[120] I just wondered why in the 1970s, when we got our

[119] Marks I M, Gelder M G. (1966) Different ages of onset in varieties of phobia. *American Journal of Psychiatry* **123**: 218–221.

[120] Archie Todrick and colleagues working at the Crichton Royal Hospital in Dumfries, Scotland, looked at levels of blood 5-HT in individuals taking antidepressants. See Yates C M, Todrick A, Tait A C. (1964) Effect of imipramine and some analogues on the uptake of 5-hydroxytryptamine by human blood platelets *in vitro*. *Journal of Pharmacy and Pharmacology* **16**: 460–463. Todrick A, Tait A C. (1969) The inhibition of human platelet 5-hydroxytryptamine uptake by tricyclic anti-depressive drugs. The relation between structure and potency. ibid. **21**: 751–762. Todrick A. (1991) Imipramine and 5-HT reuptake inhibition. *Journal of Psychopharmacology* **5**: 262–267.

license, we didn't call it an SPHT (selective potentiator of 5-HT), because you know with all this current vogue for initials, we had a drug that could have had an initial too. I think really what I am saying is that chlorimipramine was in a sense, if you believe what Archie Todrick said, really the first SSRI. So that's the story of chlorimipramine, but what is interesting about the development of chlorimipramine is that it took us, as it were tangentially, into a lot of other areas, and it's interesting what happened in those.

There were, particularly, four main areas that in a sense were to do largely with side-effects. These four areas were sleep, the control of pain, eating disorders and sexual dysfunction. Perhaps the area of sleep is the one which in relation to psychotropic drugs, apart from hypnotics, has been to some extent largely ignored, although there is a certain amount of interest for example in the relationship between rapid eye movement (REM)[121] sleep and depression, and use of markers, for example in the EEG, in this respect. I have got a tremendous feeling of *déjà vu* about eating disorders, because in those days we were very much aware of the effect that drugs like chlorimipramine had on weight, although working with Arthur Crisp and others, we never actually suggested that it was a treatment for anorexia nervosa. It was interesting that we could observe effects on weight, and again I have a feeling of *déjà vu* about the SSRIs now that I see them being licensed for bulimia, or even being licensed as drugs which will decrease people's weight. So here was another area, eating disorders, which was a kind of spin-off.

But the area I really wanted to talk about was the sexual side-effects, and the message in a way here, in relation to the things that I have been saying, is that it's very interesting that today's side-effects are often tomorrow's indications. This has certainly been the situation I think with the sexual disorders, because it all started when we were looking at the intravenous use of chlorimipramine and this is another field we have passed by – why don't we give these drugs intravenously and what about all the evidence that accrued from continental sources about the different effects of these when administered intravenously rather than orally – we haven't touched on that one either, that's another interesting subject. What happened was that I had a clinical trial running at Winwick Hospital in Warrington and I used to go there regularly to see how it was progressing. There was a patient there who was a research chemist for ICI, and as I went round the trial subjects and asked how are you doing he said, 'I've got something interesting to tell you about chlorimipramine'. I said, 'What's that?' he said, 'Do you know what it does to your sex life?' to which I replied I had no idea, so he said, 'Well I'll tell you'. 'If you continue at the full dose, as I do, it completely stops you ejaculating, but I found out that since I am on a five-day treatment course, and I am allowed to go home at the weekends, and although my five-day course is intravenous, my weekend is on capsules, I can titrate the dose of the capsules against the speed of

[121] Rapid eye movement (REM) is a stage of sleep during which dreaming occurs.

my ejaculations, and so I can control them by the dose.' I thought this was a very interesting observation and so we then started to look in our clinical trial programme to see whether other people had made this observation. In fact it had been made in quite a number of trials and, as Isaac Marks said, when we started to look for sexual side-effects in patients who were receiving chlorimipramine, they were common.

Then I had another report which was very interesting from a GP in Peterborough, who wrote to me, well he wrote to the company – it was my job to answer the inquiries when they came in – he said, 'Do you know that women who take *Anafranil* don't have orgasms?' I said, 'No I don't' and so again I went and talked to him about it. So we started to look in our clinical trial reports and also found was that anorgasmia was very common amongst women patients who were taking chlorimipramine. All very *déjà vu* this, isn't it, in the light of what we now know about SSRIs? But I thought well maybe here's an area of opportunity.

I knew a physician in Manchester who's a specialist in sexual medicine and I said look this compound does something to ejaculation, and I know that premature ejaculation is one of the commonest problems that you see, why don't we turn this to our advantage. So we did a clinical trial in premature ejaculators, using chlorimipramine, and what we indeed found was that you could control ejaculation and that moreover you didn't have to take it all the time. A very tiny dose, about 5 mg, was sufficient to have the effect, and you could take it about four hours before intercourse. It did introduce a certain amount of premeditation about when you were going to have relationships, but nevertheless it could be taken four hours before, so that when it reached peak plasma level then it would relieve premature ejaculation. We thought this was a wonderful discovery and I organized a Symposium in Jersey, where the results of this study were reported.[122] I didn't think the press were present, in fact I am sure the press weren't present, but somebody must have leaked the story to them, because when I got back to the office on Monday morning, the managing director of Geigy pharmaceuticals stormed into my office and slapped down a copy of one of the tabloids on my desk and said, 'George, what the hell is all this about?' and I said, 'What's all what about?' and he said, 'Splashed all over the front of the newspaper is this story about a wonder drug for your sex-life'. Geigy being a very Calvinistic company he said, 'We're not having anything to do with this, stop it'. So there and then the whole clinical trial programme on sexual disorders ground to a halt. Now it's interesting

[122] The Symposium on *Anafranil* was held in Jersey from 4 to 7 April 1973, under the chairmanship of Professor W Linford Rees, and the formal papers of the meeting were later published in a special edition of the *Journal of International Medical Research*. See for example Todrick A. (1973) The laboratory assessment of the anti-depressive action of clomipramine (*Anafranil*). *Journal of International Medical Research* 1: 292–295. Beaumont also presented his findings and in the course of noting that the side-effects might have a therapeutic role, he detailed an adverse events report from a primary care physician noting delayed ejaculation. A story about drugs to enhance sexual functioning appeared in the *Sunday Mirror* several days later.

really that that was happening in 1970, because now we are in a situation where I go to the BAP (British Association for Psychopharmacology) meeting in Cambridge and I hear people say sexual disorders are the greatest area of opportunity for the pharmaceutical industry. I see that Pharmacia Upjohn are making millions out of Caverject injections. We see Trazodone being used, we've got Yohimbine and when I looked in *Scrip* I found that there are now several new compounds being energetically developed by major pharmaceutical companies which will be licensed in the next few years for the treatment of sexual disorders.[123] So it's interesting how the pendulum has swung in this direction and the message really is that one historical perspective is that today's side-effects may well be tomorrow's indications.

Healy: Does anyone wish to come in quickly on this one now before we proceed to the next presentation?

Steinberg: I could come in just by saying that we had a drug in the late 1960s, a benzodioxane derivative, which increased mounting in male rats, and it only did this if they had a low mounting rate normally, so that it was selective to that extent.[124] But the company that made it was taken over by a very traditional German company, who decided that it was improper to continue with that sort of drug because all the Fräuleins would be endangered, and so a very promising piece of research stopped. I have recently been talking to one of the members of that company, and he said, 'We'll try and reawaken it', and so maybe something will come of it.

Healy: This is an issue that recurs quite often. There was the Roussel compound RU 486, which they did actually proceed with in the end, but they thought long and hard about it and felt that at one point that they wouldn't actually proceed with it, because not only would there be areas of the world that wouldn't be willing to have it, but that all of their other compounds would be hit in those areas of the world also, so these are tricky calculations at times.

Pines: I was talking just a day or two ago with a colleague who works at Maudsley in the sexual dysfunction clinic, and she was saying that this tremendous rise in the popular awareness of potency problems and clinics and the advertisements that you can now get a quick and easy cure treatment for impotence. She found it very

[123] The two new main compounds are alprostadil (prostaglandin E_1; *Prostin VR*: Pharmacia & Upjohn); and sildenafil (*Viagra*: Pfizer).

[124] Dorr M, Steinberg H, Shapero M. (1975) Stimulation of sexual behaviour in rats by a benzodioxane derivative. *Experientia* **31**: 91–93.

alarming, she called it the detachable penis, all the problem is in the penis and it's not in the relationship, it's not in the whole marital situation, it's not in the changing roles of males and females, and the anxieties and problems that this is creating for people and how so many people want to have that and they don't want to look inside at themselves at all in terms of their own happiness, their own capacity for fully functioning as persons. But I am not at all against the use of drugs in these situations, but it is the same thing again, how to keep it among the holistic viewpoint.

Beaumont: I agree with that to a large extent, although one ought to remember, for example, if you are looking at the new drugs that are being developed for erectile impotence, that a substantial number of patients who suffer from these disorders have diabetes or hypertension, so there is an enormous number of people who, ignoring this sort of holistic situation we are talking about, are simply disadvantaged by the fact that they have illnesses which cause impotence.

Curzon: How much is sexual dysfunction produced by unhappiness, and how much is unhappiness produced by sexual dysfunction? Another question I wanted to ask you when you said only a very low dose of clomipramine affected premature ejaculation beneficially. What happens with the doses that are used in the treatment of depression.

Beaumont: In clinical doses, they get delayed or absent ejaculation.

Harrison-Read: To those people here who don't prescribe drugs, it's worth mentioning that of course you don't have to wait for the companies to license drugs for a particular indication before you can use them. As a prescriber, you can still prescribe drugs for these purposes, you just take more responsibility for any adverse effects. A good example is the use of SSRIs for premature ejaculation. Another example would be the use of antidepressants, SSRIs in particular, for irritable bowel syndrome and hopefully one day that will be a licensed indication.

Marks: With medicine becoming so much more defensive, and litigation becoming such a major issue, many people now would be afraid of using a compound in an unlicensed indication. Just on the point about unrecognized possibilities for the indications for drugs, the tricyclics have traditionally been thought of as antidepressants, but in fact some of them have uses as analgesics and a good use for migraine, for example, and these differential indications tend to get missed by a classification of their use.

Beaumont: Yes, we did do a lot of work on pain, I am not sure that we paid very much attention to migraine. Certainly there is a fairly extensive literature using them as adjunctive therapy in neurological disorders and in arthritis.

Healy: What I propose to do now is to move onto another area and ask Hannah to have a word. Hannah Steinberg is probably the first psychopharmacologist formally designated as such.

Steinberg: Thank you. Sitting here listening was most instructive, and I also have this *déjà vu* experience, simply because I have been at it probably longer than most people here, and so almost anything that was mentioned, we'd done some work on with various people like Philip Harrison-Read and Elizabeth Sykes and quite a few others who are not here. I don't know what one does about this, because clearly there are lots of drugs which are in the literature, which have not been followed up. I wondered if one could ask the Wellcome Trust to do something about it, because these drugs could save a lot of money and increase human happiness. By resurrecting some of these substances and bringing them to the attention of industry, who probably don't even know about them, one could do something very useful. The companies could go back to the earlier drugs and discern what they have to offer to us now with our much better knowledge and techniques, rather than do more and more experiments with new substances, which we cannot interpret.

My second recommendation is in connection with the sex drug: that is to use drugs as tools for discovering how the brain and the mind works, which is coming very much to the fore. Again, there is a lot of literature. I did my PhD with nitrous oxide, laughing gas, in different concentrations, where you can get people coming in out of consciousness, which is very relevant nowadays to the discussion of consciousness as a phenomenon; we should not be hijacked by the computer people.[125] A point was also made that there was little behavioural work at one time and that is now very different. It's really rather strange how, as has been said, in some ways we have advanced enormously, and done lots of biochemistry and so on. In other senses, we haven't advanced very much and we still don't know what mental illness is actually about and how to define it.

I am glad that J H Gaddum was mentioned,[126] because I was a fan of his and he was one of the big brains in pharmacology and also very wise and a sort of guru. I complained to him early on that I was feeling quite lonely because nobody else

[125] Steinberg H. (1954) Selective effects of an anaesthetic drug on cognitive behaviour. *Quarterly Journal of Experimental Psychology* **6**: 170–180. See also Steinberg H. (1956) 'Abnormal behaviour' induced by nitrous oxide. *British Journal of Psychology* **47**: 183–194.

[126] op. cit. notes 38 and 45 above.

was doing the kind of work that I was, and I'd like to do something else and give this up. And he said, 'No, no you mustn't give it up, you are doing the most important thing in biology, which is studying how the brain and the mind work and so you must persist' and, of course, he turned out to be right because now it's a big subject and we are all waiting for more.

Finally, I should like to say that drug combinations, though they may have problems with the Americans, do already exist. There is a combination called '*Limbitrol*' (Roche), which is a mixture of amitriptyline and chlordiazepoxide and that, I think, is licensed in the USA; therefore it is not completely hopeless. One should explore what can be done by combining drugs rather than always looking for new ones. The overall point to make is that the idea that drugs must be wonderfully specific and only go for one little thing, like one little receptor for a particular mental illness, is perhaps not realistic. While attempting to discern a relationship between receptors and the backward walking effects we were getting,[127] two of us, Elizabeth Sykes and I, consulted several experts, including Professor Sakmann of Heidelberg,[128] but had to conclude that there was no easy answer.

Healy: There's a few things that Hannah has alluded to there. The receptor really is the key image of the era. It's the thing the magic bullet will hit and it's where the lesions are, you know, the 5-HT receptor isn't working, the dopamine receptor isn't working, and we are going to fix this with our pill. What George [Beaumont] mentioned in a sense blew that out of the water, because if 10 mg of clomipramine four hours before intercourse will change behaviour as hugely as this, it should have taken care of the amine theory completely, because of course it acts on brain receptors to produce the change. So the idea that we have got to wait for two or three weeks for the antidepressants to work by chiselling slowly at brain receptors that aren't working right, has to have been all wrong. Does anyone wish to pick up on this receptor idea?

Crisp: It's not quite the receptor idea, although it relates to it. It was George's [Beaumont] point really. He made it in passing, i.e. the need to distinguish between the effect of these drugs on drive and on mood and also their involvement in the sleep process. If I could digress for a moment, I used to teach medical students in the one hour available for this subject in their six-year course, that sleep is the optimal condition in life and that wakefulness is the interlude! The

[127] Davies C, Stanford C, Steinberg H, Sykes E A. (1986) Unusual behavioural and binding effects after co-administration of clenbuterol and chlordiazepoxide in mice. *British Journal of Pharmacology* **89**: 531P.

[128] Professor Bert Sakmann has been Director of the Department of Physiology at the Max-Planck-Institut für Medizinische Forschung, Heidelberg, since 1989. He received (jointly with Ernst Neher) the Nobel Prize in Physiology or Medicine in 1991 for patch-clamping.

justification for that you can argue quite cogently, in that sleep is active, anabolic and synthetic and probably includes information-processing and problem-solving activities within the mind. In contrast you only need wakefulness to secure food supplies and ultimately to reproduce. As humans, with established social bonds, we have the potential to enjoy wakefulness but, basically, we neglect sleep at our peril as an essential element in our growth and development. I also have an idiosyncratic view of the nature of depressive illness. Namely, that it is borne of sleep.[129] Within sleep we are no longer distracted. Once again we are confronted, predominantly within REM, by our fundamental problems, largely these days existential and probably barely recognized by us during wakefulness. We address them and, if we cannot solve them during sleep, then we waken inert and helpless. We want more sleep and complain of its inadequacy, for we find ourselves without drive or the capacity to act. Hence the classical diurnal variation of mood and activity in severe depression. Incidentally, of course, you can block depression so long as you deprive the individual of sleep. Now, years ago, with the help of George, we looked at the impact of clomipramine on sleep and wakefulness. We showed that its impact on appetite was instantaneous as is its impact on sexual function. There is no three-week delay. These drugs are popularly said to reduce REM sleep but actually they do not. If by REM sleep you mean rapid eye movements, these are there just as before. What the clomipramine does in particular is to interfere with the capacity of muscle tone to reduce. Muscle tone happens to be the way that we often measure REM sleep in the tracing. We found that clomipramine actually increases muscular activity.[130] That was also our observation with amitriptyline, often said to be a sedative drug, but which increases activity within sleep; hence, probably, its value in nocturnal enuresis. I think that we have neglected sleep as a forum in which to examine the neurophysiological and neurochemical impact of these drugs. If there is any substance in the idea that depression to some extent is borne of sleep, then there may be some answers to the mystery of it awaiting us within sleep. Sleep is a more manageable medium within which to examine neurobiological systems. Meanwhile, perhaps the effect of the tricyclics and tetracyclics is promptly to increase drive behaviour (e.g. appetite) through their impact on both sleep and wakefulness. This reactivates the depressed person to re-engage with life's problems and occasionally solve some of them over the subsequent weeks, leading to ultimate recovery from the 'depression'.

Curzon: Receptors. I think some people feel about receptors the way I feel about molecular biology. I don't know anything about it, and I wish it would go away,

[129] Crisp A H. (1986) 'Biological' depression; because sleep fails. *Postgraduate Medical Journal* **62**: 179–185.

[130] Lacey J H, Crisp A H, Crutchfield M, Hawkins C, Hartman M. (1977) Clomipramine and sleep. *Postgraduate Medical Journal* **53**: 35–40.

but I know at the same time it won't go away. Now it may well be right from the physiological point of view that there are very few receptors. I can imagine there being only one physiological serotonin receptor. Nevertheless there are 15 or so pharmacological receptors for it, and there are drugs that will act selectively on one or other of them. So from the point of view of treatment, I don't think that this area can be ignored and a thing that I am rather obsessed with is, as I mentioned before, that so many of the drugs used in psychiatry affect the availability of transmitters at a whole range of different receptors.

Marks: Arising out of Professor Curzon's point, and Hannah Steinberg's and George Beaumont's, is the idea that specificity of drug action is rather unrealistic. This specificity idea is partly driven by the requirements of the FDA and the CSM, that one doesn't get a drug indication unless one shows specific diagnostic indication. Maybe we need to look at how this form of drug regulation has come about and whether it's done a disservice to the area.

Harrison-Read: Hannah's point about reducing the emphasis on receptors I think is important, because it cautions against an overly reductionist approach to mental disorders and effects of drugs on the mind. And this is a thing that patients object to so strongly. They don't like to be thought of as a bag of receptors into which we are putting chemicals in order to change their behaviour. We do need to think very carefully about how we regard and employ the psychological effects of drugs. For example, the early research that was done on hallucinogenic drugs was, I think, very sophisticated. The idea that chemicals are merely setting the scene for cognitive and other mental changes to take place, which will be very much affected by the individual's personality and their experience of the world, is I think a useful way of looking at the situation. It is more helpful than viewing people as just a series of chemical reactions. Patients object to this and I can understand why.

Healy: There's an awful lot of people who I am sure would feel the same way as you, but the field is heading in the opposite direction, and I guess one of the queries is, why? But could we move on at this point and introduce a few more things and then we'll actually have some time to pick up on all of the issues. One of the issues, I think, that the receptor brings with it is the idea that if a small amount of the bullets failed to work, give more. Psychiatrists have been described as heroic GPs, yet when a GP decided to get involved in the whole area and help set up the British Association for Psychopharmacology (BAP), there was uproar from the psychiatrists, particularly from the Maudsley, who didn't want it happening – it was not the place of a GP to do this kind of thing – and this perhaps relates to the lithium issues that were raised earlier. There was perceived to

be a lot of hostility from the Maudsley to drug treatments. Psychopharmacology in the UK and the US is very much a thing that happened in the periphery, not the centre. The people who were involved in the foundation of the British Association for Psychopharmacology were people from the periphery, not from the centres of excellence. David, would you like to pick up on this.

Wheatley:[131] Well, I have to delve back into the recesses of time and my own memory to recall the events that led to the foundation of the British Association for Psychopharmacology[132] and in fact the whole development of professional organizations in this field of medicine. Many, many years ago, before I saw the light, I was in general practice, but getting rather bored with it, and getting interested in drugs, I conceived the notion of founding a group of GPs who would be prepared to do drug trials for pharmaceutical companies on selected products. Of course, methodology was primitive in those days, and this was perceived as a very harmless sort of exercise, but one which would be of interest and use to our colleagues. And so I founded this organization, which was called the General Practitioner Research Group,[133] and after it had been in existence for a while a colleague of mine in the States phoned me up and said next time you come to the States, go down to Washington and see this guy Jonathan Cole,[134] because he is a psychiatrist and he's very interested in what you are doing with GPs. To cut a long story short, they thought that this was rather worthwhile doing in the field of psychopharmacology, because they had no input, no clinical input, from GPs in the States, only from centres of excellence and from hospital areas. They felt that because GPs were the ones mainly prescribing these drugs, they ought to have some knowledge of what was going on in general practice. So they supported me in this field, with very generous grants, which went on for 12 glorious years, and I may say I rode on the crest of the wave. Since then, it has just been a matter of keeping my head above water. But anyway, that was how I became involved in the field of psychopharmacology.

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[131] See biographical note 86 above.

[132] The British Association for Psychopharmacology was established in 1974. On the origins of the BAP see Wheatley D, Healy D. (1994) The foundation of the British Association for Psychopharmacology. *Journal of Psychopharmacology* **8**: 268–278. Stolerman I. (1995) Origins of the BAP. *Journal of Psychopharmacology* **9**: 287–288.

[133] The General Practitioner Research Group was founded in 1959 to undertake therapeutic trials in general practice. See Wheatley D. (1960) The General Practitioner Research Group. *Practitioner* **184**: 500. Refer also to Reynolds L A, Tansey E M. (eds) (1998) *Research in General Practice*, this volume.

[134] Dr Jonathan Cole was then Chief of the Psychopharmacology Service Center of the National Institute of Mental Health in Bethesda, Maryland, USA. See Cole J. (1996) The evaluation of psychotropic drugs. Interview in Healy D. (ed.) *The Psychopharmacologists.* Vol. 1. London: Altman, 239–263.

I remember the first meeting I went to was the CINP (Collegium Internationale Neuropsychopharmacologicum),[135] it was in Munich, I can't remember how long ago, maybe 30 years, and I found this a very pleasant occasion, it was very interesting, there was a lot of clinical work there. I subsequently attended all the CINP meetings, but it soon became obvious that there was dissension, that there were two opposing factions here, one faction consisted of the clinicians who were treating the patients and doing clinical trials of new drugs, and the basic scientists, who were doing the work in developing the drugs and finding out how they worked. Furthermore there was a sort of see-saw effect, that from time to time one would be in the ascendancy and the other at the low point, and depending on where the ascendancy was, so depended the actual type of the meeting, as to whether it was clinically orientated or more research orientated. And, of course, to clinicians a lot of the research work involving as it did rats mainly I think, (what happened to the guinea pig?), was not of interest. Then I found out that as a result of my grant I was required to go to two meetings in the States, one of which was the ACNP, the American College of Neuropsychopharmacology,[136] which at that time was the only national college, and so I attended that and I found that there it was more to my liking, because it was much more clinically orientated. In particular there was a considerable interest from psychologists, which I certainly hadn't seen at CINP. So, anyway, one day I was talking this over with Alec Coppen, saying why don't we have an organization in England and he said, 'Well why not, you start it'. I did nothing about it, but a little way later I talked to Anthony Hordern, who was a psychiatrist at Kings, he's now in Australia, and he said, 'Come on David, let's do something about this'. Anyway to cut a long story short again, I contacted a few people, but they were all clinicians, because I only knew clinicians; I didn't know that Merton Sandler existed in those days, more's the pity. And so we set this up and we started it up with a peculiar name, the British Academy of Psychopharmacology, mainly because we couldn't call it a college because of the Royal Colleges and we felt that society wasn't grand enough, but inevitably we had of course missed out all the basic scientists. We didn't have any basic scientists, and so naturally they took offence to this and said, 'Look how can you found this and call it this, without including us'. They said, 'If you'd called it the British Academy of Clinical Psychopharmacology, yes, you would have our blessing and we'll form our own organization'.

Someone asked about Hannah Steinberg. I am not sure whether she was on the original working party or whether she joined us later. I can't quite remember how you came to us, Hannah, but I am so thankful that you did.

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[135] Collegium Internationale Neuropsychopharmacologicum (CINP) was founded at the Second World Congress of Psychiatry in 1957 and held its inaugural meeting in 1958, see Hippius H. (1996) The founding of the CINP and the discovery of clozapine. In Healy D. (ed.) *The Psychopharmacologists.* Vol. 1. London: Altman, 187–213, 191–192.

[136] The American College for Neuropsychopharmacology (ACNP) was founded in 1960.

Steinberg: There was a letter in the *Lancet* or the *British Medical Journal* and I just saw it and went along and I couldn't actually understand what all the trouble was about quite honestly.[137]

Wheatley: In founding the BAP, that was a very serious omission, which we very rapidly put right, and I hoped that that particular breach was then healed, and things then proceeded in a much more equitable manner. The other points that we did consider – we considered the American College. In those days the ACNP was sponsored by one pharmaceutical company and they provided them with all their finances and I think they more or less ran it for them. We felt that this was not very desirable and it would be better for a professional organization to be completely free of any input from the pharmaceutical industry, so we made yet another enemy by, I think the original letter had the phrase, 'our relationships with the pharmaceutical industry'[138] and of course naturally physicians in the industry took exception to that and that was another mistake which was made with good intention, but in the event it was rather unfortunate. So we had already made two enemies. We made a third enemy – the Maudsley was mentioned – and I think that was because some very important psychopharmacologists were in fact omitted and quite why, I don't know, but it did happen and again that was quickly put right too. So we started from a very stormy background, but I think after that things proceeded very amicably, I find that much the same things happen in BAP, and perhaps we should have learnt this by experience that, as with CINP, there is a see-saw which goes up and down, I think at the moment it is more on the basic side and that is not of so much appeal to the clinicians. I think the important thing is to try and cater for all tastes and I think the only way you can do that is to be very, very careful with the composition of your council and to try and have a balance, no matter who's voted for who, but to try and maintain that balance between the clinicians and the basic scientists. Because I am sure it will swing the other way and then the basic scientists will be dissatisfied. So anyway that really is what happened in the case of the BAP, and of course since then many other organizations of a similar nature have evolved, the European College, there was even at one time a Turkish College. I think I am still a foreign corresponding member of that, but I haven't heard of any activity in the last 20 years.

I would just like to make one observation which has got nothing to do with all that, and that is on the way in which we are going in the production of new drugs. I think we have come round in a circle. We started off looking at nature, did

[137] Brandon S, Coppen A, Hamilton M, Holden M, Hordern A, Imlah N, Jenner A, Shaw D, Wheatley D. (1974) British Academy of Psychopharmacology. *British Medical Journal* **i**: 366–367. Professor Hannah Steinberg wrote later, 'We had an election for the first council by secret ballot, and I was among those elected. I believe that I was at that point the only laboratory scientist on the council'. Letter to Dr Daphne Christie, 26 May 1998.

[138] op. cit. note 132 above.

we not? When I went into practice we had things like tincture of gentian and tincture of digitalis; well look what happened to digitalis, we had one of the most valuable drugs that we have in the whole of clinical medicine as a result of proper investigation, refinement and then ultimate synthesizing of the active compound, digoxin. There are many others, morphia again is a very potent example. Then of course we got into the whole concept of synthesizing thousands and thousands of chemicals, and then looking around and finding if there was something any of them would treat. I think we should come round now and I am glad to say it's happening, into the field of phytomedicine, and going back and looking at plants. It's going to Third World countries, seeing what the witch doctor uses, getting what he uses, doing a proper clinical trial on it, trying to isolate the active compound, and so on.

I was recently at the International Congress of Phytomedicine in Munich, because I have an interest in *Hypericum*, St John's Wort, which has antidepressant properties and the work that's being done is fascinating. Take valerian which we used to use long before we had barbiturates even, and we used it as a tranquillizer and to induce sleep. Now somebody has done a double-blind controlled trial with polysomnography, and what does valerian do? It increases deep sleep. It selectively increases deep sleep. All your benzodiazepines, prolong sleep by prolonging the light stages of sleep, but what good is that to our physiology I wonder, and they may in fact reduce deep sleep. So here we have an interesting observation, an observation which could be put to good clinical use. Taxol is another case in point. A drug that they have in America which prolongs life in women with breast cancer and which originally came from the bark of a particular elm. But there weren't enough of these elms growing in the States to treat more than one patient for a year, so the US Government started planting forests of them all over the place, until somebody found a means of culturing the cells of the elm bark and so they are now able to produce it in quantity. They still don't know what the active constituent is, but it is an enormous advance, and I very much hope that this is the way that psychopharmacological research is going to go into the future, back to basics. It would have great help in patient cooperation. Patients are very suspicious of drugs these days. They read about side-effects, they have the mistaken belief that because a product is a natural product, it's safe. Of course, we know it's not necessarily so, but in many instances, it may be and it may have advantages over those that we are using.

Healy: The point you make about they have no belief in the drugs, but they have great belief in the natural products is interesting, because of course what you are saying in one sense is that they have belief in drugs, but they haven't got belief in prescribed drugs, which means that they haven't got belief in the prescribers I would have thought to some extent. But let me just quickly mention one or two

other bits that I drew out of what you said. One is that you said the BAP was formed because you had been at ACNP meetings and seen how they worked. A few people, it seems, had the same idea, they'd been to ACNP meetings which are held in Puerto Rico in the middle of winter and it's extremely nice and you are there in the sun and you've got colloquial discourse and things like that and this seemed to be a good idea to transport over to the UK. Meetings of this sort, however, are often meetings which owe quite a bit to the pharmaceutical industry. Without the support of the industry, they can't actually happen. A person who wrote about all this as a theme which could actually be introduced here was Arthur Koestler, who wrote about the phenomenon of science in our day, where we have the conferences in very interesting, nice costly places and you have to have the support of an industry of some sort to go to them. Nate Kline, who's been mentioned earlier, brought Arthur Koestler, who wrote a book on all this called *The Call Girls*,[139] to talk at an ACNP meeting, at just the point when you would have been there probably, hatching the BAP.

A further point is about the old drugs which you mentioned. The thiazides I guess are a good case in point. The thiazides, for those of you who grew up in the hypertension field, have as of last year been recommended in the guidelines for the treatment of hypertension, as possibly the best drug there is. We have gone through an entire cycle of producing the beta-blockers, the angiotensin-converting enzyme (ACE) inhibitors and a range of other drugs, and it turns out thiazides, used in a much lower dose than was used during the 1950s, turn out to be the optimal treatment, it appears, for hypertension. So there's an awful lot of curious things happening here.

Gelder: Before tea you asked us the interesting question whether most of the discoveries really stopped in the 1960s and if so, why? I thought it would be interesting to hear people talk about that. It seems a very interesting question and one of the things which looking back on the history might answer. The first question is whether this history is very unusual; after all, major advances in any branch of medicine are not very frequent and I asked Sir Christopher Booth at tea to consider other fields such as neurology and gastroenterology, and say how often you make a major advance. Putting that aside and assuming that we have got rather stuck, what we have heard is first that some of the major discoveries were made by trying out new compounds on conditions which they had not been intended for. Now that was something that you could do in the 1960s which is very difficult to do now, because of regulatory procedures. Chlorpromazine would be an example. Nobody now, I think, would dare to use a drug that was licensed for use in anaesthesia in psychiatry. It's too far out of its agreed field and as you were saying

[139] Koestler A. (1973) *The Call Girls.* New York: Hutchinson and Random House.

earlier, even using a compound within the field in a slightly different area, now causes anxiety. The third question is how you look for new drugs. The pharmaceutical industry has adopted as a way forward, a model of the drug's action on particular receptors that are supposed to work in a particular way, so in a way they only find what they are looking for, and just go on producing similar drugs over and over again. It seems to me that this is one of those areas – pharmacology isn't the only one – in which trying to make things safer for people, has actually made it harder to be original and to move forward. The idea of looking outside pharmacology is an interesting one and that, looking back, is where reserpine came from. Reserpine was used for a while, it was used first in India as a traditional medicine and was brought here for use in schizophrenia.[140] I wonder what other people think about these ideas, first whether we have got more stuck than other areas of medicine, I think probably we have, although we shouldn't be too hard on ourselves; and whether it is this wish to regulate and be safe that actually stops innovation and how we could get round that.

Marks: That's an important issue, that increasing safety might decrease creativity. There is an uneasy tension between the relationships of the researchers on the one hand and industry on the other, and paying for us to go to conferences in nice places was also alluded to. The question is, how to improve this relationship, what can be done? I myself was refused a slot in the program of the annual conference at the American Psychiatric Association (APA) to present the results of an Anglo-Canadian-controlled trial showing that exposure therapy was at least twice more effective than alprazolam. Nor could I get the results published in an US journal. We therefore submitted our paper instead to the *British Journal of Psychiatry*, which published our results very quickly without a line being changed.[141] Of course many of the anxiety disorder researchers in the whole world had been supported by the drug company concerned and the response to our producing this report, was for the drug company to commission various people to try and rubbish our results. This is a familiar story of 'damage limitation'. The drug company didn't manage to stop publication, but we do know that in many instances, a publication of negative results is prevented by the industry. There is a censoring of which data actually comes to see the light of day in the medical press. What can be done to improve the situation? We know that regulation has made the licensing of new drugs increasingly costly. We are now told that the average new drug costs $300

[140] In 1952, a plant root (*Rauwolfia serpentina*) was being used in India for the treatment of hypertension, snakebite and insanity. In 1953, Ciba reported that it had isolated an active salt from the root, which it called 'reserpine'. Kline was awarded the Lasker Prize in 1957 for his role in demonstrating the sedative and tranquilizing effects of reserpine. See note 32 above.

[141] Marks I M, Swinson R P, Baþoðlu M, Kuch K, Noshirvani H, O'Sullivan G, Lelliott P T, Kirby M, McNamee G, Sengun S, Wickwire K. (1993) Alprazolam and exposure alone and combined in panic disorder with agoraphobia. A controlled study in London and Toronto. *British Journal of Psychiatry* **162**: 776–787.

million from inception to being licensed. That's a lot of money to have to recoup and so the pressure to try and suppress negative evidence increases. What can we do about this? I told the drug company at the time (about 1992), that they had had us test two different treatments, alprazolam on the one hand, behaviour therapy on the other. The behaviour therapy was twice more potent, so the obvious thing to do was to try and market the behaviour therapy. We were very willing to help them do this, but at that time it fell on deaf ears. However, now that disease management is beginning to come in, the pharmaceutical industry is more ready to consider packages of different treatments, including behavioural ones, that can be used together, so perhaps a more broadminded view of treatment possibilities is spreading. There is an uneasy tension here and the question is, how can we improve the balance?

Beaumont: One small comment about that from the publication point of view – I have to be careful what I say now – but I just wonder to what extent publication policy has influenced the way treatments are developed. If I put my hat on as an editor of a journal, I have to say that one of the things that is beginning to concern me, is the sort of process which we have regarded in the past as so sacrosanct, refereeing, because although you know that when we publish papers we very carefully ask that they should be properly refereed before they are published – what you have to say in all honesty, is that if you choose your referees carefully enough, you can say what you like. One wonders really whether we ought not to be going back to the old approach of saying publish and be damned, rather than inviting referees, because you know in the case of your paper if the publisher choses the 'right' referees, you'd never get it published.

Wheatley: May I say a word about conferences in nice places? There are very good reasons that conferences should be held in nice places. They have got to be held somewhere, so they are held in the places that most people will want to go to and, of course, most people includes spouses, partners I think they are called here, in America I think they call them significant others, who don't necessarily like their principal going off to a conference on his or her own. They like to accompany their partner and very often it can be combined with a following holiday, which reduces expenses generally. So I think there is everything to be said for conferences being held in nice places.

Also, one has to consider that at one time the ACNP, and I am sorry this is something we couldn't copy with BAP, used to have two hours in the afternoon, between two and four, which was set aside for 'unofficial discussion around the swimming pool'. Now what could be better than that? I learnt more in unofficial discussion around the swimming pool, than I did from any of the formal

presentations, because I met people, I talked to them informally, and I got many ideas and contacts from that very nice relaxing two hours. There is a lot to be said for not overburdening your conferences with too many papers. So often these days, conferences have so many sessions going on at the same time, you would like to go to one, you find it clashes with something else. You spend your time aimlessly wandering from lecture theatre to lecture theatre, often only to find the paper you wanted to hear has been cancelled, rushing back to the other one only to find that's over. There is, I think, an important aspect in making conferences simpler these days and maybe BAP should consider these. What are people going to get from the conference? If you overburden them with a lot of knowledge, much of which may not be relevant to their own speciality, then it might have been much better if you'd simplified the proceedings so that they could really benefit from the main purpose of the conference, which is exchange of knowledge. If you like, the formal lectures and presentations are only the catalysts which catalyse the exchange of knowledge which very often follows informally after the lecture theatres have closed.

Healy: Can I ask anyone who wishes to come in on this theme to focus not on how we should reorganize conferences now, but the growth of a complex. We began with research happening in Portacabins and very small labs, we've now got huge institutes, major multi-tier conferences, that's where we have gone, but how did we get there?

Sir Christopher Booth:[142] I was merely going to take up Michael Gelder's point about whether psychiatry in terms of drug development since 1960 is on its own, and I don't really think it is. I mean, an awful lot of what has happened in the rest of medicine since 1960 has been what David Weatherall refers to as patch-up medicine,[143] which means you repair a coronary artery, you put in a new heart, you put in a new kidney and that sort of thing, and a huge amount of the advances during this period have been related to that. In that area, of course, there has been one very major drug discovery and that is cyclosporin which has made a big difference to the success of transplantation. If one takes other areas of medicine – I can speak a bit for gastroenterology, and Sir James Black's discovery of the H_2 receptor antagonist postdates 1960, but of course the concept of receptors on which he was working, and which he did with beta-blockers in the heart came before that. If I consider gastroenterology, there are, as in psychiatry, some very,

[142] Sir Christopher Booth (b. 1924) trained as a gastroenterologist and was the first Convenor of the History of Twentieth Century Medicine Group, Wellcome Institute for the History of Medicine, from 1990 to 1996 and Harveian Librarian at the Royal College of Physicians from 1989 to 1997. He was Director of the Clinical Research Centre, Medical Research Council, from 1978 to 1988.

[143] See Weatherall D. (1995) *Science and the Quiet Art. Medical research and patient care*. Oxford: Oxford University Press.

major uncertainties, things like inflammatory bowel disease, Crohn's disease, colitis and so on. Nobody has made any impact on any of those subjects at all. I would have thought the work on schizophrenia that's going on now and, more recently, the work on Alzheimer's and the possibly of acetylcholine-based drugs being involved in some capacity are developments which are possibly going to be of very major importance in the future.

Harrison-Read: To return to the point about international psychopharmacology meetings, or meetings in general, I think that the way they are currently organized, may actually militate against the optimal exchange of information. Holding meetings in very attractive or exotic places may make the temptation to be a tourist rather than a delegate or participant difficult to resist. Also having many parallel meetings is a way of paying lip-service to the ideal of comprehensive exchange of scientific information, whereas in reality, this will inevitably be limited. In connection with what Professor Marks was saying earlier, I have an uneasy feeling that the pharmaceutical industry may be unduly influencing the dissemination of information about psychopharmacology through their heavy involvement in the organization and funding of international conferences. I remember that when I attended the First and Second British Lithium Conferences in 1977 and 1987 respectively, these meetings were not sponsored by the pharmaceutical industry to any great extent and were held in Lancaster and Wolverhampton, not particularly glamorous settings I think! There were no parallel meetings, the conferences were of high quality and well-attended, and there was a very useful exchange of a large amount of new scientific and clinical information. Without wanting to over-state the case, I think that some international psychopharmacology meetings nowadays may not be best doing the job that they are intended for because of the over-involvement of the pharmaceutical industry and the bias and unofficial censorship that may result.

Healy: Well, that begs the question of what is the job that they are actually intended for? One of the things that one needs to keep in mind is that there is a big difference between psychopharmacology and neuroscience. Neuroscience is about the development of techniques and great men and great women who've got great ideas. Psychopharmacology inevitably involves itself with the culture of the period, the market, what is feasible. It is involved with the marketing of ideas, and the marketing of the evidence in a way that neuroscience isn't perhaps and perhaps there are angles there that we need to keep in mind.

Wheatley: I would like to just make a comment if I may on the presence, if you like, of the pharmaceutical industry at meetings these days. In this respect the

ACNP is notable. Fortunately I have been able to get to ACNP now for the last few years and one of the features of ACNP is that there is no pharmaceutical exhibition. It is the only major meeting I know that does not have one and I gather that this is the policy of the organization, which is in fact still a very restricted organization, I think it's limited to something like 500 members, each member can bring one guest. It's something of that sort of order, whereas of course other organizations such as CINP for example, are thrown open to anyone who would like to come. And the last CINP that I went to in Washington I was quite frankly rather appalled at the dominance of the pharmaceutical industry. I hope there is nobody here from the industry who'll take offence at my remarks, but it seemed to me that this was really a meeting put on by the industry for each other and so many of the sessions were sponsored by a company, with a selective influence on the contents. I have stopped going to meetings like that, because they are so vast, you never meet anybody you want to and, as I say, to me the importance is meeting people and it's the personal contact with other investigators, perhaps you don't see them over the years, perhaps they come from the other side of the Atlantic, and that is what I would like to see the emphasis on at meetings in the future. Fortunately, there are still small meetings, ACNP is a small meeting. The New Clinical Drug Evaluation Unit (NCDEU of NIMH), which is an entirely clinical meeting put on by the NIMH which is in Boca Raton, again a rather pleasant ambience in Florida, is a relatively small meeting. I think last year there were fewer than 1000 people there. These are the meetings I like to go to and these are the ones I try and concentrate on.

Beaumont: I just want to come back to a former point, because I think one thing that concerns me is that there is still a massive gulf between what the pharmacologists tell us about the action of psychotropic medication and what we observe clinically. We've seen, I think, what is a very interesting phenomenon with the antidepressants for example, that after all this thrust towards selectivity what is now happening is that we are almost back to square one in the sense that the most recent introductions like venlafaxine are really to all intents and purposes tricyclic antidepressants with a slightly cleaner profile. So all this emphasis on separating neurotransmitter systems and identifying receptors seems really to have got us nowhere and we have gone back full circle more or less to where we started in the 1950s. It's even worse in the field of anxiety, because if you look at all the effort that's gone into identifying the various 5-HT receptors, if you look at the work by people like Brenda Costall, for example, suggesting that all sorts of clinical indications would come from agonists or antagonists of the various 5-HT receptors or you look at the work on partial agonists of the benzodiazepine receptor, suggesting that here was a new group of drugs which would be immensely valuable, none of these observations have proved to be of much use

clinically. Virtually all the clinical trials of agonists and antagonists of the various 5-HT receptors have produced results which are either equivocal or really of no great clinical significance and now we have got antidepressants that seem to be going back to the 1950s. Somehow, somewhere, I think the gulf between pharmacology and clinical practice has not yet been satisfactorily bridged.

Healy: I think it is true that the SSRIs haven't been as good as we thought they would be and we have moved back now to more complex compounds, but the idea that inhibiting 5-HT uptake might be a useful therapeutic principle, was an idea that had to be tested out and the only group with the clout to test it out were the pharmaceutical industry. There are an awful lot of clinical trials that happen in this country, but they are all run by the industry. There is very little independent work in this country. There are much more independent trials happening in the US, even though it is a much more, supposedly, market economy than there are here. Since the MRC trial in 1965 there have been very few independent trials happening in this country. What independent trials there have been, such as the MRC trials, haven't convinced people, because most people have felt that they have got the wrong answer, even though it was an independent trial. Where there are loads of independent trials, that all yield the same result, as in the use of an methylphenidate for hyperactivity, no one pays any heed to that. Then we have got the actual trials being run by the industry which are not aimed at answering scientific questions, they are aimed at something else and these are issues that aren't really picked up on often.

Dr Trevor Turner:[144] I am interested in the discussion about meetings in particular, having attended two or three in the last year, the World Psychiatric Association (WPA)[145] for example in Madrid. Everyone there from Britain was paid for by a drug company, no doubt about it. No one else would have gone for any other reason. On the other hand, there were people there who needed to go to such meetings, people from Eastern Europe. I actually listened to a talk by a psychiatrist from Azerbaijan, which I can recall was wonderful, because he was the only one in Azerbaijan, and I think there is a way in which the psychopharmacology industry does actually help such individuals attend meetings and get some kinds of details and at least buy a few well-made pens for example. The other point about them, is that it is quite clear they do attract now, and increasingly will attract, antipsychiatric establishments. The Scientologists were very prominent in Madrid

[144] Dr Trevor Turner (b. 1948) has been Consultant Psychiatrist at St Bartholomew's Hospital and Homerton Hospital since 1987 and Member of the Royal College Psychiatrists since 1981.

[145] The World Psychiatric Association (WPA) was established in 1950. It comprises 106 national psychiatric societies, representing more than 140 000 psychiatrists worldwide. The secretariat is presently located in New York.

and I suspect that these kinds of areas are going to be increasingly attacked, used as demonstrations of a very antiscientific group, who are very powerful nowadays, which is why one worries about the extent to which they are allowed in. My final point though is we have to ask ourselves, 'All right we are critical of the psychopharmacological industry and some of its motives and profits, but who else is providing funds for modern psychiatric research?' There is more money put into caring for aged donkeys than looking after people with serious psychiatric illnesses. It's one of the tragedies of modern health and research, as was pointed out by the Mental Health Foundation last year in their annual report and I wonder what could be done in that respect to try and attain better general funding; for example, the new Culyer approach to funding research,[146] needs to be considered in this respect. They are there because there is a great big gap and no one else is doing it.

Steinberg: *Hypericum perforatum* [St John's Wort] has been mentioned. It is an example of a herbal extract which is jolly impure as far as I can tell, and the idea of herbal medicine seems to be that such a compound is different from the constituents, so that you have to use the whole plant extract rather than try to isolate the active principles, as pharmacologists usually do. Now this seems to me, again going back to the beginning, and to link up with what has been said, that we've got too carried away by the scientific method. I agree very much with what you say about refereeing. I think that's got out of hand entirely and delays papers, and delays dissemination of information, and so maybe the conclusion from a group like this would be to say, 'Let's go back to history, let's look at the way in which big discoveries were made early on and see what they or we have missed.'

Jenner: Perhaps my point does follow on from that, because I thought I was going to comment on Michael Gelder's point. The point about the great discoveries seems to me that they were made by serendipity. They weren't made by the right research establishments. In one sense they were made by other people, and they weren't made as Michael might be suggesting really, by people not being willing to give them to unusual conditions, but noticing when they gave them to what they thought to be useful for, they noticed something else. Lithium was originally used by Cade to dissolve renal stones, to make lithium oxylate which he thought would be more soluble, but he noticed the behavioural change. The antidepressants, as we have just heard, were noticed by Kuhn, because they were given for schizophrenia. They were antidepressant. Well, penicillin is an obvious example and the benzodiazepines as far as I know, were originally produced to get rid of worms in rats and someone noticed they changed their behaviour more than the satisfaction

[146] Research and Development Task Force. (1994) *Supporting Research and Development in the NHS: A report to the Minister of Health*. London: HMSO. Chaired by Professor Anthony Culyer, Professor of Economics and Deputy Vice-Chancellor at the University of York.

of the loss of anal irritation. The phenothiazines were antihistamines introduced for surgery under conditions of 'hibernation'.

Professor Elizabeth Sykes:[147] Professor Marks's comments were, I think, very pertinent when he drew attention to the amount of money invested in a potential new drug. In fact only yesterday it was said in the national press that the pharmaceutical industry in Great Britain brought in the second largest part of the gross national product, second only to North Sea oil, which underlines the power that the drug firms have. It seems to me that David Wheatley's comments on phytomedicine are becoming very relevant in the present climate – especially when one thinks of the new courses in herbal medicine that are being started in some universities. Maybe that is one of the ways forward? Particularly when it looks as though some of these plants contain several active principles which reinforce each other. [148]As a preclinical psychopharmacologist, I was wondering to what extent we can break away from what is becoming mounting pressure from the pharmaceutical industries to produce 'acceptable' results, which usually involves looking for one active principle at a time? In addition, the current climate is tending to prevent basic laboratory work from being carried out and a large number of laboratories have been closed as a result. In fact much of the early work on mescaline and its analogues, in which I was closely involved, could only be done with difficulty now.[149] I think we have got to start taking a radical new view with new approaches, new test methods. I am very against reinventing the wheel, which is what we are tending to do.

Healy: My hunch is that if you interview the chemists within the industry, they will have very little sympathy as such with the herbal approach. They'll say there's always an active principle in there and let's try to get hold of the active principle and perhaps modify it so we can improve on its activity. To do anything else will be antirationalist. And so we are into very big issues here, the change over a period of 30 to 40, to 50 years. Psychopharmacology began in an era of heroic medicine, these were major breakthroughs, it was a rational and optimistic period. We are perhaps entering a less clear-cut period now, at the moment. One of the other things though is as a prescriber, I think we are quick to talk about the influence of

[147] Professor Elizabeth Sykes (b. 1936) has taught psychopharmacology at the Universities of Edinburgh, Wales and Middlesex, as well as in the United States, researchs on antidepressants and anxiolytics, given alone or in combination. Recently she has analyzed the psychological benefits of physical exercise and the possible role of endorphins in mediating these (see note 67 above).

[148] Professor Sykes wrote: 'The pharmaceutical companies themselves are at last coming round to accepting the therapeutic value of drug combinations or multi-action psychoactive compounds.' Fax to Dr Daphne Christie, 29 June 1998.

[149] See for example Smythies J R, Sykes E A. (1966) Structure-activity relationship studies on mescaline: the effect of dimethoxyphenylethylamine and N:N-dimethyl mescaline on the conditioned avoidance response in the rat. *Psychopharmacologia* **8**: 324–330.

the industry and their power and their wealth, and things like that, but I think for those of us who are in clinical practice here, who prescribe drugs, and who earn our living out of what's a very controlled market, no one else can get into it. The psychologists can't get into it, the social workers can't get into it, and of course we are much better paid than either of these, and this all came about with the new drugs as well. You know, there are our interests there as well. We can't be purer than pure, whiter than white and say, 'oh there's the pharmaceutical industry over there, and we are the good guys'.

Beaumont: We are really back to your receptor theory again aren't we? One of the things that alarms me is that the way that drugs are developed now is that you just sit in front of a computer with a diagram of a receptor and anything that you can make that fits into it is tomorrow's potential new drug. It seems to be a rather odd way of going about making major discoveries.

Healy: I could add on this. This is also an issue that we have gone through here, which has been picked up. There was a point where we were quite happy to use combinations of drugs and this was what we were at during the 1950s and 1960s. That fell out of favour, perhaps we were in the business of trying to produce magic bullets which were pure, but also because it was inconvenient for the FDA to try and work out how they were going to regulate and licence combinations of drugs. We have then moved on towards producing purer drugs through the 1960s, 1970s, and 1980s. Now when we get to the stage of trying to produce drugs that will hit particular brain receptors and things like that, we find that we can't do it. That what you get is, whatever the molecule is, and almost the smaller the molecule, the more likely it is to hit a few different receptors. The compounds we're using, which are supposedly pure now, and this includes the SSRIs, are cocktail compounds. There's poly-prescribing within the one drug. It's been part of the mythology up to this that they'd been pure, but there's an issue here of science and myths, and we've been selling myths. When you sell *Prozac* you sell a myth, or a range of myths. This is part of the interest – how do these evolve in the culture?

Beaumont: You have got to look at it from the point of view of the cost of development, because if you go back to the discovery of chlorpromazine, the discovery of the antidepressants, whether it's a monoamine oxidase inhibitor or tricyclic, you were in a climate where that kind of 'suck it and see' exercise could take place, now you are in a climate where the development of a new agent, because of the requirements of the regulatory authorities, is a multi-million pound business. So in order to get from the point of synthesis to the point of marketing, you are spending billions of pounds which you have to recoup. Therefore the only

markets you can enter are those in which there is a chance, albeit a small one, of a small share of a large cake. A whole share of a small cake isn't worth having. So you find that many diseases will be neglected, you will only find people going into markets like hypertension and depression, because here is an enormous potential for recouping the cost of research. If you want to go into the 'suck it and see' area you are not going to get the basic development to meet regulatory authorities which is required before you can actually administer the compound to a patient, so you will never make those kinds of discoveries again.

Wheatley: I'd like to make a comment on the back to basics theme. I am not suggesting we should reinvent the wheel, but we could put a tyre on the wheel and that would be looked upon as progress. It's not a question of going back to herbal preparations and using them as they are, but going back to them as a possible source for isolating, improving, concentrating the active principle, and I don't see why the pharmaceutical industry can't do that, instead of synthesizing endless chemicals. Go back to basics to look for the sources of their drugs.

Healy: We aren't in the business of trying to advise the pharmaceutical industry, we are in the midst of trying to see how we got from here to there.

Harrison-Read: In the same spirit, I think we could look harder at some of the chemicals that we already have. This has been done already in the case of the atypical antipsychotic drug clozapine which has been around since 1965, but was rediscovered as a 'wonder drug' in the late 1980s.[150] Examining different aspects of substances which we already find useful clinically may give us new ideas for drug development in the future. It is not at all likely that we will get much help from the pharmaceutical industry to do this, particularly if we are interested in drugs which are out of patent, or are the products of companies with very little research money or commitment. I think we have to persevere with small, well-controlled clinical studies, carried out by independent research groups in order to look at new aspects of drug action in a creative way. I know that this sort of work is still going on, certainly in the UK, and I think it should be supported as much as possible. It will probably always be small-scale work, and may never get much funding from the pharmaceutical industry, partly because it is too risky and speculative, and it

[150] The first paper on clozapine (the dibenzodiazepine derivative which was to become the prototype of 'atypical' antipsychotics) appeared in the *Medical Journal of Vienna* in 1966; Gross H, Langner E. (1966) Das wirkungsprofil eines chemisch neuartigen breitband-neuroleptikums der dibenzodiazepingruppe. *Wiener Medizinische Wochenschrift* **116**: 815–816. The report of Idänpään-Heikkilä and associates in 1975 on 18 cases of agranulocytosis in Finland led to its total withdrawal. See Idänpään-Heikkilä J, Alhava E, Olkinuora M, Palva I. (1975) Clozapine and agranulocytosis. *Lancet* **ii**: 611. By the end of the 1980s clozapine was rediscovered following recognition that with special precautions, fatalities from agranulocytosis could be prevented.

may be damaging to too many vested interests. One example may come from the development of risperidone. From a pharmacological point of view, this atypical antipsychotic drug may not have been necessary because comparable effects could have been obtained from the combination of a typical neuroleptic with ritanserin, a selective 5-HT_2 receptor antagonist which had already been available for sometime. It had been shown that such a combination would be useful, but nonetheless the industry took trouble to develop risperidone at great expense, presumably because the financial rewards would eventually make it worthwhile, otherwise why not persevere with ritanserin?

Healy: But they couldn't, they couldn't. That's the point that's been made earlier, because the FDA wouldn't licence ritanserin on its own.

Harrison-Read: I'm not implying that it was all the industry's fault, but I mean the circumstances produced an anomalous situation where the development of risperidone had to happen, mostly for commercial reasons. Other available compounds might be put to good clinical use, if commercial considerations and licensing regulations were more encouraging.

Healy: Yes, it's a point worth mentioning and one not looked at really, which is the FDA and the CSM set the rules of the game and this is of crucial importance.

Curzon: Dr Wheatley's remarks provoke me to say that the term 'herbal medicine' rather puts my back up, because it's got a kind of implication that nature is basically benevolent and she just ain't. She's pretty indifferent. But I think one point to remember is that organic synthesis has only been going on in the laboratory since about the beginning of the nineteenth century, while nature's organic synthesis has been going on for much longer and has had time to develop all kinds of fantastical molecules that the organic chemist wouldn't have dreamt of. I think it is Merck Sharpe and Dohme that have got a kind of trawling project going on in the jungle somewhere in South America and are taking all kinds of plants, making simple extracts and putting them through a battery of tests, and something might come from this. It is of course true that psychiatrically useful drugs have been revealed accidentally, but when you think how short a time basic psychopharmacology has been going on, I don't think we ought to give up on it. With Goya, I am all against the sleep of reason but unfortunately there is now a tendency in that direction.

Healy: Can I ask you and the others here who've been working since the 1950s, it seems to be that there has been a change during the 1950s and the 1960s, there was the idea that scientific progress was good and it was a good thing to be rational. Since the 1960s, since 1968 say, that's much less clear, the green movement as it were, and a certain anti rationalist stance has appeared on the scene and grown. Now I am not saying that we were right there and we are wrong now, but is that the way people perceive it, and do people have views on why this has happened?

Curzon: I think the basic reason why this has happened is that there was once the general belief that science was necessarily beneficent; you spoke about this before. This was associated with the myth of the inevitability of progress which started with the French Enlightenment around 1750, started to fade away between 1914 and 1918, and has now almost disappeared. Also, in our area, science, to the general public, means drugs, and drugs means the drugs industry which is very much mistrusted, partly for good reasons and partly because of ignorance as to the restrictions under which it now works.

Healy: There was also the idea that nature was dangerous 30 or 40 years ago in a way that it is not perceived to be now, that it's perceived to be helpful, holy in a sense, now. It's a huge trend isn't it?

Steinberg: Yes and no, I think. My early training was obviously very scientific indeed and I find these ideas about herbal medicine and so on quite difficult to swallow actually. At the same time, there seems to be a demand for something like that, and the clinics that these people have set up are booked up for months ahead.

Wheatley: Yes, I think this is very important. It's very important, and that is public opinion, we rather ignore it, but of course the public are very opinionated these days through the efforts of the media and they know far more now about drugs and doctors than they ever did before. What they now learn is that this is no Garden of Eden and that there are certainly plenty of snakes lurking around, and they read these horrific accounts in the newspapers of side-effects of drugs and profits of drug companies and so on, and there is a movement against drugs. I get patient after patient who says, 'Doctor I know I am depressed, but I don't want to have any drugs' and I have a great difficulty in trying to persuade them; usually they won't. Now there is a magic about "herbal", it's simple, and I know and I say to them, 'Well, look, herbal remedies are not as safe as drugs, because they are not subject to any licensing in this country', but it's no good. They think, 'But it's a natural remedy, doctor, I can go and buy, I don't need a prescription from you, therefore it must be safe'. Now we need to educate the public I think here and we

also need to heed public opinion. If the public are dissatisfied with what we do, then we should put our own house in order, and see what we can do to meet those public concerns.

Marks: Just to take your point, David [Healy], that the FDA and CSM set the rules of the game and we have had reference several times this afternoon to how those rules can in fact impede progress, how can we help the FDA and the CSM to change the impeding rules, while preserving their benefits?

Healy: That's a whole new meeting I think. Thank you very much for your participation.

Tansey: On behalf of the Wellcome Trust can I thank all of you who have taken part in this meeting, and especially thank David Healy for his excellent chairing.

GLOSSARY*

Note: Unless otherwise stated, the trade names are those in common use in the UK.

Adrenocorticotrophic hormone (ACTH; corticotrophin) – Stimulates the synthesis and release of adrenocortical hormones.

Alprazolam (*Xanax*: **Upjohn**) – A **benzodiazepine**, used to treat severe anxiety with strong autonomic overactivity (panic disorder) and anxiety associated with depression.

Amitriptyline (*Trypitizol*: **Morson**) – One of the earliest tricyclic antidepressants and still much prescribed. (*Lentizol* is the slow-release version).

Amphetamine – Central stimulant and sympathomimetic amine; now only used in the treatment of narcolepsy (see **dexamphetamine**).

Amylobarbitone (*Amytal*: **Eli Lilly**) – A barbiturate used for daytime sedation and in the treatment of insomnia, superseded by **benzodiazepines**.

Anafranil (**Novartis**) – Trade name for **clomipramine**.

Antihistamines – Compounds primarily used for modifying allergic disorders.

Barbiturates – Drugs used as sedative-hypnotics (e.g. **amylobarbitone**) but now largely replaced by the **benzodiazepines**, except in induction of anaesthesia.

Benzodiazepines – Sedative–hypnotic drugs, many with muscle-relaxant properties, popular as a result of a combination of their pharmacological actions and their relative safety. More than 3000 have been synthesized, over 120 have been tested for biological activity, and about 35 are in clinical use in various parts of the world. Also used in the treatment of alcohol withdrawal (see **chlordiazepoxide**).

Buspirone (*Buspar:* **Bristol-Myers**) – An anti-anxiety drug, a partial **5-HT**$_{1A}$ agonist introduced in the 1980s.

Caverject – Injectible alprostadil (a vasoactive agent) for the treatment of erectile dysfunction.

Chloral – One of the early sedative–hypnotics; **Chloral hydrate** was the first synthetic hypnotic (1869) introduced into medical practice as a sedative which was followed in the early 1900s by the **barbiturates**. Characterized by an unpleasant smell and taste.

Chlordiazepoxide (*Librium:* **Roche**) – The first successful **benzodiazepine** developed in the late 1950s. Chlordiazepoxide has anti-anxiety and muscle-relaxant properties.

Chlorpromazine (*Largactil*: **May & Baker; ***Thorazine:* **Rhône-Poulenc, USA**) – An early **phenothiazine** antipsychotic drug, still widely used, also referred to in the text as **4560 RP**.

Clomipramine (*Anafranil*: **Novartis**), also known earlier as chlorimipramine – A tricyclic antidepressant, used particularly for treating obsessive compulsive disorder (see note 108 above).

Cortisone (*Cortisyl*: **Roussel**) – An adrenocortical steroid, the first biologically active glucocorticoid to be synthesized in large amounts.

Desipramine (*Pertofran:* **Geigy**) – A tricyclic antidepressant, particularly used in the treatment of attention deficit hyperactivity disorder.

Dexamphetamine (*Dexedrine*: **Evans**) – A central nervous system stimulant used in the treatment of attention deficit hyperactivity disorder in children.

* We are very grateful to Professor Hannah Steinberg, Professor Elizabeth Sykes and their student, Fran Cronin, for their considerable help in compiling this glossary.

Dexamyl – see ***Drinamyl***.

DOPA – 3,4-dihydroxyphenylalanine, a precursor of **dopamine**.

Dopamine – A central neurotransmitter and the immediate precursor of noradrenaline and adrenaline.

Drinamyl (**SK&F**) – A combination of **dexamphetamine** and **amylobarbitone:** ratio 1:6:5 (USA: ***Dexamyl***). Colloquially known in the UK as 'purple hearts'. Used to treat minor anxiety and/or depression. Their availability was restricted in 1964.

Fluoxetine (*Prozac*: **Eli Lilly**) – An antidepressant without sedative action and few unwanted effects; a **selective 5-HT-reuptake inhibitor** (**SSRI**). Widely prescribed.

G 22355 – see **Imipramine**.

5-hydroxytryptamine (**serotonin; or 5-HT**) – A neurotransmitter in the central nervous system. Also enhances platelet aggregation and is an effector on various types of smooth muscle. An indole amine. Lack of it is thought to underlie some depressive illnesses.

5-hydroxytryptophan – A precursor of **5-HT.** When coadministered with L-5-hydroxytryptophan, **selective 5-HT reuptake inhibitors** (**SSRIs**) elicit a profound activation of serotoninergic responses. **SSRIs** are among the newest and most widely used treatments for endogenous depression (e.g. ***Prozac***).

Hyoscine (***Scopoderm TTS***: **Novartis**) – An alkaloid which inhibits the parasympathetic autonomic system; may be used during general anaesthesia. Also used for motion sickness and irritable bowel syndrome.

Imipramine (***Tofranil***: **Novartis**) – The first tricyclic antidepressant; still widely prescribed. Also referred to in this seminar as **G 22355**.

Iproniazid – One of the first **monoamine oxidase inhibitor** (**MAOI**) antidepressants. Antidepressant effects were first observed in 1951 during its use in the treatment of tuberculosis, in which it inhibits the multiplication of the tubercle bacillus. It is the isopropyl derivative of **isoniazid** (1-isonicotinyl-2-isopropylhydrazide).

Isoniazid (isonicotinic acid hydrazide) – Developed in 1951; still the most important drug world-wide for the treatment of all types of tuberculosis.

LD_{50} – The median lethal dose of a drug.

Limbitrol (**Roche**) – A mixture of **chlordiazepoxide** and **amitriptyline**, ratio 1:2.5. Used in the treatment of mixed depression and anxiety.

Lithium (***Camcolit***: **Norgine;** ***Liskonum***: **SK&F;** ***Priadel***: **Delandale**) – The lightest of the alkali metals, used primarily in the treatment of manic, depressive, and mixed-mood phases of bipolar disorder, and also as a prophylactic. May also be used in prevention and treatment of unipolar disorder, often combined with a tricyclic antidepressant.

Lysergic acid diethylamide (**LSD;** ***Lysergide***) – A nonselective **5-HT** agonist and potent hallucinogenic drug.

Lytic cocktail – A combination of three drugs: pethidine, a morphine-like, synthetic drug; **promethazine**, an antihistamine; and **chlorpromazine**. Used by Laborit during the 1950s to induce artificial hibernation (a condition believed to diminish shock and facilitate surgery); to potentiate anaesthesia; and to intensify the action of barbiturates and narcotics.

Mescaline – A phenethylamine hallucinogen and a selective **5-HT** agonist. The active principle of *Peyote* cactus.

Methaminodiazepoxide – An early benzodiazepine, later called **chlordiazepoxide**.

Methylphenidate (***Ritalin***: **Novartis**) – A piperidine derivative structurally related to amphetamine. One of the preferred drugs for attention deficit hyperactivity disorder.

Monoamine oxidase (**MAO**) – An enzyme that catalyses the metabolic breakdown of monoamines including the catecholamines adrenaline and noradrenaline, and also of **5-HT**.

Monoamine oxidase inhibitors (**MAOI**) – A group of antidepressants, which act by inhibiting the enzyme **MAO**. The MAOIs are considered drugs of second or third choice for the treatment of severe depression mainly because of their side-effects and necessary dietary restrictions (see the cheese reaction, note 83 above). Nevertheless, MAOIs sometimes are used when a tricyclic antidepressant has been unsatisfactory and when electroconvulsive therapy (ECT) is refused.

Paraldehyde – Introduced into medical practice as a sedative drug during the last century; followed in the early 1900s by the **barbiturates**. The current clinical use

of paraldehyde is restricted largely to hospitalized patients for the treatment of abstinence phenomena (especially *delirium tremens*) and other psychiatric states characterized by excitement.

Parstelin **(SK&F)** – A 'combination product' of trifluoperazine hydrochloride (1mg) (a **phenothiazine** tranquilizer) plus tranylcypromine sulphate (10mg) (a **monoamine oxidase inhibitor – MAOI**). Used to treat depression complicated by anxiety.

Phenobarbitone – A **barbiturate** and the first synthetic organic agent recognized as having antiseizure activity. It inhibits seizures at doses that cause minimal sedative effects.

Phenothiazines – Dopamine antagonists. A group of widely used antipsychotic agents (neuroleptics), which have sedative, antiarrhythmic, antihistaminic, and antiemetic properties (see **chlorpromazine**).

Promazine (***Sparine*****: Wyeth**) – A **phenothiazine** used as an adjunct to short-term management of psychomotor agitation, e.g. acute severe mania; also for agitation and restlessness in the elderly.

Promethazine (***Phenergan*****: Rhône-Poulenc**) – A **phenothiazine** with antihistaminic properties; also used as a long-lasting hypnotic.

Reserpine (***Serpasil***) – An antihypertensive agent and depressant derived from the root of *Rauwolfia serpentina*, blocks the accumulation of noradrenaline and other amines in synaptic vesicles. Originally introduced in 1954 as an antipsychotic, it is now considered obsolete, although it is occasionally used in combination therapy of hypertension (usually with a **barbiturate**). The root of the plant had been used for years in the Indian subcontinent as a remedy for mental illness.

Risperidone (***Risperdal*****: Janssen Pharmaceutica**) – A neuroleptic particularly effective in treating the negative symptoms of schizophrenia. A potent **5-HT** receptor antagonist.

Ritanserin – A **5-HT**$_2$ receptor antagonist.

RU 486 (Mifepristone; ***Mifegyne*****: Exelgyn)** – A progesterone antagonist, used primarily to induce medical abortion in the first trimester of pregnancy.

Serotonin – see **5-hydroxytryptamine**.

SSRIs (selective serotonin reuptake inhibitors) – A class of modern antidepressants (e.g. ***Prozac***, see **Fluoxetine**).

Sodium valproate (***Epilim*****: Sanofi**) – A mood stabilizer, also an antiepileptic.

Substance P – A neurotransmitter involved in the perception of pain.

Trazodone (***Molipaxin*****: Roussel**) – A potent antidepressant with anxiety-reducing activity. It also has strong sedative properties.

Venlafaxine (***Efexor*****: Wyeth**) – A combined **5-HT** and noradrenaline reuptake inhibitor.

Yohimbine (***Yocon***) – A competitive alkaloid antagonist selective for α_2-adrenergic receptors. It increases blood pressure and heart rate, enhances motor activity and produces tremors. It does not have an established clinical role, but has been successfully used in the treatment of some types of impotence.

THE MRC COMMON COLD UNIT

The transcript of a Witness Seminar held at the Wellcome Institute for the History of Medicine, London, on 13 May 1997

Edited by E M Tansey and L A Reynolds

The Medical Research Council's Common Cold Unit, based at Harvard Hospital in Salisbury, was a unique establishment, which combined laboratory research in virology with epidemiological work, and experimental clinical studies on infected volunteers. It has also appeared, in fictional form, in *Under the Net* by Dame Iris Murdoch. Chaired by Sir Christopher Booth, this Witness Seminar examined the creation of the Unit in 1946, and its subsequent work and achievements. Witnesses included the former director, Dr David Tyrrell, administrative and scientific staff from the Unit, as well as some of the volunteers. Administratively, the Unit was, for much of its history, a part of the MRC's National Institute for Medical Research, it later became a component of the MRC's Clinical Research Centre, and these administrative arrangements and their consequences were also discussed.

THE MRC COMMON COLD UNIT

Participants

Dr John Andrewes
Dr Ian Barrow
Dr John Beale
Mr Tim Boon
Sir Christopher Booth (Chair)
Dr Donna Chaproniere
Mr Michael Cox
Professor Nigel Dimmock
Dr Norman Finter
Dr Tom Flewett
Dr Peter Higgins
Dr Sheila Howarth
Dr Owen Lidwell
Dr James Lovelock
Mrs Betty Porterfield
Dr James Porterfield
Sir John Skehel
Dr Tilli Tansey
Dr Hugh Thomas
Mr Keith Thompson
Dr David Tyrrell
Professor Miles Weatherall
Dr Peter Williams

Others present at the meeting and apologies: Dr Ita Askonas, Dr Derek Bangham, Dr Wendy Barclay, Dr A F Bradburne, Mrs Pamela Bradburne, Mrs P K Brown, Miss Morag Forsyth, Professor John S Oxford, Dr Tim Powell, Dr S E Reed, Dr G M Scott, Dr Lise Wilkinson, Mrs Jennifer Acornley, Dr A S Beare, Professor Derek Burke, Dr Keith Dumbell, Professor Andrew McMichael, Dr E J Stott, Professor D Taylor-Robinson.

Sir Christopher Booth:[1] I will start by introducing Tilli Tansey, who is the Historian of Twentieth Century Medical Science at the Wellcome Institute, and, more importantly, the Head of the Twentieth Century group here. Her particular interests have been in the physiology of neurotransmission and, more recently, the history of the National Institute for Medical Research, first of all at Hampstead and then at Mill Hill. So I can't think of anybody better to ask to start us off on the historical background.

Dr Tilli Tansey:[2]

> 'It was through the common cold that I first met Hugo. This was in a period when I was particularly short of cash, and things went very ill indeed with me until I discovered an incredibly charitable arrangement whereby I could get free board and lodging in exchange for being a guinea pig in a cold cure experiment. The experiment was going forward at a delightful country house where one could stay indefinitely and be inoculated with various permutations of colds and cures. I dislike having a cold, and the cures never seemed to work when they tried them on me, but on the other hand it was free, and one got fairly used to working with a cold, which was good practice for ordinary life. I managed to get a lot of writing done, at least until Hugo appeared.'

Thus are Jake and Hugo the two main characters of Dame Iris Murdoch's first novel, *Under the Net*, introduced to each other. The relationship gets off to a tricky start, as Jake is feeling somewhat unsociable, he's had particular permission to live alone and then this room-mate is foisted on him, as he continues

> 'I was further irritated by the fact that whereas I had only the cold, my companion was given both the cold and the cure, so that while I was choking and sneezing and using up a sackful of paper handkerchiefs, he remained in complete possession of his human dignity, and looking the picture of health. It was never clear to me on what principle the

[1] Sir Christopher Booth was the first Convenor of the History of Twentieth Century Medicine Group, Wellcome Institute for the History of Medicine, from 1990 to 1996 and Harveian Librarian at the Royal College of Physicians from 1989 to 1997. He was Director of the Clinical Research Centre, Medical Research Council, from 1978 to 1988.

[2] Dr Tilli Tansey is Convenor of the History of Twentieth Century Medicine Group and Historian of Modern Medical Science at the Wellcome Institute for the History of Medicine.

> distribution of inoculations was made, although it always seemed that I got more than my fair share of colds.'[3]

The two men started talking, and they scarcely stopped. They frequently returned to the establishment to continue their conversations, and after half a dozen visits, arranged to take it in turns to have the cold, so that only one of them was feeling ill at a time. It seemed never to dawn on them that they could meet elsewhere than the Cold Cure establishment, until they are turned out by the authorities, for fear they would do permanent injury to their health, if they carried on having colds with such enthusiasm. The Common Cold Unit[4] is probably unique amongst MRC research units in being celebrated in modern fiction by Dame Iris Murdoch.

It was not only socially unique: it was also a unique scientific establishment. It arose from the National Institute for Medical Research, the NIMR, in Hampstead which in the 1920s had spearheaded work in experimental virology, most notably with a research programme on canine distemper, that resulted in the 1930s in a successful vaccination programme. The work was also important because the scientific staff developed experimental procedures of isolation and selective inoculation that were to be used later for other animals, including human volunteers, and for other diseases. The experimental animals used principally for the canine distemper work, ferrets, were also shown to be susceptible to human influenza. Influenza was still a great scourge in peoples' minds. This was the early 1920s. The pandemic that had followed the First World War had caused as many as 15–20 million deaths, more than double the casualties from the preceding conflict. The ferrets that had been used in the canine distemper work were successfully inoculated with the infected throat washings of influenza patients, from influenza sufferers amongst the Institute staff. Indeed there's a later story of such a ferret sneezing in the face of one of the scientists, much to his delight of course, because his resulting illness proved a successful transmission of the infection. This was the first successful attempt, in spite of many efforts, to transfer the human disease, influenza, to an animal model so that it could then be further studied and manipulated and in 1933 the virus was isolated, although attempts to provide a comprehensive vaccine were largely handicapped by the variety and changeability of the virus particles.

Influenza, of course, is quite a different disease from the common cold, but it was work on the former, that suggested lines of research which could be developed to attack the problem of the latter, of the common cold. Dr Christopher

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[3] Murdoch I. (1954) *Under the Net*. London: Chatto & Windus. Quotes on pages 55–56 of the 1960 Penguin edition.

[4] Strictly speaking the correct title of the unit under discussion here is the Common Cold Research Unit, and this is the title that appears on all publications, etc. However colloquially the Unit is always referred to as the Common Cold Unit, and participants at this meeting consistently referred to it as such. Therefore the term Common Cold Unit has been used throughout.

Andrewes,[5] of the NIMR, was particularly interested in the work of Dochez[6] in New York, who reportedly had cultured viruses that could then induce colds in human volunteers. After a visit to New York, Andrewes returned to Britain and tried with very limited finance and resources, to set up a similar scheme, using Bart's medical students as his subjects, but the work could not be repeated. Even a visit from Dochez with fresh cultures again proved only negative results and the work was halted. A number of years elapsed in which little further work was done and a World War intervened. It was after that War, in 1946, that a number of synergistic events occurred. Christopher Andrewes and his staff at the NIMR decided that it was time to try a fresh attack on the problem of the common cold. Andrewes prepared a report for the MRC, outlining the kinds of facilities that he required to develop an extensive research programme. He submitted it to Council in March 1946 and the MRC agreed to support it in precisely the way that he had proposed. The only animals known to be susceptible to the common cold, chimpanzees, were too expensive, so an extensive programme using human volunteers was planned.

At the same time, Harvard Hospital in Salisbury became available. During the War the Harvard Medical School sent to Britain staff and equipment to assist in the control of epidemics that were expected to arise after the bombing raids. Prefabricated buildings were sent over from the United States and erected on a Ministry of Health site outside Salisbury. At the end of the War the buildings and their facilities and equipment were handed over to the Ministry of Health and by 1946 they were used mainly to house stores. This, then, was the site that Andrewes used to develop the MRC Common Cold Unit. The MRC provided the medical, laboratory, and office staff, and the Ministry of Health provided the catering and maintenance staff. The huts were partitioned to provide segregated units, to keep volunteers in isolation. The first arrived in July 1946, just four months after the MRC had given their approval to Andrewes's request. The initial staff were from the Division of Bacteriology and Virus Research at the NIMR. In 1946 the Air Hygiene Unit, staffed by Doctors Lidwell and Lovelock, also from the NIMR, moved to Salisbury and for many years the Common Cold Unit was an outstation

[5] Sir Christopher Howard Andrewes FRS (1896–1987) set up the Common Cold Unit in Salisbury in 1946 and remained in scientific charge of the Unit until his retirement in 1961. He joined the scientific staff of the Medical Research Council in 1927; became Head of the Division of Bacteriology of the National Institute for Medical Research in 1940 and Deputy Director of the Institute from 1952 to 1961. See Tyrrell D A J. (1991) Christopher Howard Andrewes: 1896–1987. *Biographical Memoirs of Fellows of the Royal Society* **37**: 35–54. For an account of virology current at the time, see Andrewes C H, Pereira H G. (1967) *Viruses of Vertebrates*. 2nd edn. London: Baillière, Tindall and Cassell.

[6] Dr Alphonse Raymond Dochez (1882–1964). See Dochez A R, Shibley G S, Mills H C. (1930) Studies in the common cold: IV Experimental transmission of the common cold to anthropoid apes and human beings by means of a filterable agent. *Journal of Experimental Medicine* **52**: 701–716. For a description of Sir Christopher Andrewes's visit to Dochez, see Andrewes Sir Christopher. (1973) *In Pursuit of the Common Cold*. London: William Heinemann Medical Books Ltd, 1–5.

of the NIMR. Sir Christopher Andrewes became the first director, until his retirement in 1961. He was succeeded by Dr Alick Isaacs,[7] who died tragically young, in 1967, and Dr David Tyrrell, until the unit closed in 1990. After the creation of the Clinical Research Centre (CRC) at Northwick Park in 1970, it was formally transferred from the NIMR, and in 1990 finally closed.

It is something of the history of those intervening years that we hope to record this afternoon. Here today we have scientists, technical staff, administrative staff, and volunteers, and we have with us 'Tom', Keith Thompson, who's written a wonderful history of the volunteers of the Harvard Hospital.[8] We are particularly grateful to Dr David Tyrrell for his help in organizing this meeting. We hope that all of you will contribute your reminiscences to help future historians understand the role of the Common Cold Unit and we look forward to hearing your accounts.

Booth: Well thank you very much indeed for that excellent introduction. Just a couple of points regarding Sir Christopher Andrewes. The reason he recruited Bart's students, was because he was a Bart's man, and had in fact worked with Francis Fraser, who was the first Professor of Medicine after Sir Archibald Garrod went to Oxford in 1920. He knew the background of Bart's, and his father had been Professor of Pathology there. There is now an Andrewes ward at St Bartholomew's Hospital, for patients with infectious disease.

Tansey: And I believe in the audience today we actually have at least one of the Bart's students who was there in the early days, and Dr Andrewes's eldest son. Would you like to comment Dr Andrewes?

Dr John Andrewes:[9] Perhaps I could just add one word to this question of the Andrewes's family history, in passing, though it is not exactly relevant to the present day: it is that my daughter Helen is about to take her finals in medicine and on the occasion of the opening of the Andrewes ward at Bart's, she was actually doing her stint in infectious diseases on the ward. So she was able to represent the next generation of the Andrewes family. I imagine you would like me to give a bit of insight into Sir Christopher's [Andrewes] thinking on the common cold. This I don't think I can do. It's all too much in the far distant past. I used to walk on a Sunday morning across Hampstead Heath with my father from our house up to

[7] Dr Alick Isaacs FRS (1921–1967) joined the scientific staff of the National Institute for Medical Research in 1950 with the Laboratory of the World Influenza Centre, which had been established at the Mill Hill laboratories by the World Health Organization in 1947. Isaacs succeeded Andrewes as Head of the Division of Bacteriology and Virus Research from 1961 to 1964. See Andrewes C H. (1967) Alick Isaacs 1921–1967. *Biographical Memoirs of Fellows of the Royal Society* **13**: 205–221.

[8] Thompson Keith R. (1991) *Harvard Hospital and its Volunteers: The story of the Common Cold Research Unit*. Warminster: Danny Howell Books.

[9] Dr John Andrewes (b. 1928) is a general practitioner in Canterbury and the eldest of the three sons of Sir Christopher Andrewes.

the Institute at Hampstead and he used to tell me all his ideas on medical research that were in progress, but memories of them are rather a blur and I don't think I can give you any new insights into his ideas on the common cold than those you no doubt know already. He asked me if I would act as representative at Cambridge University in the process of recruiting students, so I was given a whole lot of information and students used to come to my room to get forms and so on. My father was slightly embarrassed about this and when somebody asked him about this once, whether the recruiting agent at Cambridge was anything to do with him, he said vaguely, 'I believe there is someone of that name there'. Anyway, I myself went up as a volunteer to the unit on three separate occasions and nobody succeeded in giving me a cold, I indulged in a rigorous programme of cold baths each morning, in the hope of forestalling this, so whether I actually frustrated my father's plans or not, I don't know. We had a thoroughly enjoyable time. On one occasion when we were there, we met a girl whom we had met previously, who'd been on one of the earlier trials, and became very friendly. So during the course of the trial we saw to it that the telephonist of the unit, on going off duty for the night, would connect our phone through to her and her friend's phone, and we used to play all sorts of extraordinary games over the telephone, like three-dimensional noughts and crosses, and charades, with the result that by the end of the fortnight, we were actually extremely well aquainted. Unfortunately, one member of the quartet has disappeared to the other side of the world, having made an unsuitable marriage, but the remaining three of us are all now married independently and have remained firm friends. What else can I say? I don't think I have anything to add to the scientific activities at the unit.

Booth: Thank you very much for those comments. I think one other thing we ought just to tease out. Who was the individual that the ferret sneezed at?

Dr David Tyrrell:[10] Well, that's interesting, because you see Stuart-Harris[11] became the Professor of Medicine...

Andrewes: I think it was Wilson Smith.

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[10] Dr David Tyrrell FRS (b. 1925) was a member of the scientific staff of the MRC Common Cold Unit, Salisbury from 1957 and Director from 1982 until his retirement in 1990. He was chairman of the Tyrrell Committee, later the Spongiform Encephalopathy Advisory Committee (SEAC), from February 1989 until 1995.

[11] Sir Charles Stuart-Harris FRCP (1909–1996) was Sir George Franklin Professor of Medicine at the University of Sheffield from 1946 until his retirement in 1972; he then became Postgraduate Dean at the Sheffield University Medical School and at the Sheffield (later Trent) Regional Health Authority until 1977. For the 'transmission from the ferret', see the *Report of the Medical Research Council for the Year 1935–36*, in Thomson A L. (1987) *Half a Century of Medical Research. 2: The Programme of the Medical Research Council (UK)*. London: MRC, 123. See also Crane W A J. (1979) Professor Sir Charles Stuart-Harris. *Postgraduate Medical Journal* **55**: 71–72. Anon. (1996) Professor Sir Charles Stuart-Harris (obituary). *The Times* (20 March).

Tyrrell: There is some confusion about the story actually. The paper that was finally written was under the authorship of Wilson Smith, Andrewes, and Laidlaw.[12] It's correct that Wilson Smith, who did some of the initial experiments, did catch influenza right at the beginning and the original type strain of influenza (called WS) was obtained from his throat. It was some time later, actually when they'd been working with the virus in the laboratory, and my understanding was that Stuart-Harris, a clinician, who by then had joined the firm and was being trained as a laboratory virologist, was inspecting the animals (doing a round of the ferrets, just like he did a round of his patients). He was sneezed at and developed flu, and they showed that the virus which was recovered from his throat was actually a laboratory strain and not a wild strain. As you have said, this completes the final, third, clause to Koch's postulates, that is to say that the virus was recovered from man, passed in the laboratory (where it reproduced disease in the ferret) and then returned to man and caused influenza.[13]

Booth: I think for those interested in networking, the point is that Stuart-Harris became Professor of Medicine at Sheffield, where one of his most distinguished students was David Tyrrell. It was Stuart-Harris, who I think introduced Dr Tyrrell to infectious diseases, particularly to viruses in Sheffield at that time. Well, now any other points about these early days? Can we just get the American story quite straight. Dochez was working at Columbia, which was associated with the Rockefeller at that time wasn't it? What did he actually show? Had he got some viruses that would produce colds or not?

Tyrrell: There had been a number of other experiments, trying to prove that colds were due to viruses, and other people continued to argue that they were due to bacteria, which were easily cultivated from throats. Dochez set out to sort this one out and he did the best and the most meticulous experiments for which Christopher Andrewes had a very high regard. He showed first of all that if you cultured the bacteria meticulously from the throats of various people, as their colds came and went, there was no correlation at all between whether they had a particular bacterium or had lost it or whether they had a cold or lost it. But in order to show that there was a virus there, he had to do another experiment. In those days this meant inoculating susceptible animals, and he used both

[12] Professor Wilson Smith FRS (1897–1965) was a member of the scientific staff of the National Institute for Medical Research from 1927 to 1939, and Professor of Bacteriology at Sheffield University from 1939 to 1946 and at University College Hospital Medical School, London, from 1946 until his retirement in 1960. See Smith W S, Andrewes C H, Laidlaw P P. (1933) A virus obtained from influenza patients. *Lancet* **ii**: 66–68. For the 'ferret catching the cold', see Andrewes C H. (1965) Obituary: Professor Wilson Smith FRS. *Nature* **207**: 1130–1131. Evans D G. (1966) Wilson Smith 1897–1965. *Biographical Memoirs of Fellows of the Royal Society* **12**: 479-487.

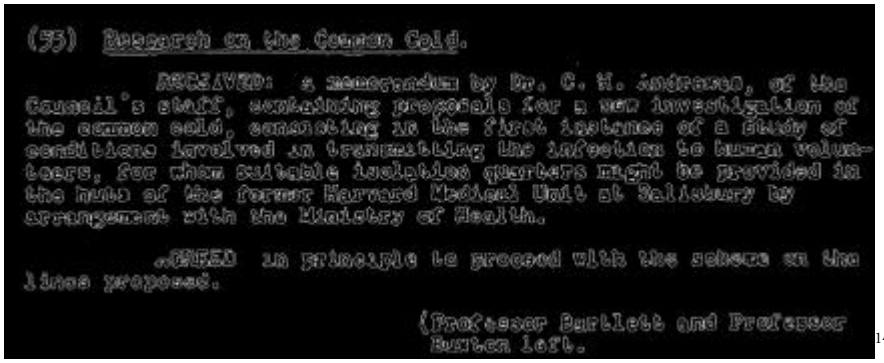
[13] Smith W, Stuart-Harris C H. (1936) Influenza infection of man from the ferret. *Lancet* **ii**: 121–123. See Tyrrell D. (1998) The discovery of influenza viruses. In Nicholson K G, Hay A J, Webster R G. (eds) *Textbook of Influenza*. Oxford: Blackwell Healthcare Communications, 19-26.

chimpanzees and human volunteers, very strictly isolated. They were put in cubicles, everything that they touched and was fed to them was all sterile and they were able to show by these rigorous experiments that there was something there which was infectious, which caused this typical disease in man, and which would pass the filter, a bacteria-tight filter. This was the experiment that showed there was a virus present. They then went on to grow the virus as they thought, in the tissue cultures of the day, and people like Dr Flewett, sitting next to me today, will no doubt remember these. It was minced up tissue in broth covered with paraffin, which is certain death for living cells which viruses must have if they are to grow, but it's also rather irritating stuff. With that powerful instrument, the retrospectroscope, you can see what happened. They put this rather irritating material up people's noses, or monkey's noses, and they began to sneeze and snuffle and they thought they'd transmitted the cold. What Christopher Andrewes tried to do in the 1930s was to repeat these experiments in London, and he didn't succeed. However he didn't have such a good system as Dochez had, because in those days he had to use Bart's students going back and forth to lectures (they had to be *pre*-medical students, so they wouldn't do anything dangerous, like giving colds to people on the wards at St Bartholomew's Hospital). They therefore didn't get colds in a clearly defined manner, the way they did when he gave them filtered nasal washes. So he was doubtful of Dochez's findings. But Dochez was very big in medicine and science, while in those days Andrewes was still up and coming, so he never really wanted to say Dochez had got it wrong.

Booth: Well, I think there's one other thing we ought just to ask Dr Tansey about and that's the nature of decision-making in the MRC in 1946. The time span between a Council meeting in March and the first volunteers in July of that year is a timescale that in my time with the MRC would have been unbelievable. Christopher Andrewes was not a director of a division, he was a member of the scientific staff of the MRC at Hampstead, so I presume he then put up a proposal to Harington who was Director, who would have put it to Council, and the man to have convinced at Council would have been the Secretary, who was then Sir Edward Mellanby. Well, how did it happen? I don't know nowadays whether at Mill Hill you just have to put up an idea and the Director can let you get on with it, or what the procedure is?

Tansey: Well, we could ask the present Director [Sir John Skehel FRS], who is here with us today. [Laughter] Certainly, what happened in 1946 is that Andrewes wrote a report that presumably went to Harington, I don't know I have ever seen that it did go to Harington, but I have found it in MRC records. Here is a copy of the MRC minutes,

MRC Minutes of Council: 15 March 1946, MRC 46/54


(55) Research on the Common Cold.

RECEIVED: a memorandum by Dr. C. H. Andrewes, of the Council's staff, containing proposals for a new investigation of the common cold, consisting in the first instance of a study of conditions involved in transmitting the infection to human volunteers, for whom suitable isolation quarters might be provided in the huts of the former Harvard Medical Unit at Salisbury by arrangement with the Ministry of Health.

AGREED in principle to proceed with the scheme on the lines proposed.

(Professor Bartlett and Professor Burton left.

[14]

this is the approval of the proposal. You can see the length of the report: it says that they received a report from Dr Andrewes on the Council staff containing proposals for a new investigation of the common cold, consisting in the first instance of a study of conditions involved in transmitting the infection to human volunteers. Suitable isolation quarters might be provided in the huts of the former Harvard Medical Unit at Salisbury, by arrangement with the Minister of Health. The next line says, 'Agreed in principle to proceed with the scheme on the lines proposed.' That was 15 March 1946, and according to Tom's [Keith Thompson] book,[15] I think it was 17 July 1946, that the first volunteers arrived.

Dr Owen Lidwell:[16] I think one simple thing that should be made clear is that the MRC at that date was a very much smaller body. I have a photograph of the total staff of the NIMR in 1940 and it comprises under 40 people. It was much quicker to do things.

Tansey: Yes, at that time of course, 1946, the NIMR was still at Hampstead, it hadn't been involved in that major expansion to Mill Hill.

Sir John Skehel:[17] One of the graphs that I was shown at a recent review of the Institute's resources indicated that our budget is continuously increasing compared

[14] Medical Research Council. Minutes of Meeting (15 March 1946, Minute 54), Sixth Minutes Book, 1942–1946, Public Record Office: MRC Archives FD1/5259. Reproduced with the permission of the Chief Executive of the Medical Research Council.

[15] Thompson K R. (1991) *Harvard Hospital and its Volunteers: The story of the Common Cold Research Unit*. Warminster: Danny Howell Books.

[16] Dr Owen Lidwell (b. 1914) was a member of the scientific staff of the National Institute for Medical Research at Hampstead from 1939 to 1946, then as Medical Research Council external staff at Harvard Hospital from 1947 to 1950. In 1952 he joined R E O Williams to form an Air Hygiene Unit within the Streptococcus and Staphylococcus Reference Laboratory at the new Public Health Laboratory Service laboratories at Colindale and remained there from 1952 until his retirement in 1978. From 1978 to 1983 he returned to Harvard Hospital with a research grant and retained an office there until the closure of the unit. See Williams, R E O. (1985) *Microbiology for the Public Health*: *The evolution of the Public Health Laboratory Service 1939–1980*. London: PHLS, 52–53.

[17] Sir John Skehel FRS (b. 1941) has been Director of the National Institute for Medical Research since 1987 and of the World Influenza Centre from 1975. He joined the scientific staff of the NIMR in 1971 and was Head of the Division of Virology from 1984 to 1987.

with the MRC's. But actually, when we look at how the budget has changed since the MRC started and when the Institute was its only source of expenditure, it's gone precipitously down, so that's my favourite graph. [Laughter] In the 1940s we were clearly a more substantial component of the MRC.

Tansey: It changed a great deal in 1945–1946, because there was a policy decision in the MRC to set up research units and I think this was obviously to the detriment of NIMR.

Booth: I think in 1946 there were really only two MRC units, or maybe more.[18] There was Carmichael at Queen Square, and Grant at Guy's, and I suppose they must have taken a policy decision to develop new units. In Himsworth's time between 1949 and 1969, I think the unit numbers went up to over 80. They were an important development in that post-war period. I think it is fascinating to see the speed at which things happened and I think that was the case in those days, that the Secretary of the MRC could take a decision and get on with it and things happened.

Dr Peter Williams:[19] My only qualification for saying anything at this meeting is that I was a member of the Head Office staff of the Medical Research Council from 1955 to 1960. That was Himsworth's time, but I don't think that things had changed greatly. It was a small office and could take speedy decisions. Harington would have rung up Mellanby. Mellanby would have said, 'Good idea, I will get Landsborough Thomson to put it on the agenda for our next meeting, if you will let him have some details.' The Council members would have discussed the proposal, without reference to expert panels and peer review and made up their own minds. They had faith in their own authority if they received a good proposal, and did not run around trying to spread the responsibility. So a decision could be taken in a very short time.[20]

Booth: Well, I think that's an important point to establish – the MRC framework in which this was taking place in medical science. I think we could probably move on from that introduction. We go on to James Lovelock who was an early scientist at the Unit and worked particularly with hygiene. Betty Porterfield, James Porterfield's wife, was also with him in the early 1950s.

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[18] op. cit. note 11 above, Appendix C, MRC Research Establishments, 352–370.

[19] Dr Peter Williams FRCP (b. 1925) was medical officer on the headquarters staff of the Medical Research Council from 1955 to 1960. He joined the Wellcome Trust in 1960 and was its Director from 1965 to 1991 and Director of the Wellcome Institute for the History of Medicine from 1981 to 1983.

[20] Sir Edward Mellanby FRS (1884–1955) was Secretary of the Medical Research Council from 1933 to 1949; Sir Harold Himsworth FRS (1905–1993) was Secretary of the MRC from 1949 to 1968; Sir A Landsborough Thomson was Second Secretary of the MRC from 1949 to 1957, undertaking special duties from 1957 to 1970.

Dr James Lovelock:[21] Fifty-six years ago I joined the National Institute for Medical Research at Hampstead at the age of 21. I was a research assistant to Robert Bourdillon, that was my appointment. They were pioneering the subject of air hygiene in those days. That whole Institute had a wonderful atmosphere. Nowadays I suppose it would be called elitist in many ways, but I think that was a good thing, because it produced lots of good science. Bourdillon and Lidwell were wonderfully inventive and produced instruments like the slit sampler which was quite novel.[22] It was a way of measuring the number of bacteria-carrying particles in the air at any given time – they could have timed histories of what was happening in any situation where infection might be being transferred. It's a pity it didn't work with viruses, since it was dealing with pioneering work, it was fine stuff. Obviously, I can't go on telling you of all the wonderful things that happened at Hampstead and I do hope that Tilli will come and see me sometime, because I am so delighted that she is preparing a story, an account of what happened at the two National Institutes, before we are all dead. There was so much that went on there that was wonderful stuff and the output was phenomenal, that I think it should be recorded.

Anyway I think the only virus-like thing that I have to mention is that during the War one of the problems that was tackled at the National Institute was that of typhus, particularly a desire to produce a vaccine for scrub typhus which it was thought that troops entering South-East Asia might encounter.[23] They didn't know about the atom bomb then. Talking of a ferret sneezing and people catching influenza, it was much more deadly and much more serious at the old Institute. Cotton rats I think were the animals then used, and an awful lot of people caught the laboratory typhus and then the more serious one, I've forgotten which one it was, and it was rather scary, before people went on to work on scrub typhus, a disease where all laboratory infections so far as I know were fatal, but they did and I think we helped a little bit in tracing the source of the infection. It turned out to be the cotton rats sneezing in their cages after they'd been taken from the closed-circuit ventilation system.

Anyway I won't go into any more of that, because we are supposed to be talking about Harvard Hospital. At the end of the War, Owen Lidwell and I were moved to the London School of Hygiene, to form a kind of air hygiene unit. We

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[21] Dr James Lovelock FRS (b. 1919) has been an independent scientist since 1964. He was a member of the scientific staff of the National Institute for Medical Research from 1941 until 1961, working at the MRC Air Hygiene Unit located at Harvard Hospital from 1949 to 1951.

[22] See Bourdillon R B, Lidwell O M, Thomas J C. (1941) A slit sampler for collecting and counting airborne bacteria. *Journal of Hygiene* **41**: 197–224.

[23] Dr James Porterfield wrote: 'We now know that typhus fevers are caused by *Rickettsiae*, which are intracellular bacteria, not viruses. Andrewes, Stuart-Harris and others developed laboratory infections while trying to produce typhus vaccines, so the hazard James Lovelock refers to was very real. In *The Natural History of Viruses* (op. cit. note 45 below) there is a chapter covering typhus under the heading "Not really viruses"!' Letter to Dr Tilli Tansey, 31 January 1998.

felt it was a temporary affair, but we were not privy to what was going on in the MRC, we weren't quite tuned in at that time. And then suddenly, after a year, we were summoned to Hampstead and in Sir Charles Harington's manner everything was done very quickly and decisively. It was, 'Can you go down to Harvard Hospital next week?' and this whole affair started with a matter of free board and lodgings at this Harvard Hospital. We were having a big struggle on a small income with two children near Hampstead, and the prospect of moving to Harvard Hospital where all was found, all board and lodging I think for £5 a week in those days, was a temptation that could not be resisted.

And so we went there and all sorts of things began. One of the things I remember most fondly about the days at Harvard Hospital were visits from the parent institute in London of Christopher Andrewes, Forrest Fulton, and other scientists, and there would be the most long and intensive discussions on the virology of the problem. Andrewes had a wonderful trick of suddenly coming into one's lab in the afternoon and saying, 'I say, would you like to go for a walk in the New Forest?' He had a car and, of course, in those days very few people did, and we would be driven into the New Forest and he would be carrying his butterfly net, because his side line was entomology,[24] and there whilst walking along the path, one would talk about what experiment should be done next on the common cold. I think he actually used me mainly as bait, I couldn't think of any other reason for it. In a short slot of time it is difficult to think of anything except the odd things which happened. One of the odd things were the claims by an American scientist, Ward,[25] that he had grown the common cold virus on the membrane of hen's eggs. Attempts were made to repeat the work at the Unit, but it never worked, nothing ever happened. Then allegedly infectious material was dispatched from America and produced colds. It says something of the gentlemanly nature of the people there at that time that it never occurred to them that it might be one of those bits of scientific fraud that we hear so much about nowadays, and I am afraid that I was the one that, having perhaps grown up in a somewhat rougher background in Brixton, suggested that maybe they should look for human protein

[24] Andrewes' interests and achievements in entomology are discussed in Tyrrell D A J. (1991), op. cit. note 5 above.

[25] Dr Thomas Ward (b. 1911) was Assistant and Associate Professor of Microbiology at Johns Hopkins between 1945 and 1956; Professor of Virology at the University of Notre Dame and Associate Director of the Lobund Institute from 1956 to 1960. From 1960, he was Director of virus and production research, Microbiological Associates Inc, Washington DC, and later at Rockville Medical Associates, Rockville, MD. Dr James Porterfield wrote: 'To my knowledge, Ward published two papers on his common cold studies: Ward T G, Proctor D F. (1950) Isolation of a common cold virus in chick embryos and the clinical manifestations it produces in human volunteers. *American Journal of Hygiene* **52**: 91–106. Ward T G. (1950) The use of radioactive phosphorus in studies of chick embryo infections with a common cold virus. *American Journal of Hygiene* **52**: 106–132. Both papers refer to "strain WW of a common cold virus", and egg-passaged WW virus was the material tested at Salisbury.' Letter to Mrs L Reynolds, 31 January 1998.

and this was greeted with absolute shock by Andrewes and everybody else. Nevertheless they did it, and sure enough...

Booth: Now let's get that quite clear. What was the significance of the human protein?

Lovelock: Only that I thought that what had been sent over from America was not an egg culture, but just straight washings from the nose. The lab assistant there was blamed. It was an unsatisfactory affair. One can't really condemn them totally because we don't know what went on in his lab, but it's the kind of story that keeps surfacing in America in recent years.

Booth: And obviously it faces us with a standard historical conundrum of whether it was a 'cock-up' or a 'conspiracy' – probably a cock-up rather than a conspiracy, because people are very bad at being conspirators.[26]

Lovelock: One of the interesting things that we did at Harvard Hospital, when I say we, it was the whole group, there was Keith Dumbell,[27] Edward Lowbury [28] (he's not here today) and Owen and myself, was to see if we could quantify the transfer of infection from somebody with a cold to a recipient. What we did with the volunteers was to arrange that a fluorescent tracer was introduced into their nose, when they had a runny nose, and then follow the transmission of the fluorescent material around and in many ways it was quite illuminating. It showed very clearly that large quantities of secretion could be transferred across from a volunteer with a cold to a potential recipient by direct contact. The amount transferred on fomites was at the milligram level, whereas the quantities that could be transferred by airborne particles were way below microgram quantities. This led

[26] T H Flewett wrote: 'When I was at the NIMR a press report appeared purporting to show that a hydroxy analogue of sulphathiazole had an inhibitory effect on polioviruses. CHA [Sir Christopher Andrewes] asked me to investigate. I went along to the Chemistry Department. Could they make some for me? Would 7g tomorrow be enough? I was sent off to try this in mice using a very similar-to-polio mouse virus. No joy. It didn't work. We didn't publish our results, because about five papers appeared in the *Proceedings of the Society for Experimental Biology and Medicine* to the same effect but before we could have got ours out. In the early 1950s, publication in the UK was much slower than in the USA. Technicians were employed in some places in the USA in those days (and later, as I discovered, in Germany and in Sweden) to do all the bench work. In the early 1960s I had a very well academically qualified German medical veterinarian looking for a job in my lab. He came from a famous centre in Germany. But he hadn't a clue about how to do lab work: I even had to show him how to hold a pipette! Everything in his previous lab was done by technicians! In the above case, I think that the technician told his boss what he thought his boss might like to hear; and his boss published what he had been told, without further checking. He made the mistake of holding a press conference about it before it was even properly published. It ruined him. So I suspect that Thomas Ward's material may have been adulterated, without his knowledge, with throat washings.' Letter to Dr Tilli Tansey, 9 September 1997.

[27] Dr K R Dumbell was a member of the scientific staff of the MRC Common Cold Unit from 1947 to 1952. Unfortunately Dr Dumbell was unable to attend the Witness Seminar.

[28] Dr E J L Lowbury was a member of the scientific staff of the MRC Common Cold Unit from 1947 to 1949.

to the common cold experiments at Harvard where children with colds were put on one side of a small room and they were separated by a blanket from the volunteers on the other side and the air was stirred vigorously. No colds were transmitted under those conditions, but when the children played cards with the volunteers, they were transmitted fairly freely. This was very useful work. Unfortunately very little of it was published and it wasn't really done on a large enough scale to be statistically sound. There was a tendency in those days, I think, for enthusiasm to rule. Everyone from the seniors downwards was carried away with enthusiasm to find answers, instead of plugging away and getting something very sure.

I spent some of my time there inventing, because it was a little bit of a scientific vacuum to work in. There was nobody really to tell you what to do, and one of my interests was invention. I invented a device, an ionization anemometer that was so sensitive it could measure air speeds as low as a foot a minute and this was very useful in habitability measurements. Its justification in measurements connection with the common cold was to help to dispel the idea that draughts could cause colds. You had to have something to measure draughts with. Well, this would certainly measure draughts, there's no question about it, but no controlled experiments were done using this instrument. It was however used in a strange site and that was on HMS Vengeance doing the cold-weather cruise in 1949 in the Arctic. The Royal Naval Personnel Research Committee (RNPRC) were interested in the habitability of the mess decks on war ships.

Booth: That was then under the chairmanship of G L Brown, Professor of Physiology at Oxford, wasn't it? Was he involved in that himself?

Lovelock: He was involved in obtaining permission for me to travel on the ship but was not involved with the research done on the ship. The research was published as a report prepared for the Warship Ventilation Panel of the Climatic Efficiency Subcommittee of the RNPRC in April 1949. The title was 'Air hygiene, heating and ventilation in HMS "Vengeance" during the British Cold Weather Cruise 1949'.

Booth: We were talking about the schoolchildren one side of a blanket and so on, and one of the things that's always taxed historians of infections is the distance between individuals which will determine infection. I think that with smallpox most people would agree that you have got to be pretty close, maybe three feet or so.

Lidwell: Sorry to interrupt at this point, but there are a number of reports which suggest a different point of view; that the infection can be carried over substantial distances. These are discussed in the latest edition of Topley and Wilson. The most

detailed study is that from a German hospital where infection spread throughout the building.[29]

Booth: That's smallpox. But the common cold, let's take that. Was there anything about the minimal distance or the maximum distance that you can transmit it?

Lovelock: I don't think you do. Not in that sense.

Booth: You mean you chaps had all this money from the MRC all that while, and you can't answer a simple question like that! [Laughter]

Lovelock: For what it's worth, the experiment I described suggests that close contact is needed to transmit the common cold and therefore airborne infection doesn't come into it. I would like to have seen it done though – at least ten times, not just two or three.

Booth: Now Betty Porterfield, you were there at that time. Do you want to comment?

Betty Porterfield:[30] Nothing important to add to what Jimmy [Lovelock] was saying.

Booth: You entirely support what he said?

Betty Porterfield: As Jimmy has just said, it was a place full of enthusiasm and as a young student I was delighted to work with Jimmy and I had his guidance and it was full of fun all the time.

Booth: But did you feel intellectually isolated, which I think was a point our speaker was making.

Betty Porterfield: Jimmy encouraged going up to MRC at Mill Hill[31] frequently to meet people and read at the library, so that we didn't get too isolated.

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[29] See Lidwell O M. (1990) The microbiology of air. In Linton A H, Dick H M. (eds) *Topley and Wilson's Principles of Bacteriology, Virology and Immunology*. *I. General Bacteriology and Immunity*. 8th edn. London: Edward Arnold, 226–241, particularly 235. Fenner F, Henderson D A, Arita I, Jezek Z, Ladnyi I D. (1988*) Smallpox and its Eradication.* Geneva: WHO, 192–193 on the Meschede Hospital airborne spread in 1970.Wehrle P F, Posch J, Richter K H, Henderson D A. (1970) An airborne outbreak of smallpox in a German hospital and its significance with respect to other recent outbreaks in Europe. *Bulletin of the World Health Organization* **43**: 669–679.

[30] Miss B M Burch, later Mrs Porterfield, was a member of the scientific staff of the MRC Common Cold Unit from 1950 to 1951.

[31] Mill Hill refers to the National Institute of Medical Research which relocated there from Hampstead in 1949.

Booth: So the Mill Hill link was crucial in preventing intellectual isolation. There's another example of that in the MRC and that is the foundation of Thomas Lewis's Department [of Clinical Research] at University College Hospital, which of course never developed close links with Hampstead at all really, but your unit did.[32]

Lidwell: Well actually, Sir Christopher [Andrewes], of course, was a major link in that context.

Booth: So he was an active Director?

Lidwell: I think so.

Tyrrell: Can I add a couple of things? One is that I think it should be made clear that the Common Cold Unit was in some ways a rather atypical MRC unit because it was really just an extension, a field station so to speak, of Sir Christopher Andrewes's department at Mill Hill, and at Hampstead before that. Therefore, because of the sort of people around, there was a constant interchange of ideas and enthusiasm, practical cooperation, whereas the other units to which you referred, and I think there were about ten formed at about the same time, were quite separate and didn't actually have a research parent in the same way that we had. The second point that I would like to make is, when Jimmy [Lovelock] and I were talking the other day, we almost could recite the same little rubric together, because there was a particular atmosphere about the sort of direction that Sir Charles Harington gave which meant that you could actually take advantage of this relative isolation and go off and try out ideas you'd just had. Well you tell your own story, because you apologized to Sir Charles like I did, saying, 'I am not doing something which is actually concerned with colds'.

Lovelock: Can you now prompt me a bit more David? He said something like, 'It doesn't matter to me as long as it's good science'. Well, this relates to two directors, the one before Sir Charles Harington was, of course, Sir Henry Dale, and I am old enough to have been there in his time and I vividly remember there was a coffee room at the old institute at Hampstead and it was a place only for scientists. Senior administrators and secretaries didn't like it a bit, that it was for scientists only, and a great deal was discussed there and I used to listen intently to the other scientists and learnt an awful lot. I remember Sir Henry Dale saying one day, 'Well you know in science, it doesn't matter a damn what you do, as long as you do something and keep your eyes open' and this sustained me at Harvard Hospital and, similarly as David says, Sir Charles Harington's view was quite similar and he

[32] The MRC Department of Clinical Research was directed by Sir Thomas Lewis at University College Hospital Medical School, London, from 1919 to 1945. The Department was disbanded in 1974 on the retirement of its second Director, Sir Edward E Pochin. op. cit. note 18 above, 353.

would always encourage you to use your own judgement as to whether a course of work was scientifically worth doing rather than expect to get directions from him.

Booth: Now let's just get Sir Christopher's position clear. At the end of the war, 1946, he was a member of scientific staff. At what stage did he become a divisional director? Did he have a division of his own later, of which the Common Cold Unit was part?

Tansey: The Hampstead institute wasn't structured in the same way at that time. If you look at the staff handbooks and the annual reports, there are lists of departments, but it doesn't seem, from talking to people of the time, that it functioned in that way.

Lovelock: He was effectively head of, I don't know what the division was called, whether it was called virology or bacteriology, when I went there, because as a youngster when I came in I was introduced to him and to Sir Charles Harington as the two 'sort of' supervisory persons in charge.[33]

Tansey: But there weren't strict divisional demarcations at all.

Lovelock: It was like the Quaker meeting. You were a member of the scientific staff. If you were a member of the scientific staff that was quite something.

Booth: You could stand up and say what you wanted. But I have always felt that the divisional structure, this may or may not be true, was regarded as rather rigid in later years. It became accepted in Himsworth's time rather than Mellanby's, is that right?

Tansey: It certainly had something to do with moving to Mill Hill, with the expansion of Mill Hill, compared with Hampstead.

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[33] Dr James Porterfield wrote: 'The gradual emergence of virology as a separate discipline is reflected in the "drift" of the name of the Department or Division under successive heads. What was originally the Department of Bacteriology under Douglas became the Department of Experimental Pathology and Bacteriology under Laidlaw, and later the Division of Bacteriology and Virus Research under Andrewes at Hampstead. After the move to Mill Hill the name changed to the Bacteriology and Virology Division under Andrewes and this title prevailed in 1961 and 1962 when Isaacs succeeded him and for two more years under Pereira. By 1965 there was a major "shift" or "recombination" and the name was changed to the Division of Bacteriology, becoming the Division of Virology in 1968 for the remainder of Pereira's leadership and under later heads. Dr W C Russell shared Pereira's interest in adenovirus structure and replication and succeeded him in 1974, being followed by Dr J J Skehel (1984 to 1987 and 1990 to the present). Dr R W Honess joined NIMR in 1977 and began his work on *Herpes saimuri*, for which, by the time of his premature death in 1990, he had established an international reputation. He was Head of the Division between 1987 and 1990.' Letter to Dr Tilli Tansey, 31 January 1998. See also Porterfield J S. (1995) Famous Institutions in Virology. The National Institute for Medical Research, Mill Hill. *Archives of Virology* **140**: 1329–1336.

Booth: So the space allocation at Mill Hill would determine it. And what year was that – 1948?

Tansey: 1949. They started moving in 1949, and had all moved by 1950.

Tyrrell: I remember the thing being explained to me when I first got involved, because by then Mill Hill was quite big and they had to subdivide it. It was divided into divisions. This was for administrative convenience, but when it came to deciding what to do and how to do it and who to do it with, you ignored all the boundaries. This was actually very beneficial, for instance because Christopher Andrewes didn't believe in chemistry, he never thought we would have a chemical handle on viruses. Fortunately people who saw things differently were able to go and work in Tommy Work's department,[34] officially working on chemistry, but they were still studying virology, and people like Klemperer and others, did that sort of thing. It was a very beneficial scheme. Chris [Booth] and I tried to reproduce it when we went to the Clinical Research Centre at Northwick Park, we had the same view. It was perfectly alright for me to go and collaborate with the man who was called a biophysicist, but who happened to have the electron microscope and knew how to use it. There was complete freedom in that way and, I think, did us all a favour.

Lovelock: I think that was the secret of its success.

Tansey: I think you have to remember, if you think of Hampstead, there wasn't even a director until 1928 when Henry Dale was appointed. For many years, each individual member of staff had been personally accountable to Council.

Tyrrell: That's right, you didn't go through a director at all.

Booth: I think we can move on from this. Owen Lidwell was very much involved with the same period.

Lidwell: After this interruption, it becomes quite confusing to put one's oar in at the appropriate places. I joined the MRC on the auspicious day of 1 September 1939. As it was a Sunday and the day war was declared, I didn't turn up until the following day. But this fact did of course have an influence on all the subsequent activities that we indulged in. After a few months, what I had come to do with Dr Bourdillon faded into the background. I had a background in physical chemistry and I took my doctorate in what was proton transfer reactions. That doesn't sound very appropriate for dealing with cross-infection problems, but, in fact, the department in Oxford where I served as a demonstrator for a time, was known

[34] Dr Thomas Spence Work (1912–1997) was appointed to the scientific staff of the NIMR in 1938 and was Head of the Division of Biochemistry from 1956 to 1977.

locally as the soap-box school of chemistry and that, I think, will give you some idea of the sort of adaptability, and an ability to construct one's own bits and pieces, which as Lovelock has commented on already, was a considerable feature of our early work in this field.

When I joined the MRC at the start of the war, there was considerable concern about the possibility of epidemics following the disruption and air-raids, and this was the sort of thing that set us off onto cross-infection problems. It was just about the time when W F Wells in America had reactivated the notion of airborne transfer of diseases and had conducted experiments in schools, some of which claimed to show that with ultraviolet light you could prevent the transfer of things like measles.[35] So what we started doing was looking at the nature of the particles which might be expelled from people's upper respiratory tract. We took flash photographs of coughs and sneezes. We realized rapidly that the particles are not like those that we have been talking about, small droplet nuclei which floated about forever and didn't settle. They did settle. We developed, as James [Lovelock] has already said, a sampler for them, a slit sampler, and then we did a whole lot of studies on a variety of bactericidal agents in the air – hypochlorite, ultraviolet light, a whole range of hydroxyacids and other things, all of which worked to some extent, but they were much less effective against naturally dispersed material, than they were against sprayed culture, which was what most people had tested these things against up until then. In fact, we used a thing called a spraying spit as our test object. You gathered the saliva behind your lips and squirted it out at high velocity. This produced much more realistic particles for testing against, and what it showed was that they were not killed very easily and that the larger particles among them were not large aggregates of many bacteria, but masses of gooh in which were embedded one or two bacteria, and this gooh was highly protective.

Booth: Protective to what?

Lidwell: Protective to the bacteria. So it was in fact much more difficult to kill them than other people supposed. Now that was roughly the point at which I came down to Harvard. Dr Bourdillon retired from that field and went off on forays of his own, and left James [Lovelock] and me rather in the air, and we were shunted down to Harvard.[36] I actually got onto a fairly positive piece of work fairly early – almost at once – which continued our interest at the NIMR, where we tried ultraviolet light in half a dozen schools in Southall. This involved about 3000 children being continuously monitored. Half the school rooms had ultraviolet light in them and half didn't. We monitored their diseases and we carefully

[35] Wells W F, Wells M W. (1936) Airborne infection. *Journal of the American Medical Association* **107**: 1698–1703; *idem* Airborne infection: Sanitary Control. ibid. 1805–1809.

[36] Bourdillon R B, Lidwell O M, Lovelock J E. (1948) Studies in air hygiene. *Medical Research Council Special Report Series*, no. 262. London: HMSO.

monitored the ultraviolet light to make sure it was of a reasonable intensity and we also took bacteriological samples. This went on for about three years. The effect on the total bacteria in the air was very small, although if you took *Streptococcus salivarius* as an indication of respiratory contamination of the air, then ultraviolet light reduced this to about one-third. But there was still no effect on the general disease level among those children; with the exception of one or two specific diseases, which formed a very small fraction of the total, things like asthma, chickenpox, scarlet fever, were all reduced quite significantly, but they were a tiny fraction of the actual disease experience of the children.[37] The most interesting thing from the point of view of scientific study was that we obtained a very good correlation between the secondary attack rate of measles in the classroom and the level of *Streptococcus salivarius* air contamination in that room, which was the best evidence, that there has ever been I think, that in fact measles was transmitted in those classrooms by an airborne route.[38]

Booth: Tell us, when did the term 'droplet infection' come in?

Lidwell: Immediately preceding the war, the late 1930s. It came from W F Wells in the States, who talked about droplet nuclei. But he was aware that not all of these were so small that they remained suspended indefinitely. He knew that they did settle at a rate dependent on their size.

Booth: A concept you were aware of?

Lidwell: Oh yes, that's what stimulated Bourdillon, I think, at that moment to step out in that direction. Of course, the idea of using *Streptococcus salivarius* as an index of air pollution from the respiratory tract goes way back to Gordon at the beginning of the century.[39] So that was the first thing that I got involved in and that prevented me being too much at a loose end at that time. There was a real danger that one might be, having been detached, from any direction and left to carry on on one's own. The next thing that came up, which was mentioned in our briefing for this meeting was the question of dust. Dust was considered to be a

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[37] Air Hygiene Committee. (1954) Air disinfection with ultra-violet radiation. *Medical Research Council Special Report Series*, no. 283. Prepared by Lidwell O M, Reid D D, Williams R E O. London: HMSO.

[38] Reid D D, Lidwell O M, Williams R E O. (1956) Counts of airborne bacteria as indices of air hygiene. *Journal of Hygiene* **54**: 524–532.

[39] Dr Lidwell wrote later: 'I doubt that he used the specific term *Salivarius*. The classification and nomenclature for the streptococci of the mouth has undergone several changes during this century. The strains found in the air were analysed by Williams R E O, Lidwell O M, Hirch Ann. (1956) The bacterial flora of the air of occupied rooms. *Journal of Hygiene* **54**: 512–513.' Letter to Dr Tilli Tansey, 10 December 1997. See Gordon M H. (1904) Report on a bacterial test for estimating pollution of air. In *Supplement to the 32nd Report of the Local Government Board: Report of the Medical Officer for 1902–03*, Cd 2213. London: HMSO, 421–471. In *British Parliamentary Papers*, Session 1904, Vol. 26.

serious problem in hospital as an infection transfer agent and so Dr Lowbury and I collected samples of dust from a variety of sources and exposed them at different humidities to different kinds of illuminations. The results were not unexpected. First of all, the dust in dry, dark conditions. The bacteria, including things like *Staphylococcus aureus* and *Streptococcus pyogenes* survived for longish periods, 20 days or more. Which seemed to imply that if you were cleaning a place out properly the half-life hardly came into the situation. It was a difficult study, because the samples were so unhomogeneous. If you took a sample and divided it into 20 portions, the variation between the portions was so enormous that any statistical analysis became very difficult. But the death rate increased greatly as the humidity was raised. The various illuminations also increased the death rate, up to five-fold. So illumination was a significant factor in the level of bacterial contamination. But I think this work was not very useful, because it became apparent later on that in hospitals the dust was a relatively unimportant vehicle, because it didn't in fact come up and significantly get into the air very easily. And then the third thing which went on when I was there at that time was the study of colds in the Chalke valley. Dr Sommerville organized that and families in villages in the Chalke valley were visited regularly, records of the colds experienced were taken over a period of about two years.[40]

Booth: The Chalke valley – is that near Salisbury?

Lidwell: Five rivers meet at Salisbury and the Chalke valley is the one down which the river Ebble flows, and there's a string of villages all the way up. These were included in the study and the analysis of the data proved more interesting I think than Dr Sommerville had expected. First of all the incidence of colds in those families was very largely affected by the presence of schoolchildren. If there was a schoolchild in the family, the total number of colds suffered by that family was approximately doubled. They introduced colds into the families three times faster than anybody else. Another thing was that the infants picked up colds much more rapidly than anybody else. So we had a picture there, that in this set of virtually isolated communities the school was a centre whereby the infection was being transmitted through the community.

Now these three things were those that mainly occupied my time at Harvard during the three years I was there. There were lots of other little bits and pieces,

[40] Dr Thomas Sommerville was medical officer at the MRC Common Cold Unit from 1947 to 1951. His epidemiological studies of the Chalke Valley involved weekly visits to all the houses in the village of Bowerchalke and were continued by his successors, Dr A T Roden (Medical Officer from 1951 to 1956) and Dr John Field (Medical Officer from 1956 to 1957). See Lidwell O M, Sommerville T. (1951) Observations on the incidence and distribution of the common cold in a rural community during 1948 and 1949. *Journal of Hygiene* **49**: 365–381. Lovelock J E, Porterfield J S, Roden A T, Sommerville T, Andrewes C H. (1952) Further studies on the natural transmission of the common cold. *Lancet* **ii**: 657–660.

which as Lovelock has indicated would be taking us off onto all sorts of side tracks. I'll come back to his remark about airborne or contact transfer in a moment at the end. But immediately after I left Harvard, which was in 1950, and joined up with Dr (later Sir) Robert Williams at the Central Public Health Laboratory, we started a major study of the epidemiology of the common cold in the offices of the Pensions and National Insurance up at Newcastle. This was a very good place from the point of view of studying methods applied in the workplace to reduce the transfer and incidence of colds, because the whole thing was based on buildings rather like Harvard Hospital, a lot of separate huts, housing about 40 people, each of which was different from another, only in the sense that they dealt with a different part of the alphabet. So we had a large number of very similar rooms, which one could compare. We not only took records in the office, but we also visited the families. The treatments which we applied to these rooms in the hope that they might make some difference were (1) increased ventilation, we put the ventilation in some rooms up from around about two changes per hour, which it was naturally, to about seven, which is quite a substantial ventilation rate. (2) We treated them with various chemical agents and (3) we also used ultraviolet light. Similarly to what I was saying earlier with regard to ultraviolet in the schools in Southall, these treatments only affected the airborne flora to a relatively modest extent, not unlike the schools, there was about a 20 per cent drop in the total and about a 50 per cent or a little more in the number of *Streptococcus salivarius*, which are more directly related to the respiratory tract and, not being a dry material, therefore tends to be more susceptible to these kinds of agents. But we had absolutely no effect on the incidence of colds. This is perhaps not surprising in view of the many other ways in which colds could be transmitted among the people, going back to their homes and travelling away. As far as the families were concerned, in this situation, there was very little effect of schoolchildren. The only people who seemed to be affected by the presence of schoolchildren were mothers who didn't go out to work, who presumably had a much closer contact with their schoolchildren. Another interesting thing about that study, both in families and in the offices, was that studies of serial intervals between successive colds in the same individual showed fairly convincingly that there was a refractory period following a cold, which lasted up to eight or ten weeks. You only got back about two-thirds of the susceptibility in four or five weeks, which seems to imply some sort of systemic thing, it could have been perhaps interferon hanging around for a bit. There was no effect from the use of public transport at all.[41]

The other thing that we did with that study, which was perhaps the most interesting thing of the lot, was we attempted to analyse the seasonal variations in

[41] Lidwell O M, Williams R E O. (1961) The epidemiology of the common cold – I; The epidemiology of the common cold – II: Cross infection and immunity. *Journal of Hygiene* **59**: 309–319; 321–334. Kingston D, Lidwell O M, Williams R E O. (1962) The epidemiology of the common cold – III: The effect of ventilation, air disinfection and room size. ibid. **60**: 341–352.

colds. As everybody knows, you get more colds in the winter, than in the summer in this part of the world. You can correlate that with almost every factor that you can think of, because everything goes up and down, summer and winter. So we did a rather more sophisticated analysis based on the difference in the number of colds in a given week following the smoothed value that we expected, and the difference of the factors from their smoothed values at that time. When these correlations were examined there were two factors which appeared to influence the numbers of colds. These were: a temperature that was lower than expected produced more colds than were expected; a reduced water vapour content produced an increase in colds. The temperature difference correlated most closely with colds that appeared three or four days later, which is the most likely incubation period. The water vapour correlated best with the actual day itself, and so might well be influencing the expression of symptoms rather than the transmission of infection. The sum of these two effects was large enough to account for the whole of the winter/summer difference in the incidence of colds.[42]

Booth: Can I just clarify something. This was work now done from the Public Health Laboratory Service (PHLS) with Sir Robert Williams, is that right?

Lidwell: That's right, yes.

Booth: You then retired and came back to Salisbury.

Lidwell: I did eventually in 1978. When I went to Sir Robert Williams at the PHLS I was still a member of the Medical Research Council external scientific staff, which I remained throughout my working life.

Booth: So you maintained a very close link with the Salisbury set-up?

Lidwell: I did have some link, but not very close. After leaving Harvard around 1950, I was still MRC staff and not PHLS staff, until I came back in 1978 after I retired, when I became PHLS staff paid by the MRC!

Booth: Sounds just the sort of thing that can happen. Dr Flewett have you any comments about that period?

Dr Tom Flewett:[43] I went to Hampstead in 1948 and the egg experiments were still going on. Forrest Fulton had started them and he got the idea, or somebody

[42] Lidwell O M, Morgan R W, Williams R E O. (1965) The epidemiology of the common cold – IV. The effect of weather. *Journal of Hygiene* **63**: 427–439.

[43] Dr T H Flewett FRCP FRCPath (b. 1922) was a member of the scientific staff of the National Institute for Medical Research from 1948 to 1951; lecturer in bacteriology at the University of Leeds from 1951 to 1956; and Director of the Regional Virus Laboratory in Birmingham from 1956 until his retirement in 1987.

got the idea, that although eggs inoculated by every possible conceivable route didn't cause colds when you dropped the product into volunteers, one might perhaps be able to modify the egg, so we tried to make it more susceptible. Forrest and I tried making little cannulae to see if we could perfuse the allantoic cavities with fluids of different pHs but that was really most unsuccessful, because the wretched cannulae kept on getting blocked up; and I don't know why we never thought of putting the eggs into an atmosphere rich with CO_2 or some other means of confusing the biochemistry. But the perfusion system didn't work.

Thomas G Ward, who has already been mentioned, came over with his material. He'd done an enormous amount of egg culture and he told me that there was a useful byproduct from the egg culture – the embryos looked perfectly normal and as his wife was giving a cocktail party, he took the embryos out and fried them all and put them on little bits of biscuit, but that really was about the only useful byproduct. He brought his material over, tried to reproduce it in England and really couldn't, which was rather sad because I am sure he did himself believe in it. I don't believe for a minute that he was trying to falsify his results or produce confusing results; he was most disappointed when it didn't 'go' in England.

The next thing was to try tissue culture and I went off to talk to Honor Fell in Cambridge about setting up explant cultures and thought that the only possible hope was to try human tissues and we wanted, really, tissues of human nasal mucosa. The best way of getting that was to get embryonic material and of course there were no legal abortions in those days, so we had to catch what spontaneous abortions occurred. So somebody rang up someone fairly senior at the Department of Health. Anyway, I got a phone call and they asked, 'What do you want?', so I explained what I wanted. 'Oh I'll put you in touch with a very helpful young chap called Godber'.[44] I explained to young Godber exactly what was needed and he said, 'Right I'll fix it' and every so often I would get a phone call that there was a fresh abortus somewhere or other and I would go haring off in whatever transport happened to be available, perhaps off to Queen Charlotte's on the other side of London, and collect the abortus. Dulbecco's trypsinization technique hadn't come in then, it only came in about 1951 I think; and I would put up explants of human embryo nasal mucosa in roller tubes[45] and the roller tubes had 199 Medium in them, which I had to make up myself, because you couldn't buy it ready made

[44] George Godber, later Sir George (b. 1908) joined the Ministry of Health in 1939, became Deputy to Sir John Charles, the Chief Medical Officer, and succeeded him in 1960. He retired in 1973.

[45] Dr T H Flewett wrote: 'The tubes were rolled, with open mouths (only cotton wool plugs) in an atmosphere of about 4 per cent CO_2 (exhaled, held, breath). I breathed into them, after holding my breath. Epithelium with cilia and fibroblasts did grow out.' Letter to Dr Tilli Tansey, 9 September 1997. C H Andrewes describes this tissue culture technique: 'For many purposes cells growing on the walls of test-tubes do better when slowly rotated on a "roller drum" so that fluid bathing them constantly washes them, bringing food and oxygen and removing waste products.' Andrewes C H. (1967) *The Natural History of Viruses*. London: Weidenfeld and Nicolson, 25.

in those days and had to get some biotin from Rosalind Pitt-Rivers[46] – she complained mightily about the cost.

Booth: Just before we go on, can we just pick up the question of ethics. Nowadays you are not allowed to use embryonic tissue of any sort without full ethical committee approval and so on. What was the position in 1950 and 1951?

Flewett: There was no position at all as far as we were concerned.

Tyrrell: Tom can I ask you a question, because I have long wanted to know how did this work go on in relation to what was happening at Salisbury. I presume you inoculated these cultures when you made them with some virus which came from Salisbury perhaps – and then did you send it back – to Salisbury and what did they do with it there? It's not in any of the papers?

Flewett: Well I can explain why it's not in any of the papers. We did get some colds with the first original culture material. I tried to get subcultures.

Booth: Can we get it quite clear what you are taking. You are taking material grown in tissue culture, where was that done?

Flewett: That was done first of all at Hampstead, but the original infective agent came from Salisbury and it was a single variety of infective agent, because this was the one that was used in all the human transmission experiments.

Booth: Then you sent supernatants back to Salisbury, but none of that work was published?

Flewett: No it wasn't published, because we couldn't get anything to grow in subculture and Sir Christopher [Andrewes] reckoned that really it just wasn't publishable.

Booth: Well, I think there we might just move on to James Porterfield at this point, because we have had a very good background to the common cold, embryology, droplets and all the rest of it. We have heard from Lovelock and Lidwell, and James Porterfield of course a virologist was so much involved in getting that virus to grow.

Dr James Porterfield:[47] Well thank you. I should start by thanking Dr Tansey for calling together this meeting. It's a very nostalgic one for me and for many of us.

[46] Dr Rosalind Venetia Pitt-Rivers FRS (1907–1990) joined Charles Harington at University College Hospital London and moved with him in 1942 to the Medical Research Council's National Institute for Medical Research and became Head of the Chemistry Division from 1969 to 1972. She worked on the biochemistry of the thyroid gland and discovered the thyroid hormone triiodothyronine.

My background was very different from those of James Lovelock and Owen Lidwell. I qualified in medicine 50 years ago in March this year, in March 1947. I graduated at the University of Liverpool, did a house job there and then Professor Downie who was the professor not of virology – there were no professors of virology in those times – he was professor of bacteriology in Liverpool, although he was a world-distinguished expert on smallpox.[48] He invited me to join his department as a temporary assistant lecturer in bacteriology. My intention initially was to spend a couple of years doing an MD in the laboratory and then to return to clinical work. I discussed what I would do with Professor Downie and although in the laboratory he, Keith Dumbell, Kevin McCarthy and others were working on smallpox and an Australian girl, Peggy Hayward, was working on herpes virus, he felt that even if I had intentions of doing virology later, it would be a good initiation if I had an introduction to classical bacteriology. So the subject for my thesis was the streptococci of subacute bacterial endocarditis. What I did was to bleed people as they were having dental extractions and grow *Streptococcus viridans* from their blood; this was related to the pathogenesis of a human heart disease.

Towards the end of my two years I was thoroughly hooked on laboratory work and when Professor Downie spoke to me and said that he had heard from the Medical Research Council that they were seeking a successor to Dr E J Lowbury at the Air Hygiene Unit in Salisbury, and 'was I interested?' I said 'yes' and in March 1949 I came down by train to Hampstead. I found the Institute, was sent up the stairs to Dr Andrewes, as he then was, who was seated at his bench with a syringe in one hand and a mouse in the other. I waited until he had finished inoculating his mice and he then spoke to me and explained the strange things that were going on in Salisbury. The fact that I knew something about oral streptococci may have been slightly to my advantage, but anyhow I was then sent down to see Sir Charles Harington and the same afternoon I caught a train to Salisbury, taking a Thermos flask containing some of Tom Flewett's material which had to be handed over to Dr Sommerville. I arrived at Salisbury station, Keith Thompson met me and took me up to Harvard Hospital. The Thermos flask was duly delivered. The letter that Dr Andrewes had given me for Tom Sommerville remained in my pocket until I got back to Liverpool. I had to post it with some embarrassment later, but the MRC did not hold this against me. In a matter of three or four weeks I received a letter from Dr A Landsborough Thomson appointing me to the unit and I started work there, on 1 July 1949. Now this was,

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[47] Dr James S Porterfield (b. 1924) was a member of the scientific staff of the National Institute for Medical Research from 1949 to 1977 and then at the University of Oxford until he retired in 1989. He was at the MRC Common Cold Unit from 1949 to 1951.

[48] Professor A W Downie FRS (1901–1988) joined the MRC's National Institute for Medical Research in 1939, and was seconded to their Emergency Public Health Laboratory Service lab in Hertfordshire, later Cambridge. In 1943 he was appointed to the Chair of Bacteriology in Liverpool until his retirement in 1966. See Tyrrell D A J, McCarthy K. (1990) Allan Watts Downie 1901–1988. *Biographical Memoirs of Fellows of the Royal Society* **35**: 98–112.

as Owen Lidwell and James Lovelock have said, an interim stage. I was nominally part of the Air Hygiene Unit, but I was expected to take over from Keith Dumbell, my predecessor, as the virologist. He was a 'proper virologist' who knew all about smallpox and respectable viruses; I went round with Keith Dumbell and we collected washings from people with colds. These were filtered and I think that I should point out the importance of these gradocol membranes [the Elford membranes], which had been made at Hampstead by Dr W J Elford.[49] These filters were vitally important in separating bacteria from viruses. Bacteria we could grow; if we couldn't grow anything we called them viruses and that was about as much as we knew about the common cold viruses at the time. The pedigree viruses were filtrates taken from people with 100 per cent colds, meaning clinically unquestionable colds and there were a number of these pedigree stocks in the deep freeze at Salisbury. Some of this material would be taken up to Hampstead to be used for inoculations into tissue cultures or eggs there and then the supernatants from those would go back to Harvard to be tested. Of the other things that were going on, there were still the tail end of some abortive experiments in animals. I think James Lovelock mentioned all sorts of animal experimentation. We still had hedgehogs in the animal house in Salisbury in those days, but they were not sensitive to cold viruses.

Lidwell: And pigs. They were certified unfit for human consumption, so we had them in the unit.[50]

Porterfield: The ritual of the ward round. The medical officer in those days, Dr Tom Sommerville, did a round of volunteers with matron, Miss Macdonald, a very formidable lady, and recorded the score in terms of how much secretion they had, how many handkerchiefs they used, and various other markers.

Booth: Just stop there. The method you used then for measuring the severity of a cold was simply measuring the weight of a number of tissues was it?

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[49] Dr William Elford FRS (1900–1952) was a member of the scientific staff of the National Institute for Medical Research from 1925 to 1952. Dr T H Flewett wrote: 'W J Elford FRS invented these collodion filter membranes. He worked at the NIMR. He was a super chap, always so helpful to me.' Letter to Dr Tilli Tansey, 9 September 1997. See Andrewes C H. (1952–53) William Joseph Elford, 1900–1952. *Obituary Notices of Fellows of the Royal Society* **8**: 149–158.

[50] Sir Christopher Andrewes wrote: 'In several instances we attempted to recover virus from the inoculated animals but found no evidence that virus would survive for even a few days in any of these species. When no symptoms developed in the pigs, members of the staff cast covetous eyes upon them, for at that time rationing was still in force and meat was scarce. But pigs were supposed to be handed over to be slaughtered and dealt with according to official regulations. Fortunately a doctor was found to certify that because of the inocula they had received the pigs were unfit for consumption. Oddly enough, staff members were found willing to take a chance about that!' op. cit. note 6 above, 43.

Porterfield: Not so much weight as quantities. There were several different markers.[51] How many handkerchiefs they used, whether they were sneezing and coughing; these would be recorded for each volunteer and then at the end of the trial these would be totted up. There was a three-day isolation or quarantine period after people arrived, before they were given any material. What they were given was control-positive pedigree material, control-negative material, normal saline, or broth or some fluid not expected to cause the common cold and the third category was the experimental material which could be any one of a number of things, such as Tom Flewett's embryo material or egg culture material. The allocation of which volunteer or pair of volunteers received which material was done by the laboratory people, either Keith Dumbell or myself, and the code was kept in a sealed envelope until the end of the trial. Then this was opened and there were sighs of despair when people realized that nothing very dramatic had happened.

I too would like to say a little about the Tom Ward experiments. I think that I differ slightly from James Lovelock's presentation. My recollection of things was that the material directly from the United States was highly infectious, and produced very respectable colds in volunteers. It was when we tried to propagate the Ward agent in eggs that we failed. I thought at first that this was my incompetence, that I couldn't inoculate eggs properly, so Ward material was sent from Salisbury to Hampstead and egg inoculations were repeated there, but we never got any colds at all, or only extremely questionable colds, with Ward passage material. At this stage James Lovelock raised the query about contamination, and did the tests which showed that the original material from Ward's lab definitely contained human protein, although by the time this had been through a number of egg passages so that human protein should have been diluted out and be no longer detectable. The sad conclusion was that we had been misled.

If I could mention quickly – I had the idea that possibly another source of human nasal material might be from ear, nose and throat surgeons who removed polyps from people's noses. Polyps were fairly readily available and I collected a number of these and did Maitland-type tissue cultures with these.[52] Maitland had been my external examiner when I did my MD so that I was aware of the work that he had done in 1928, but we got nothing out of inoculating polyps with cold filtrates. I also tried grafting bits of nasal epithelium onto chorio-allantoic membranes, in the hope that nasal epithelium would survive longer, and inoculated these. We did get, I think, one positive cold out of a number of experiments, but

[51] Dr James Porterfield wrote: 'See Andrewes C H. (1962) The Harben Lectures, 1961. The Common Cold: I – The Background; II – Recent Laboratory Work; III – Epidemiology and Possibilities of Control. *Journal of the Royal Institute of Public Health and Hygiene* **25**: 31–37; 55–63; 79–88. This gives a clear account of the methods used for evaluating colds and is an excellent review of the whole field.' Letter to Dr Tilli Tansey, 31 January 1998.

[52] See Maitland H B, Maitland M C. (1928) Cultivation of vaccinia virus without tissue culture. *Lancet* **ii**: 596–597.

this clearly wasn't particularly significant and, again, I don't think this appears in any published reports, because it was not repeated or repeatable and the whole of the experience was really rather disappointing. It was left to my successors to have much more success in the propagation of the common cold virus and I think I should close now.

Booth: So basically you reached the stage where you could grow something and you couldn't passage it in successive cultures.

Porterfield: Well no, the Ward material was frozen egg material, which was capable of causing colds in volunteers, but when we passaged from that in eggs we got nothing in volunteers, and when we passaged Ward material further we got nothing. When we passaged our pedigree cold material in eggs we got nothing in volunteers. I also found a source of human embryo material in Salisbury and we did some human embryo tissue culture experiments but again the only colds in volunteers were with control-positive filtrates.

Booth: Well thank you very much for that. This is a very important transitional stage of the story really isn't it?

Flewett: As far as the experiments with the Ward material went, as far as I recall we went to the lengths of getting the exact breed of hen which had provided Tom Ward's white eggs. Somebody suggested that maybe you're not using the right breed of egg from the right hen, so we had eggs imported from the States that were right. I remember them arriving.[53]

Tyrrell: I would like to say two things about this. Firstly, just to add a little detail. It was human blood group substances which were detected and this was a particularly unambiguous test done quite independently and I think Andrewes and his colleagues wanted to be very sure before they faced Ward with this, because it was a very serious thing to say. The other thing is that it strikes me that the Common Cold Unit was doing extremely valuable work here, clearing up what was an incorrect claim in the literature, and whatever the origin of it, it was there, it had been published in *Science*,[54] a very prestigious journal, and it returns me to a theme which Christopher [Booth] and I have discussed before. Sometimes science gets off the track and what is needed is somebody scrupulous who goes over the

[53] Dr James Porterfield wrote: '...but again egg-passaged material proved negative.' Letter to Mrs L Reynolds, 13 September 1997.

[54] Dr David Tyrrell wrote: 'There were two papers in *Science*, which Andrewes in his book, *In Pursuit of the Common Cold* [op. cit. note 6, above, 40–43], implies were also prodding them to work in eggs. I went and checked.... They are: Topping N H, Atlas L T. (1947) The common cold: A note regarding isolation of an agent. *Science* **106**: 636–637. Pollard M, Caplovitz C D. (1947) Experimental studies with the agent of the common cold. *Science* **106**: 243–244.' Letter to Dr Tilli Tansey, 29 July 1998.

ground and says 'this bit's right, that bit's wrong' and on the basis of that foundation people could move forward. Helio Pereira, our mutual good friend, was then able to go ahead in the next years after you had left. He could say 'well, we have got new methodologies which Enders has developed for growing poliovirus and we will put eggs behind us and start trying to grow viruses from colds in this way'.

Tansey: Was Ward actually confronted with this?

Porterfield: He came over, yes, before this was finally negatively sorted out. He was an extraordinary man. What happened to him after that I don't know.

From the audience: He worked for one of the big American pharmaceutical biological firms and was a highly successful entrepreneur in a sense.

Booth: Whatever it was it needed to be shown, as David Tyrrell said. It was a very important staging post, if you like, to the next stage. Other comments about that period.

Skehel: It wasn't something as simple as just adding serum to saline?

Porterfield: No certainly not. That point was considered and we asked Ward specifically what diluents they had used. Had they added human serum as a diluent in their egg inoculations and the answer was no. If I could digress very slightly to Dr Andrewes, Sir Christopher Andrewes, in a more personal way. Our chairman has mentioned that with James Lovelock was a certain Australian girl, Betty Burch, who came and joined him. Sir Christopher had three sons but no daughters, but he gave away as brides three of the Harvard staff, of whom my wife was the first and this was followed by a young lady, Annette Harding, from South Africa who was given away the following year and I can't remember quite who the third bride was, but Harvard Hospital was a very intimate association.

Booth: Might we just put a date on those events?

Porterfield: July 15th 1950 as far as I was concerned. [Laughter]

Booth: I was thinking more of the Ward affair.

Flewett: It was 1950 when Ward came over.

Dr Hugh Thomas:[55] Could I just ask a question. In the areas of hygiene and so on, did you have any liasion with groups like the MRC Pneumoconiosis Unit at

[55] Dr Hugh F Thomas (b. 1952) is an epidemiologist at the MRC Epidemiology Unit, Llandough Hospital, Penarth, South Glamorgan.

Llandough, near Cardiff, or the MRC Air Pollution Unit at St Bartholomew's Hospital, London, run by Professor Patrick Lawther? They were all working in a sense on particle physics and the spread of droplets and I just wondered if you were linked with their occupational hygiene research as well.

Lidwell: I had quite a bit of contact with the Pneumoconiosis Unit from time to time. I don't think it influenced us much. They really got more involved in questions of allergies: allergies spread in ventilation plants and that sort of thing to a large extent. I don't think the pneumoconiosis people ever handled bacteria, they were all into dusts.

Booth: You are thinking of the Air Pollution Research Unit at Bart's on dust pollution.[56] Were you involved with them?

Lidwell: I knew them too. I had contact with Dr Lawther and all these people from time to time. No specific programmes were set up with them. It was more an exchange of ideas and things like that that would be the nature of the involvement. And there was no air hygiene unit as such until I left Harvard and joined up with Sir Robert Williams and then there was a formal designated air hygiene unit which was at the Central Public Health Laboratory.

Booth: There's one other MRC link that I would like to ask you and Porterfield about. The control of trials was very important. The double-blind arrangements that Bradford Hill developed with MRC support between 1946 and 1952 covers the period you are talking about.[57] Was he involved? or other statisticians?

Lovelock: We used 12 or 15 volunteers, of whom about a third would be positive controls and I am sure Owen looked at the figures at the end in a statistical way, but they were not really at that level of significance. They were common sense. You could say this meant something or this didn't mean anything.

Lidwell: I think Harvard took the double-blind trial philosophy thoroughly on board. I am not quite sure where that actually orginates historically. Yes, I had a lot of contact with Bradford Hill and, in fact, I was at the London School of Hygiene for one or two years.

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[56] Group for Research on Atmospheric Pollution, later Air Pollution Research Unit at St Bartholomew's Hospital, London (from 1962, St Bartholomew's Hospital Medical College), 1955–1962. Director, Professor P J Lawther FRCP. op. cit. note 18 above, Appendix C MRC Research Establishments, 361.

[57] Sir Austin Bradford Hill (1897–1991). Hill's first attempts to introduce the concept of randomization in controlled trials were for the MRC. See Wilkinson Lise. (1997) Sir Austin Bradford Hill: medical statistics and the quantitative approach to prevention of disease. *Addiction* **92**: 657–666.

Tyrrell: Following on your point about the design of trials, I think there were two important things that should be said. One was that at the very beginning they had problems in identifying, diagnosing, colds. I think James [Porterfield] was around when that debate was going on. Very mild symptoms would appear and it was a real problem to know whether you should take notice of them or whether you shouldn't. Finally they did have a fairly well-validated way of identifying significant colds, because one sort would occur in the presence of people who had been given drops which were infectious, and other sorts of mild symptoms would occur in people who were given non-infectious material. That was established before I arrived and I thought that was fine. But I was not at one with Christopher Andrewes over the counting – the numbers. My training in statistics was very limited. I had read Fisher's book[58] (which is not the right book to read if you don't know anything about the subject before), but I had also been to some lectures during the war on things like quality assurance and how to tell whether there were significantly more or less faulty items in a production process, so I got the idea of basic counting and statistical evaluation, which was all you needed. When you looked at the sorts of numbers that were coming out of the Common Cold Unit you knew that for most of them there wasn't really any possibility of saying very much more than that there was a *trend* towards being active or inactive material. I was taught a useful lesson some years later when I went back to New York to see my ex-boss at the Rockefeller Institute (Frank Horsfall) who taught me laboratory experimentation and I said the MRC was moving me to Salisbury and I was going to look after the unit which deals with human volunteers as a test for the presence of viruses. He said, 'Tyrrell, remember that in these experiments, one man equals one mouse' and it was a very good lesson to learn. It meant that I didn't agree in the design of the 'quick in and quick out' experiments that you have been talking about, and which you [James Porterfield] were expected to do, I know. But I wanted to say, 'We have got to have a result where p is less than 0.05.' The results would be obtained very laboriously but would be either negative or positive, to a reasonable degree of certainty. Such results were not there and I remember talking to, I think it was you, James [Lovelock], and somewhat sympathetically, you saying that having been trained in the hard sciences, physical chemistry, it was rather difficult to cope with the situation where similar sorts of tests of reproducibility and so on were not applied.

Lidwell: I don't think I felt that sort of problem in fact. Statistics seemed to flow in very naturally into the system as far as I was concerned. I had been handling numbers, of course, for a long time.

Tyrrell: I think you contributed a great deal in the fact that you were able to handle the numbers which came out of the trials of the investigations in the Chalke

[58] Fisher R A. (1925) *Statistical Methods for Research Workers.* Edinburgh: Oliver and Boyd.

Valley. In that sense you are absolutely right, they knew they needed statistics to handle it, you provided them and the whole thing flowed in. It was in the situation when you were doing things which were the equivalent of the sort of experiment which you did with ten mice on a Friday afternoon. You try and work out what the results mean, but you can't get a definite answer. I think James [Lovelock] nods, is that right?

Lovelock: I agree with you wholeheartedly. I think this is the difference. Owen is talking about a different situation.

Booth: Well, thank you very much. Any other comments or contributions? If there are not, we are going to alter the order of this meeting a little bit and thought we'd go on now to Tim Boon, who's going to show us a video. Tim works with Robert Bud at the Science Museum and has a deep interest in the Common Cold Unit for public health reasons.

Mr Tim Boon:[59] What we are about to see is an amateur film which was made by a man called Paul Chapple [60] who worked at the Common Cold Research Unit. This film is one of about a dozen films, more or less 100 photographs, about 30 pieces of lab equipment, accompanied by 40 pieces of volunteer chalet furniture, which we at the Science Museum collected from the Common Cold Unit when it closed in 1990. We have got a fantastic resource for the Common Cold Unit at the Science Museum and a very small part of it is currently on display in our 'Health Matters' gallery at the Museum. This little silent 8-mm film, lasts about eight minutes.

> [**A silent film shown here with Dr David Tyrrell doing the narration**: The film shows volunteers of the 1960s arriving at the Unit, being welcomed and shown to their rooms in the 'hutted accommodation'. They are given informal talks about the trial. They are examined daily for symptoms and signs of colds, and nasal washings are collected to be tested for cold viruses. Apart from this they are free to go on country walks, sunbathe or play games. A few develop colds. At the end of ten days they return home. The film also shows the method of organ culture of respiratory epithelium which was organized and exploited at the Unit. A length of trachea is dissected and carefully cut into small squares, which are attached to the surface of a plastic Petri dish. These are examined by reflected light with a low power microscope and show the quivering epithelial surface of living cells with beating cilia. If cells are

[59] Mr Tim Boon (b. 1960) is Curator of public health at the Science Museum, London.

[60] Dr Paul J Chapple was a member of the scientific staff of the MRC Common Cold Unit from 1963 to 1966. He made two short silent colour 8-mm amateur films of the work of the CCU, now at the Science Museum (inventory: 1990–1994). *Harvard '64* shows the typical experiences of two female volunteers and *Organ Culture* shows laboratory work.

unhealthy or damaged there is no such movement. (During this film staff are seen with mouth-pipetting culture media which was normal practice at the time, but forbidden now.) Using such cultures, human respiratory coronaviruses were propagated and studied for the first time.]

Booth: That gives a very fine flavour of the Common Cold Unit, which I came to know when I was appointed Director at Northwick Park, which was in 1978. And in those far off days the Directors of major institutes within the MRC service had their own personal vehicle and driver, so I could sit in the back of a car and be driven all the way down to Salisbury, have a very nice lunch, because if a Director descended on Salisbury, he always got well fed and then came back home again, it was great fun and it worked extremely well. We now go on to David Tyrrell and Peter Higgins, but just before we do that and as a follow-up to the film I wonder if we could ask Tom [Keith] Thompson, who ran the administrative side of the Unit for so long just to make a comment about volunteers.

Mr Keith Thompson:[61] I was the Salisbury Common Cold Administrator from 1960. Dr Tyrrell is very used to my taking him to task. They mention in the film something about huts, no not huts – hutted accommodation. Earlier it was mentioned the speed with which the Common Cold Unit was set up. Going on from that, we are going right back down to basics at the Common Cold Unit, I joined it four weeks before the first trial. The Unit consisted of 19 acres, 22 huts and one telephone. Sir Christopher Andrewes mentioned the date which trials would start and we were all shocked that we had such a short time to get things ready. Most of us, the staff at that time were very few, were ex-servicemen or ex-servicewomen (Matron) and we didn't look at the clock. There was no 9–5. We got up in the morning and went through until we nearly dropped, getting the furniture and everything ready for the trial. There was a lot to be done. The blackouts were still up, partitions to be put up, plumbing to be done.

From there I go to the volunteers. We were told before the first trial that the VIPs at Harvard were the volunteers. All that's been said here today about experimentation, etc. etc. wouldn't have happened if it hadn't been for the volunteers and in the early days the volunteers were mainly students who came during their vacations. But as time went on, then we had to go further afield. And it was important to get the right kind of person. We know that they enjoyed it and used it as a holiday, but we didn't want kiss-me-quick hats, and sticks of rock. They were sent the details of the experiment and on the whole we did get the right type of volunteer. So let's pay a compliment to the volunteers. There were 2000 of

[61] Mr Keith R Thompson (b. 1926) became a driver for the Medical Research Council in London after his demobilization in April 1946, and was transferred to Harvard Hospital in June 1946, where he later became an administrator until his retirement in 1982. He saw the first group of volunteers into the unit on 17 July 1946 and the last out on 27 July 1989.

them. If anybody wants details, I do have them here – numbers, the kinds of people that came, etc. etc. Dr Tansey is welcome to have them, if you photocopy them and let me have them back.

Booth: Can you just tell us over the years, the total number of volunteers?

Thompson: The total number of volunteers was nearly 20 000, and we had more women than men. If you want details I can delve down into my files.[62]

Lidwell: Following Horsfall's comment to you, that's 20 000 mice, David.

Tyrrell: There was a high degree of recidivism!

Booth: I believe on one occasion there was a honeymoon couple who came and spent their honeymoon there.

Thompson: But for Sir Christopher [Andrewes] we should never have managed it. In the early days he went round to the universities to give a little talk, but he had a contingent of correspondents from London. A bus drove them to Harvard, all 78, and he gave them a talk on the Common Cold Unit, what was to be expected. He said it would be ideal for honeymoon couples and there were some takers, and some made an issue of it.

Booth: Now to the next stage, which is the actual discovery of the viruses.

Tyrrell: I can't actually talk from very close personal observation about the first virus to be grown in the Unit from a common cold washing, but there's a lady here, Donna Chaproniere, who can. The virus (she's much too modest to mention it) was given the initials DC, subsequently it became rhinovirus type 9, but as her name is Donna Chaproniere, you can guess why it got the name of DC. So Donna tell us what happened please.

Dr Donna Chaproniere:[63] I went down to Salisbury in 1952 and worked there for three years. Sometime during the year I caught a cold and, since nobody with a cold was allowed near the laboratory, after having my nose washed out, I went for a lovely walk in the countryside. From these washings came the DC strain of virus. At just about that time we received an aborted embryo (from Sweden, I suspect, for most of the very scarce human embryonic tissue we used came from there, before abortion was legalized in this country). We made roller tube cultures from

[62] Total number of volunteers: 19 911 of which 12 034 women and 7877 men. Total number of repeat visits: 12 112 of which 7225 women and 4887 men. 'Table showing number of repeat visits made by volunteers' from K R Thompson, 13 May 1997.

[63] Dr Donna M Chaproniere (b. 1929) was a member of the scientific staff of the MRC Common Cold Unit from 1952 to 1962.

this material and inoculated it with the filtered washings. Because of the scarcity of volunteers, we usually made about three passages in culture before testing the third for virus multiplication. When this material was tested in volunteers, to our astonishment several came down with colds. This caused great excitement for us and we continued passaging it in tissue from the same embryo. I can't remember how many passages we made before we ran out of tissue. To our great disappointment, when further passages were attempted in later embryos we could detect no further virus multiplication. We spent about a year searching unsuccessfully for a reason for this failure, with the dread in the back of our minds that perhaps this was a virus carried by the first embryo. Then we gave up and froze the cultured material – which we couldn't bear to discard – for future re-examination. It wasn't until some years later, as David Tyrrell will tell you, that he managed to culture it further. That was the only strain of common cold which we managed to cultivate in the three years that I spent at the CCU.

The early 1950s was an important time for both tissue culture and virology: it was the very beginning of the use of cultured tissue by virologists, following John Enders's successful cultivation of poliovirus.[64] Tissue and cell culture until then had been surrounded by mystique and ritual and was demystified and simplified by virologists for use as a tool. It was just at this time that I graduated and applied for a post at the CCU. At my interview, Dr Andrewes (as he then was) told me about Enders's work. As I wanted to learn the technique of tissue culture, I was fortunate to be hired to work under Helio Pereira at the CCU. I actually was much more fascinated by the cultured cells than the viruses and continued to study them for the rest of my career – on one project using the Rous sarcoma virus as a tool to do so. Human embryos were scarce and there were intervals when we had no tissue to work with on the common cold, so we were encouraged to work with other viruses, such as the newly isolated adenoviruses studied by Helio.[65] Since cultured tissue was a potent, convenient and novel system for the study of viruses, a number of virologists came to Harvard Hospital for a week or two to learn the technique from us and I had the great pleasure of teaching them.

Dr Andrewes was a wonderful person to work under. He came down to Harvard Hospital once a fortnight to discuss results and proposed experiments, and to keep up our spirits. Whilst I was there he founded the South Wiltshire Virology Society, to whose monthly discussions at Harvard Hospital came interested

[64] Enders J F, Weller T H, Robbins F C. (1949) Cultivation of the Lansing strain of poliomyelitis in cultures of various human embryonic tissues. *Science* **109**: 85–87.

[65] Dr Helio Gelli Pereira, a Brazilian, was a member of the scientific staff at the National Institute for Medical Research at Hampstead, working at the MRC Common Cold Unit from1951 to 1957, transferring back to the NIMR in Mill Hill. His British wife, Dr Marguerite Scott Pereira, was in charge of the Public Health laboratory in Salisbury. op. cit. note 6 above, 17, 68. Dr T H Flewett wrote: 'Marguerite Pereira was later Director of the PHLS Virus Reference Laboratory at Colindale and after that, consultant to the Government of Brazil on testing of blood transfusions. She was killed in a car crash in Rio de Janeiro.' Letter to Dr Tilli Tansey, 8 February 1998.

virologists and medical men of all persuasions from the area.[66] On his visits it was the duty of the most junior member of the staff, invariably a young lady, to accompany him on a walk for an hour or so after breakfast along the Roman road which ran close to Harvard Hospital, to gather flies for his collection. I think, as James Lovelock said, we may have been there for bait but we junior staff also acted as fairly naive listeners on whom he could try out his ideas and theories. This was, of course, a wonderful way of gaining insight on how to think about experiments. It also made for slow progress down the Roman road and as an antidote to hanging around whilst he swept the bushes with his butterfly net, I began to collect and try to identify the spiders caught therein. This was more difficult than I had anticipated and, discouragingly for me, Dr Andrewes was soon very much better at it than myself!

Towards the end of my third year at Harvard Hospital Dr Andrewes suggested that I transfer to Mill Hill to work with him on myxomatosis, which had just then spread to England. He had been asked to chair a Committee on Myxomatosis, a post to which he was obviously uniquely suited, with his dual interests in viruses and insects. He suggested that I use cell cultures to develop an *in vitro* test for the virus, which could then only be titrated on the skins of rabbits. Following this he was the supervisor for my PhD work on the host specificity of the virus in cultured cells and grafts.

Booth: Thank you very much for that vignette. Now back to David Tyrrell I think.

Tyrrell: Thank you, Donna. It was the first properly documented cultivation of a common cold virus. At the time she was doing that, I was in the United States. I went to school in Sheffield and then went to medical school there and did house physician jobs under Professor Stuart-Harris and I obtained an MRCP, but in those days I couldn't go further up the medical consultant ladder, which was really what I wanted to do, because there were so many ex-servicemen looking for posts and it so happened that the British Army, Navy, and Airforce didn't want me. But fortunately there was money from the assets of the United Sheffield Hospitals which had just been taken over by the NHS and with this I was made a research registrar and I started working on influenza virus under Stuart-Harris's guidance. So in 1951 I became an assistant physician at the Rockefeller Institute and Hospital

[66] Dr T H Flewett wrote: 'At the South Wiltshire Virology Society I met Gerald Woode, then at Compton, in late 1973. He described a virus causing diarrhoea in calves. I realized we had much the same in children. We found his virus and ours were related – something new. We called them rotaviruses. This is just an illustration of how one research programme can lead to others.' Letter to Dr Tilli Tansey, 8 February 1998. Woode was at the Institute for Research on Animal Diseases, Compton, Newbury, Berks. See Flewett T H, Bryden A S, Davies H, Woode G N, Bridger J C, Derrick J M. (1974) Relation between viruses from acute gastroenteritis of children and newborn calves. *Lancet* **ii**: 61–63.

in New York which was a great centre of biomedical research activity, but by 1954 I was back in Sheffield on the MRC external scientific staff in a small new virus research laboratory and looking for new viruses grown in tissue culture, such as adenoviruses. Incidentally, we also turned up a new enterovirus which caused rashes and aseptic meningitis. By 1956 several of our projects were rolling well and we had our first real visiting workers.[67] I certainly didn't expect the Council to do anything about the clause in my contract which indicated that if they wanted to move me they could. But I was sent to see Sir Harold Himsworth and in his office he told me that they wanted me to move to Salisbury and I wasn't attracted by the idea. I'd already been there. I knew Helio Pereira and I knew why it was that it was wise for him to move on to the NIMR. He needed to develop his work on adenoviruses and escape from the frustrations of not growing cold viruses, but in the end I felt that working at the Unit would be a new and interesting experience. This has something, of course, to do with the warm and enthusiastic personality of Sir Harold Himsworth. We thought in fact that the accommodation would be suitable for a growing family and then of course if things didn't go well, we could go back to Sheffield and our own house. I actually thought I was most unlikely to do any better than Helio, he was such a wonderful scientist. I doubted if I would do as well as him, but I agreed provided that we could go back to Sheffield after two years if we hadn't got the problem cracked by then. We didn't move until All Fools Day 1957, we waited for a judicious time!

But in the months before this, I thought about the earlier research that I had done and my own experience and tried to dream up a way of growing this new virus. Now it seemed to me that the virus Helio had grown must be different from the other viruses such as adenoviruses and things that I had been growing and therefore it probably needed to have a new rather specific sort of tissue culture in which the virus would develop as it did in cells lining the nose. While in New York I had made some very simple attempts to grow influenza viruses in roller tube cultures and found that kidney and liver cells worked rather well. And then in Sheffield I found that human embryo kidney cells would grow a wide range of viruses, including adenoviruses and our new enterovirus. However, I didn't want to rely on my own opinion only, so when Stuart-Harris had the great Albert Sabin[68] as a visitor I asked him what he thought. He was quite emphatic. He said, 'We know that any virus that grows in human kidney will grow in monkey kidney. You use monkey kidney.' And he said things in such a way that one didn't argue. I

[67] Dr T H Flewett wrote: 'I was one, just setting up my own diagnostic lab in Birmingham.' Letter to Dr Tilli Tansey, 8 February 1998.

[68] Dr Albert Sabin (1906–1993), a Russian-born US virologist, developed protective vaccines, particularly the oral poliomyelitis vaccine. He became interested in polio research while at the Rockefeller Institute from 1935 to 1939. Dr Saul Benison has written extensively on Sabin's career. See, for example, Benison S. (1982) International medical cooperation: Dr Albert Sabin, live poliovirus vaccine and the Soviets. *Bulletin of the History of Medicine* **56**: 460–483.

had also met John Enders on a few occasions, a very much more gentle character, but I decided that I would write to Boston and ask him for his opinion. He sent me a charming hand-written letter which I am afraid got lost in one of my moves, in which he advised me, probably largely on the basis of his own recent work, to use human amnion cells obtained from fresh placentas.

Now I also had the idea, which had already surfaced at Salisbury, that temperature might be important, so I borrowed a thermistor outfit to explore the question further from the physicist at the United Sheffield Hospitals (you see I knew how to use the equipment that the physicists gave me). I worked out one afternoon that although it fluctuated, the temperature in my nasal epithelium was generally about 33° C. I guessed that the virus would increase in concentration and then decline again and that it would probably produce no degeneration, so we decided to harvest the culture medium at several different intervals, whatever the cells looked like. Now I didn't want to work on the same virus that had proved so frustrating for Donna and Helio, so I thought we should try several new ones, because one of them might grow better than the others. To help us Helio left at Salisbury a present in the form of nasal washings collected when he and his assistant had marked colds and naturally we christened his washings HGP. We produced more colds with it in volunteers and made a large pool of their washings, like the pedigree colds we've heard about already. We proved that the pool contained virus by showing that the pool produced colds when inoculated into volunteers.

With such material we were ready to start our very cumbersome experiment. We thought that we might succeed at first to only a limited extent in any one or two of the many combinations possible. We had three different cell cultures, two different temperatures, two different intervals of harvesting, several different media. So to avoid confusion with virus left over from the inoculum, we decided we would only give volunteers fluid from the second passage cultures, but we also gave other fluids from test-tubes without cells in them and just inoculum. In all this we were learning from the problems that they had had earlier in the Unit. We were suspicious that there might be viruses in the apparently normal cells, so we also harvested cultures which had just been given a sterile inoculum and in order to test these we pooled the whole lot together and inoculated a larger number of volunteers than had been customary at the Unit. The reason was that if we could get a clear negative, we would know that our series of bright ideas in that experiment were all wrong and we could move on and try something else. I had been interested in statistics for some time and although I was yet to learn about formal power calculations it was helpful that someone had left a photocopied sheet with some useful notes on the size of test groups and the probability of detecting a positive sample. So I didn't do anything particularly original, but developed a rather cumbersome way of testing some possibilities which must have occurred to other people.

In the end, I needn't have been so pessimistic. We did some experiments with monkey kidney and we had no joy from them and then we started with human embryo kidney and I still remember the suppressed excitement in the coffee area in the mess when Bill Bynoe[69] (we saw him on the film), who knew what the experiment was about, but not which volunteers had been given which material, said in a casual tone, 'One or two volunteers seem to be getting colds'. I tried to be equally casual and said, 'Who were they?' But we had to maintain the double-blind until the end of the trial. As anticipated, we were perfectly willing to then test the individual components of the mixture which had produced colds to find out which had been carrying the infectious agent and we confirmed that cold virus had been grown, apparently in human kidneys, maintained at 33° C rather than 37° C, harvested at four or five days. And further experiments, however, showed that it would not grow beyond those two passages. We guessed that it was dying off in the medium, so we decided to supplement it with protein in the form of bovine plasma albumin which ought to be free of antibodies. Sure enough, it did pass better, but the cells still looked normal and we had to use volunteers to tell us whether a virus was there.

As you can imagine all these experiments went very slowly, but in parallel with this work, we'd been playing around with other systems and other questions. For example, I found that we could get large amounts of calf kidney from the abbatoir and I was able to grow influenza viruses in them and indeed demonstrate virus interference, something which I'd got interested in in New York. We also received a possible common cold virus from Lennart Philipson of Uppsala in Sweden, therefore called U-virus. It didn't cause colds in volunteers, but it turned out to be an echo (enteric cytopathic human orphan) virus type 11, produced a clear cytopathic effect (CPE) in the kidney cells and could be detected quite easily by agglutinating red cells.

It's interesting going back to what Jimmy [Lovelock] was saying. I'd been worried about spending time on these sort of peripheral experiments and when Sir Charles Harington, the Director of the NIMR, visited us I asked him whether it was all right to do that and he replied, as I just said, it was good science and he was happy and if anyone tried to discourage me from trying out my ideas, I was to go straight to him. That's an example for you John [Sir John Skehel], you see. These peripheral experiments gave us some ideas for an *in vitro* test for the virus. We took cultures in which cold virus was apparently growing and we added the U-virus. They did degenerate but when we titrated the amount of virus haemagglutinin in the medium it was significantly reduced. Griselda Worthington, who was working with me, did most of these experiments. We were both really thrilled when we broke the code of the haemagglutination titrations and showed that the yield of

[69] Dr M L Bynoe was a medical officer at the MRC Common Cold Unit from 1957 until his death in June 1969.

virus was significantly reduced and that our new virus was producing a state of virus intereference in the kidney cells.

However, Griselda was tempted off by Alick Isaacs to work with interferon with him in NIMR and she was replaced by Rosemary Parsons. And the last advance in this study was made by accident and I've got John Beale here to correct my facts if necessary. The point was that we went away on holiday. We worked hard, but we did have holidays and at the end of August we came back determined to improve the interference test. A new kidney came and we set up the cultures and had a nice row of them and it was a disaster. All the cells died in all the tubes. There must have been something wrong with our medium, Medium 199. I didn't want to waste time fiddling about to find out what was wrong, so I sent out a plea for help to colleagues in other labs using Parker's 199 Medium. 'Please help us, I don't know what's wrong, we may not be able to make good distilled water anymore, just send us everything, and we won't touch it, in case we spoil it'. When the next tissue arrived we were able to put it up in three different lots of Medium 199 and, of course, the law of perversity applied, and the cells grew perfectly well in all three batches of medium. So rather than waste these cells, we decided to do the interference test again in all of them. But once again, things seemed to go wrong. In some of the cultures, the cells seemed to degenerate, just as though we had added the U-virus to them. Had we mixed up the viruses? Things like that do happen. It was soon clear that we hadn't. Indeed it turned out that one of the firms, that firm of course, presided over by John Beale [Glaxo], had made an apparently minor change in the recipe for Medium 199 and reduced the amount of sodium bicarbonate added, without Parker's permission, I am sure, so that the medium was slightly acid.[70] It was this that was needed for the cold virus to grow so well that it killed the cells and so instead of doing a cumbersome volunteer experiment we could inoculate a tube of tissue cultures, look at the cells a few days later and recognize that a virus was present.

And now these results completely changed my view of the common cold problem. Once the interference test was working, I felt no pressure to go back to Sheffield and once we had a cytopathic effect in cultures my imagination let rip. I imagined us studying the properties of the virus, making a vaccine, measuring antibodies in serum, looking for different serotypes of virus, finding out why there were so many colds. I still remember myself bubbling over with such thoughts as I walked down the drive at the end of one working day. As you know, and we haven't got time to tell you, I'm afraid, this led to a detailed study of what came to

[70] Dr John Beale wrote: 'I knew Parker quite well from my time as a Research Fellow at the Hospital for Sick Children in Toronto. He was quite relaxed about the concentration of bicarbonate in his 199 Medium, but not of other components!' Letter to Dr Tilli Tansey, 2 February 1998. See Morgan J F, Morton H J, Parker R C. (1950) Nutrition of animal cells in tissue culture. I. Initial studies on a synthetic medium. *Proceedings of the Society for Experimental Biology and Medicine* **73**: 1–8.

be known as the rhinoviruses, and I think people like Nigel Dimmock, who is here, earned his PhD doing some of the first studies on the nature of the protein and the nucleic acid in these organisms.

Have I got time for two ethical issues which you have already referred to? I thought I should bring them up. I had been a volunteer in physiological experiments as a student and houseman, and was quite happy with the idea of experiments on fellow human beings, provided that they were genuinely volunteering (and the method of recruitment at Harvard made sure of that), and that there was no risk of any harm to the individual. That's not quite so certain when you think of it through that powerful instrument the retrospectroscope. The other issue was the use of foetal tissue. Abortions were beginning to be done more frequently at that time in the UK, but because of delays in the systems, one often had to be done by hysterotomy after the twelfth week and at this stage useful amounts of kidney tissue could be dissected out. But it was still very difficult to get them. It so happened, and we had nothing whatever to do with this, that Dr Humphrey Kay at the Royal Marsden Hospital had the idea of putting lymphocytes harvested from foetuses to repopulate the cells of patients who had been given heavy chemotherapy for malignant disease. And he and two other people went, I am told, to see Sir Harold Himsworth [then Secretary of the MRC] one afternoon. They agreed that it was a good idea and that he could have his grant, the whole matter being decided with no more formality than that. But then, having got this little laboratory set up to collect foetal tissue suitable for use in human volunteers, they had a source of human kidney and lung tissues which they weren't using for their experiments. So they were prepared to send them down to us by train. They used to manage to deliver them, I think for obvious reasons, about half past eight on Friday evening, so that was the 'convenient' time for us to start setting up tissue cultures. For reasons of confidentiality, we were never told anything about the cases, but we were assured that there was no clinical or laboratory evidence of infection in the case, and that the tissue was suitable for administration to normal subjects. I don't know whether there was a procedure for asking the patient's consent. But in my view we had nothing to do with the decision to operate, the tissue would otherwise have gone straight to the bucket and the incinerator, and so I felt that it was a worthy action to try and do something useful with the surviving cells and that's indeed what we did. Later, when we tried to repeat some of the experiments, just a year or so before the Unit closed, it was totally impossible: we couldn't get access to any tissue at all because of the legislative and ethical committee restraints.

Booth: One of the excitements of science is seeing new things happening and reading about it in the newspapers or the scientific journals and feeling, 'Oh isn't that marvellous'. Now do any of you have a recollection of the time when

rhinoviruses finally became a feature of virology in this country? Did you feel that way, or was it something you all expected to happen?

Tyrrell: It's interesting, because people often said, 'They set up that place and it never found the cure for the cold did it?' And the implication is that nothing of value was found. But, in fact, subtly we began to realize that things were changing. The phrase 'of course' is a very valuable sign that something has changed, because when we first went there people talked about 'the common cold virus' and by the time you were watching consumer programmes on TV ten years later, people were saying, 'Well of course colds are due to so many viruses that there's nothing much we can do about them'. The 'of course' indicated that what had happened with us had penetrated to the public consciousness.

I should mention by the way that what I've said here is a terribly unfair and narrow view of what was going on in science at the time. We had lots of contacts and we knew other people were detecting viruses which can cause colds in volunteers. The only thing was that they said, 'This was the cause of all colds' and we could show that they were not – in addition, of course, we showed that the rhinoviruses which we were growing then weren't the cause of all the colds we had. In fact, this led us to develop new techniques, organ-culture techniques, in order to grow some of these other viruses, coronaviruses and other rhinoviruses, and there's the little clip of film which Paul Chapple took of the organ cultures which we then used.

Booth: Can John Beale tell us what really happened over the medium?

Dr John Beale:[71] I remember the incident very well and was proud to have played a small part in the discovery of rhinoviruses. David rang me one day and asked if we could send him some Parker's 199 Medium because they had a problem with their supply. I readily agreed and the medium was dispatched and I thought no more about it until David rang me sometime later to say, 'What did you put in that medium?' He then explained that using it he had observed a cytopathic effect when cells were infected with his new common cold virus. I was soon able to tell him that at Glaxo where I was then working we found it necessary to reduce the bicarbonate by half when setting up many hundred roller tube cultures of monkey kidney cells. If we used the full prescribed amount the cultures became too alkaline before growth started and the cells all died. David was able to show that the slightly lower pH was the secret of producing the cytopathic effect with rhinoviruses.

[71] Dr John Beale (b. 1923) was Director of the Virus Unit at Glaxo from 1958 to 1969 and Head of the Biological Division at the Wellcome Research Laboratories from 1969 to 1990.

Booth: Did electron microscopy come to your aid, could you actually see the virus?

Tyrrell: It didn't really. In fact, I remember an occasion at the Royal Society Conversazione the first time I ever appeared there. It was a grand one, I think it was the 300th anniversary of the Royal Society [23 July 1960] and we had a huge Conversazione with lots and lots of demonstrations and Prince Philip came. Prince Philip, as everybody knows, gets interested in things, and we were told that he would be arriving at about quarter to eight. Well, by the time that half-past nine came I had just about missed my train back from London, and we wondered what was going to happen, but Prince Philip turned up and said he was fascinated by this and, 'Why hadn't we seen the virus yet?' He said, 'But you've got electron microscopes'. I said, 'No we haven't but we have got very good access to electron microscopes up in London'. 'Well, why haven't you looked at it yet?' and I said, 'We can calculate the number of virus particles here, and these things must be far too few to see'. 'Well, have you tried?' You can guess I was the junior midshipman being told off by the Commanding Officer. But no, seriously, it was an obvious thought but it was interesting that because the biological tests were so much more sensitive, we got a long, long way without seeing the virus. The original methods were actually rather poor, we only grew a concentration of a hundred or a thousand infectious doses. You have got to have ten million infectious doses per ml before you get into the concentration of particles you can see. So it was some years before we got down to looking at particles. Nigel Dimmock was one of the first people to really get to that level, weren't you Nigel?

Professor Nigel Dimmock:[72] It was not me, but Paul Chapple who worked on the concentration of the virus, using mainly caesium chloride centrifugation. The resulting electron micrographs were published in *Nature*.[73]

Tyrrell: Yes, but you then started working with it to see what happened when you heated a particle and see when it changed.

Dimmock: We did the first work on the isolated viral genome, showing that it was composed of RNA and that it was intrinsically infectious. We also studied the reason why virus lost infectivity at temperatures from 4–56 ºC. At physiological temperatures (and up to 45 ºC) the viral protein coat was stable, and loss of viral infectivity was due to the inactivation of its RNA genome. At higher temperatures

[72] Professor Nigel J Dimmock (b. 1940) has been Professor of Virology at the University of Warwick since 1986. He was a member of the scientific staff of the MRC Common Cold Unit from 1961 to 1966.

[73] See Chapple P J, Harris W J. (1966) Biophysical studies of a rhinovirus: ultracentrifugation and electron microscopy. *Nature* **209**: 790–792.

the stability of the protein coat was the limiting factor, and the RNA remained intact as demonstrated by its intrinsic infectivity.[74]

Booth: There's a very interesting scientific corollary to that. You probably heard Christian de Duve[75] talking about subcellular organelles. He and Palade had a long on-going, long-term, feud on electron microscopy and de Duve gave a marvellous lecture all about his organelles. His final slide was, 'By the way that's what they look like'. David, thank you very much, a superb account of that fascinating period. Dr Higgins was very much involved with all this, also and he is now going to tell us what happened after that.

Dr Peter Higgins:[76] In 1960 the PHLS exiled me to rural Gloucestershire. Part of the reason was a GP in Cirencester by the name of Hope-Simpson, who was very interested in respiratory infections.[77] So interested that he had a band of volunteers who, when they got a cold, would totter down to the surgery, pick up their card, record their symptoms, and return it at the end of their illness. I was to be involved with minor respiratory illnesses and these volunteers would be part of my sample population. Many of them would not normally go to the doctor and samples would not be available. This lead to my first contact with the Common Cold Unit, because in 1960 they ran courses to demonstrate the cultivation of rhinoviruses, as David has just described. A residential course, very pleasant. The tuition was good, needless to say. We even went to a concert of chamber music in the town hall. However, the lasting impression was of intense activity and great enthusiasm that prevailed throughout the Unit.

It was going to be over 20 years before I was to be a resident again at the Unit, but we did keep in touch. By then David had discovered the coronavirus, which was to be very important with my sort of sampling, so I had to learn this technique and, as David said, it was very simple. The other way one kept in contact was through the South Wiltshire Virology Society. This forum would meet monthly,

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[74] Dr T H Flewett wrote: 'I understand this, but, it would not be clear to a casual reader. At physiological temperatures the virus lost infectivity, but slowly. At higher temperatures the RNA could be rescued intact.' Letter to Dr Tilli Tansey, 8 February 1998.

[75] Dr Christian de Duve of l'Université Catholique de Louvain shared the 1974 Nobel Prize for Physiology or Medicine with Albert Claude and George Palade of the Rockefeller University for their discoveries concerning the structural and functional organization of the cell.

[76] Dr Peter Higgins (b. 1926) was a member of the scientific staff of the Public Health Laboratory Service from 1955, seconded to the Common Cold Unit, which he joined in 1981 until its closure and his retirement in 1990. See Higgins P G. (1974) Virus isolations from patients in general practice, 1961–1971. *Journal of Hygiene* **72**: 255–264.

[77] Dr R Edgar Hope-Simpson FRCGP (b. 1908) was in general practice from 1932 in Beaminster, Dorset, and in Cirencester from 1945 until his retirement in 1976. He also directed the Epidemiological Research Unit located at his surgery, from 1946 a constituent laboratory of the Public Health Laboratory Service, also supported by a MRC grant from 1947 to 1973. In 1960 a small virological lab was established in it until transferred to Gloucester in 1973. He and the Unit continued their epidemiological studies until 1996. See Hope-Simpson R E. (1992) *The Transmission of Epidemic Influenza*. New York: Plenum Press.

usually at Porton or Harvard, except in the summer months. If you were going to deliver a paper to a meeting, you could present it there first and get their friendly criticism. If you were half way through a piece of work and not quite sure which way to go there was a lot of useful advice to be had. It would broaden your outlook. There were not just human virologists, but animal virologists from Pirbright and Compton.[78] I even remember a session where the whole meeting was devoted to plant virology.

In 1970 there was a big change at the Unit. David and most of the staff moved up to Northwick Park, leaving a skeleton crew at the Unit of Sylvia Reed and Paul Beare.[79] Sylvia continued her work looking at the synthetic antivirals and Paul was looking at recombinant influenza viruses, trying to produce a live virus vaccine. In 1981 I came back to this country from Trinidad where I had been with the Pan-American Health Organization/World Health Organization and the PHLS were supposed to find me a post. They wrote to say there was no vacant consultancy post in the PHLS, how did I feel about going to the Common Cold Unit? I didn't let them know, but I was delighted.

David outlined the future as he saw it in a letter, adding a warning that we'd have fewer volunteers and we'd have to slide around in the mud as they erected the new Common Cold Unit. That didn't bother me. What did worry me was his preoccupation with psychology and its effect on infection and illness. As it turned out he was wrong in the first instance and right in the second. If you want to sum up that final period of the Common Cold Unit, I would use two words 'economy and collaboration'. In Tom's [Keith Thompson] day, if you got a really hot day like you saw in the film, chef would be coming round handing out ice-creams to volunteers. If there was a birthday, there would be wine on the table in the mess at lunchtime. That all disappeared. The tangy crumbly Cheddar cheese was replaced with a tasteless, soapy variant. But we were being just as economic with the volunteers. There were very few volunteers in that last phase who only went into one trial. We were doing piggy-back trials all the time.

Perhaps we might start with the psychological problem, which was a worry to me. Totman had stimulated David by showing him the relationship between psychological makeup, relation to stress, and susceptibility to infection and the severity of the illness. Shortly after 1981, the Broadbents came, enlarged on that study and confirmed it. So much so that we used to take these psychological

[78] Institute for Animal Health, Pirbright Laboratory, Woking, Surrey; Institute for Research on Animal Diseases, Compton, Newbury, Berkshire.

[79] Dr Sylvia E Reed and Dr A S Beare were both members of the scientific staff of the MRC Common Cold Unit from 1966 until 1981. See Beare A S, Reed S E. (1977) The study of antiviral compounds in volunteers. In Oxford J. (ed.) *Chemoprophylaxis and Virus Infections of the Respiratory Tract,* vol. 2. Cleveland: CRC Press, 22–55. Beare A S. (1982) Research into the immunization of humans against influenza by means of living viruses. In Beare A S. (ed.) *Basic and Applied Influenza Research*. Boca Raton, FL: CRC Press Inc., 212–234.

factors into account when we were balancing the placebo and the active groups in the analysis.[80] And then, finally, the third psychiatrist who came along was Andy Smith, and he, I think, was more interested perhaps in function. He showed that impairment of function was possible with many of the illnesses, even with subclinical infection. But he also showed that that type of impairment varied depending on the infecting viruses. We found that with influenza you get a certain type of impairment of function. At this time we did special trials – these were reliable volunteers who were very happy to come along, but we'd expect a good deal more of them. One particular batch was given three different doses of interferon intramuscularly. With the right dose they get the symptoms of flu as well as impairment of function. The unfortunate thing was that it wasn't exactly the same impairment found with the natural virus infection.

Perhaps that brings us on to interferon. In the early 1970s Cantell[81] and his colleagues in Finland produced sufficient natural human leucocyte interferon for a volunteer trial. It was said to be partially purified, but might more accurately be described as crude interferon as the content was less than 1 per cent pure interferon. Merigan then demonstrated that this material, given intranasally, would protect against rhinovirus infection.[82] However, there was always the worrying thought that it wasn't the interferon but some other substance that might have provided the protection. Cantell provided a further supply of human leucocyte interferon a decade later, but this had been purified by immunoadsorption chromatography with monoclonal antibody. This allowed Geoff Scott to repeat Merigan's experiment and show that, indeed, it was the interferon which prevented infection. If studies on interferon from this source had continued, the Finns would become a chronically anaemic race as 30–50 donations of blood were required to produce sufficient interferon to protect a single volunteer.[83] However the introduction of genetic engineering allowed us to show that both alpha and beta interferon would protect against not only rhinovirus infections, but coronavirus, respiratory syncytial virus (RSV), and influenza infections. There was one drawback, if used for any

[80] Publications in this area include: Totman R, Kiff J, Reed S E, Craig J W. (1980) Predicting experimental colds in volunteers from different measures of recent life stress. *Journal of Psychosomatic Research* **24**: 155–163. Broadbent D E, Broadbent M H, Phillpotts R J, Wallace J. (1984) Some further studies on the prediction of experimental colds in volunteers by psychological factors. *Journal of Psychosomatic Research* **28**: 511–523.

[81] Professor Cantell was Professor of Virology at the Public Health Laboratory, Helsinki, Finland. See Cantell K. (1998) *The Story of Interferon: Ups and downs in the life of a scientist*. London: World Scientific.

[82] Dr David Tyrell wrote: 'Tom Merigan from California was on a sabbatical visit to the CRC and he helped to get the interferon supply organized and then came down to the Unit and went round the volunteers every few hours spraying them with interferon or placebo.' Letter to Mrs L Reynolds, n.d., received 11 May 1998.

[83] See Merigan T C, Reed S E, Hall T S, Tyrrell D A J. (1973) Inhibition of respiratory virus infection by locally applied interferon. *Lancet* **i**: 563–567. Scott G M, Phillpotts R J, Wallace J, Secher D S, Cantell K, Tyrrell D A J. (1982) Purified interferon as protection against rhinovirus infection. *British Medical Journal* **284**: 1822–1825.

length of time in a strength that would give prevention, then it started to produce a local reaction – nasal congestion and increased nasal secretion, sometimes blood-stained. The last of the interferons to become available was immune interferon, gamma interferon, and we had great hopes of this. This would be the one that really would work. It doesn't work at all – if anything it tends to make the symptoms worse.

As Sylvia Reed would tell you, working with synthetic antivirals which looked very good in the lab is very disappointing when tested *in vivo*. It wasn't until the end of the Unit's existence that Janssen came up with a drug which would suppress a cold for as long as you gave the medication. The cold could be suppressed for as long as six days, but the snag was that after the medication was taken away, the cold would develop from 24–36 hours later.

Now mediators – what chemical entities cause the runny nose? Well, we looked at this in two ways. With Professor Kay and Peter Cole's groups, we tried directly to measure mediators in nasal secretions and then we did it the indirect way by using substances which would block nasal receptors to possible mediators. Bradykinin was suggested as a possible mediator, so we tested a bradykinin antagonist, unfortunately without success. We did piggy-back trials, and this is where a lot of the collaboration came in. We measured nasal mucociliary passage time; looked at the ciliary activity to see how much ciliated epithelium was there; and used ultra-electron microscopy to see the structure of the cilia. We used what is called brush biopsies to get a few cells off the inferior turbinate. I'll spare you the gory details when someone suggested full thickness epithelial biopsies. We even had Mats Bende come over from Sweden to measure the nasal air flow, the temperature of the blood flow in the nasal mucosa and the albumen content of secretions.

The other thing we looked was immuno-modulatory drugs. There was one which worked perfectly well in animals, but couldn't be demonstrated to do anything in humans. Paul Beare's vaccine work[84] was continued and we worked with Craig Pringle and his temperature-sensitive mutants of respiratory syncytial virus and demonstrated that one modified strain, although then not good enough for a vaccine, was progressing towards that end.[85] We passed an influenza B virus through various systems and got one where it was attenuated. In conjunction with

[84] David Tyrrell wrote: 'Paul Beare worked on live attenuated influenza virus vaccine throughout his time at the Unit. He collaborated closely with labs at the NIMR, Wellcome Research and in the USA and provided material and test results for the MRC trials on live influenza virus vaccinations.' Note to Dr Tilli Tansey, n.d., received 9 June 1998.

[85] Dr Craig Pringle (b. 1930) was a member of the scientific staff of the MRC Virology Unit at the University of Glasgow from 1968 to 1983 and Professor at the University of Warwick from 1983 to 1997, now retired.

John Oxford and Geoffrey Schild, it was shown that a single nucleotide substitution in the haemagglutinin gene was responsible.[86]

Finally we ought to mention parvovirus, because I think that this is the one, most satisfying experiment we did. Parvovirus causes a paediatric disease, slapped-cheek syndrome, a very minor illness. I think the reason, or perhaps the excuse for looking at it, was the very mild upper respiratory tract symptoms which appear in the prodromal stages. This was one of our special trials, because the volunteers were inoculated with the parvovirus. The other thing I should tell you is that if you suffer from a chronic haemolytic anaemia, a parvovirus infection can precipitate an aplastic crisis. In collaboration with John Pattison and his colleagues, we gave this virus to normal healthy volunteers and managed to monitor their viraemia.[87] We also monitored their blood and could show a fall in haemoglobin by the time the viraemia was at its maximum. Then we did a super-special trial. We got three people back who'd volunteered to have bone marrow biopsies done after they had been inoculated with the parvovirus. At ten days the precursors of the red cells were remarkably reduced and as recovery occurred, the cells bounced back to an even higher level than originally.

Booth: I think those were very interesting trials at that time.

Dr Ian Barrow:[88] Peter hasn't mentioned the zinc trials.

Higgins: Well, this was a thing that Eby found with his leukaemic daughter. He noticed that if she sucked zinc gluconate, it would prevent a cold. We got an Italian firm to make us up trial lozenges. Zinc has a very metallic taste – so getting a placebo was very difficult – they had to have a strong masking flavour. I used to warn the volunteers that these things tasted like a cross between a Madras curry and a Fisherman's Friend. In fact it did reduce the clinical scores in those taking zinc as opposed to the placebo. It had no effect on virus secretion, so it isn't an antiviral, but how it reduces the symptoms is not known.[89]

Barrow: I just wanted to know what zinc tablets I should take for my colds![90]

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[86] Dr G C Schild succeeded Dr H G Pereira as Director of the World Influenza Centre from1970 to 1975. See Anon. (1988) Influenza research at the NIMR. *MRC News* **41**: 26–29.

[87] Professor Sir John R Pattison is Professor of Medical Microbiology at University College London since 1984 and Dean of their School of Medicine since 1990. He succeeded Dr David Tyrrell as chairman of the Spongiform Encephalopathy Advisory Committee (SEAC) in 1995.

[88] Dr Ian Barrow (b. 1926) was a member of the medical staff of the Public Health Laboratory Service from 1954 to 1984, and was Medical Officer at the MRC Common Cold Unit from 1985 until its closure.

[89] See Al-Nakib W, Higgins P G, Barrow I, Batstone G, Tyrrell D A J. (1987) Prophylaxis and treatment of rhinovirus colds with zinc gluconate lozenges. *Journal of Antimicrobial Chemotherapy* **20**: 893–901.

[90] Dr Barrow wrote: 'Although not one of the major issues, I was quite impressed by the (unexplained) action of zinc in suppressing cold symptoms. Zinc had been promulgated by George A Eby, a

Higgins: Probably not worth taking as reduction in symptoms is offset by discomfort of sucking zinc tablets every waking two hours.

Lidwell: Gwaltney and his group in Charlottesville did quite a lot of work on zinc. I did go over there some years ago and visited them. I can't tell you the results in detail.[91] They were also interested in psychological influences, of course, as David has said. More interestingly they had carried out a number of experiments much along the lines that James [Lovelock] has described with a fluorescein tracer. They were able to use donors with real colds of a known serotype and potential recipients with no specific antibody. The results did not at all correspond to James's deductions. In spite of gross contamination of playing cards and other objects with nasal secretion they failed to get any transmission of infection, except when the airborne route was available.[92] Couch and others had in 1970 confirmed airborne transmission of Coxsackie A21 virus in an institutional barracks.[93]

Tyrrell: I think Peter [Higgins] has done amazingly well to cover such a lot of ground, but I would like to mention that I think that some of these papers and pieces of work really are of landmark significance. I hate doing this, because it sounds like blowing one's own trumpet. I am not. I am saying what a good job the team, the whole unit, did on a number of points. I've probably got the list wrong, but I would start with the parvovirus studies, which was referred to in an article in the American journals as a 'classic landmark paper', documenting the pathogenesis by which parvovirus induces disease in man, which is a bit unusual and we haven't got time to go into it now. Another thing which I think was really a landmark at the other end was some of the work that Paul Beare did when we had eminent Russian and Australian influenzologists saying, 'You can't have an attenuated influenza for man' and he showed that it was true that you could attenuate the virus. Obviously the genetics was very difficult and by collaboration with NIMR he only got a limited way in understanding what it was, but it changed people's

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mathematician by training, who had given zinc as one of many dietary supplements to his daughter when suffering from lymphocytic leukaemia – and therefore prone to suffer from colds. Mr Eby made the interesting observation that she suffered fewer and less severe colds when she sucked rather than swallowed zinc tablets. He subsequently expanded on the subject in a most interesting book (*Handbook for Curing the Common Cold*. Austin, TX: George A Eby Research, 1994), which reviews his own and other scientific work in detail.' Letter to Mrs L Reynolds, 24 September 1997. See also Eby G A, Davis D R, Halcomb W W. (1984) Reduction in duration of common colds by zinc gluconate lozenges in a double-blind study. *Antimicrobial Agents and Chemotherapy* **25**: 20–24.

[91] Dr Owen Lidwell wrote: 'They had considerable problems with devising a suitable placebo and failed to find any evidence of a beneficial effect of the zinc.' Letter to Dr Tilli Tansey, 15 September 1997.

[92] Dick E C, Jennings L C, Mink K A, Wartgow C D, Inhorn S L. (1987) Aerosol transmission of rhinovirus colds. *Journal of Infectious Diseases* **156**: 442–448.

[93] Couch R B, Douglas R G, Lindgren K M, Gerone P J, Knight V. (1970) Airborne transmission of respiratory infection with Coxsackievirus A type 21. *American Journal of Epidemiology* **91**: 78–86. See also Jennings L C, Dick E C, Mink K A, Wartgow C D, Inhorn S L. (1988) Near disappearance of rhinovirus along a fomite transmission chain. *Journal of Infectious Diseases* **158**: 888–892.

attitudes. Another thing that was very important was Tom Merigan's studies at the Unit published in 1973, showing that you could stop a cold by giving interferon.[94] People had said that it was impossible to administer an antiviral drug which would not cause more damage to the cells than it would to the virus and influence a cold and that finding changed attitudes. Some of the synthetic antivirals started being produced because the drug firms were influenced by the way in which interferon had worked.

The one other thing I would like to say is that Peter [Higgins] quite correctly has been dealing with the volunteer side in the trials. Now I would like to mention that all the time there was basic virological, clinical and fundamental virological work going on. I mentioned Nigel Dimmock doing some of the first work on the thermal stability, for instance, of rhinoviruses. When we got the coronaviruses up, people did not believe that such a group existed and we had to do quite a lot of work showing what sort of a coronavirus we had grown. This was done partly in collaboration with the Clinical Research Centre (CRC), with which we were linked and where we had scientific backup. There was a time when we were told that because we lived in cardboard huts there was no way we could use molecular methodology in science, you had to have concrete buildings with flashing lights in them if you were going to do that. And so we adopted the same policies as we did over the psychology work. We were told that we couldn't do any more psychology experiments because they were not very interesting scientifically, so as Peter said we decided to carry on doing them piggy-back on top of drug trials. We decided not to do molecular studies by going to Leicester University and seeing the people who had just cloned polio and the first rhinovirus and bringing their techniques down to the Common Cold Unit. They were delighted to help us, and we helped them by showing that you could use molecular techniques to diagnose the presence of virus nucleic acid in patient material, again something everybody said you couldn't possibly do. That work has carried on at Southampton University and in other parts of the country, where the polymerase chain reaction (PCR) techniques which again were first developed at the Common Cold Unit can now be used routinely for diagnosing rhinovirus infections, three to four times more efficiently than the tissue cultures could do. I am sorry I am blowing the trumpet.

Booth: That's all right – you were involved in this decision. There's one thing a director of an institute can do and that is he can preferentially shuffle resources in certain directions and I can well remember David Tyrrell and myself at CRC soon after I went there having a private conversation at which we decided that was precisely what we would do, we would push money in the direction of molecular virology, all over the institute and the Common Cold Unit. We didn't do it

[94] A useful review of this work includes Merigan T C. (1974) Clinical testing of human interferon in infectious diseases. *In Vitro Monograph* (3): 57–62.

selectively, we just said everybody who'd got a good case should be supported and I think that worked out.

Tyrrell: And the final point was the development of the enzyme-linked immunosorbent assay (ELISA). The methodology which the labs in the US used for detecting rhinovirus antibody was to do a virus neutralization test which is fairly cumbersome. People said you couldn't do the modern binding assays like ELISA tests with viruses like rhinoviruses. However Bob Philpott started the job and Wendy Barclay finished it and by the end we had a suite of tests for looking at the different antigens on rhinoviruses and looking at the different categories of immunoglobulins which bind. So they were a good lot down there, and I think it would be a shame if this goes on record without indicating that some of the lab work was quite significant as well as the volunteer-related stuff.

Booth: I entirely support that too.

Dr Norman Finter:[95] In his remarks, David Tyrrell was characteristically over-modest. It's perfectly true that Tom Merigan was the senior author of the publication which first showed that interferon given intranasally could have an antiviral effect. However, this study was the culmination of three previous attempts, in which Dr Tyrrell, as a member of the MRC's Scientific Committee on Interferons, used the most potent interferon preparation available at the time to try to show an effect against rhinovirus infections. The success eventually obtained was due to the fact that Dr Cantell in Finland was able to supply an even more potent leucocyte interferon preparation than previously.

Tyrrell: Incidentally, I dug out the notes from my lab book the other day, describing how Dick Sutton and I lay on the top of my desk in the office there and dropped interferon and then Coxsackie A21 virus up our noses to see what happened. The trouble was that I began to get a runny nose and it was the beginning of June and I couldn't decide whether I had hayfever or a cold and I was very disappointed when I discovered my nose was full of Coxsackie A21 virus.

Mr Michael Cox:[96] First of all I must apologize for coming late as I had to attend a funeral of a colleague of 30 years, but nevertheless I am very interested. I don't know whether you have had a contribution this afternoon from a volunteer [**From the floor**: Only one and he has just left the room.] I was one of your volunteers in 1948, two years after you opened, and again in 1949. I was a medical student at Bristol University and I attended with Bill Spry, my friend at the time. I dug out

[95] Dr N B Finter (b. 1924) was a member of the MRC Scientific Committee on Interferons from 1959 until its dissolution in 1971, and has continued to work on interferons since.

[96] Mr Michael L Cox FRCOG (b. 1929) was a consultant in obstetrics and gynaecology at Nuneaton Hospitals from 1967 until his retirement in 1991.

my old diary, but unfortunately it says very little, but what I do remember is that going there as young medical students the very first thing we did was to look at the list of the other volunteers. We could speak to any of them over the phone. So we looked down the list quickly where there was a Miss Somebody and a Miss Somebody in a particular hut and sure enough they usually turned out to be students of some kind or other, especially as we were going there in the university vacation time. And so one picked up the phone and made contact with those two and what could one do? Play chess over the phone, which we did a great deal. We weren't allowed to go within I don't know how many yards it was of each other, so sometimes we'd do a walk and wave at each other and all one could look forward to was the social on the final evening, which hardly gave time for any relationship to develop. We were even denied that on the last occasion, because in 1949, (normally we stayed until the Saturday and the party was on the Friday evening) and my diary says on the Friday the 15th which happened to be Good Friday, 'Came home today from Harvard a day early, because the doctor wanted a long Easter Holiday, I think' – so we missed the party as well. Anyway they were enjoyable days and I am only too pleased to have made perhaps a very tiny contribution.

Chaproniere: May I add to my impromptu contribution, for I wanted to say what a good training in experimental design it was for a budding scientist to work under the combination of Dr Andrewes, Helio Pereira and Tony Roden.[97] There has barely been a mention of Dr Roden today, although he played a very important part in the design and evaluation of the trials. He was a statistician and extremely rigorous in this respect. His own research at Salisbury was a long-term study of the epidemiology of the common cold in the villages of the nearby Ebble Valley. I therefore had a good grounding in the importance of rigorous controls both from him and from Helio, who was a very patient teacher. My years at the CCU, followed by those in the exciting environment of Mill Hill, formed an excellent foundation for my scientific career and I look back with great pleasure on my years there.

Professor Miles Weatherall:[98] There's one point in the history of the Unit that I have not got any clear picture of – the transfer of responsibility when the Clinical Research Centre opened. How did it happen? Was this scientifically of great benefit to the Unit, or did it disrupt work? Was the decision made on scientific grounds, or for administrative reasons?

[97] Dr A T Roden was a medical officer at the MRC Common Cold Unit from 1951 to 1956.

[98] Professor Miles Weatherall (b. 1920) was Professor of Pharmacology at the London Hospital Medical College, University of London, from 1958 to 1966; Head of the Therapeutics Research Division and a director of the Wellcome Research Laboratories, Beckenham, from 1967 to 1975.

Tyrrell: My understanding was that though historically the Unit had started with the NIMR, in the late 1960s and early 1970s it was becoming the policy of the MRC to think of it as broader than just a Common Cold Unit – rather a respiratory infections unit with a broader remit and related to a number of what one might call clinical problems which you have heard about from Peter – pathogenesis, immunity, vaccines, antiviral drugs – and that therefore it would be appropriate to link it to the Clinical Research Centre when it was built. You remember that it was actually being talked about in the early 1960s and so it was gradually moved in that direction, and by 1967 the buildings and so on were beginning to get out of their doldrums and the Tyrrell family moved to London. It did become a rather gradual transition from then on, with a big bump as Peter was saying in 1970, when David Taylor-Robinson[99] and his group moved out, and now instead of spending several days a week in Salisbury, I was in London virtually all the time. So there was a bump there and I think – I don't know what Sylvia would say – it probably wasn't very good for the Unit. There was an insoluble problem of how to give adequate support to the Unit and start up a new division at the CRC and the resources weren't quite up to it. All credit to Sylvia [Reed] and Paul [Beare], they kept going and produced important and interesting work over that period.

Booth: I think I can add to that. One of the ideas was (and still is) to link the Division of Communicable Diseases at Northwick Park with David Tyrrell and the Common Cold Unit. The idea was that you might be able to recruit staff from intelligent bright young registrars who did good work and research at Northwick down to the Common Cold Unit. Somehow that never worked out did it?

Tyrrell: Oh well, they came mainly to visit for specific projects. Somebody mentioned Geoff Scott (who I think has already left), he came down and actually ran the interferon trials from the Clinical Research Centre. There were a number, we won't bother with all the names, but it did work to some extent. It actually went wider than that because we had collaboration with other medical schools and other laboratories.

Dr Sheila Howarth:[100] I was in the Headquarters office from 1964 until I retired in 1980. We used to get, of course, progress reports and reports from committees which visited the Common Cold Unit. As David said, there were always one or two dismal jimmies who used to say, 'Well, what's it done? It was set up to find a cure for the common cold, but it doesn't seem to be getting any further'. But of course the basic science was so good that they were downtrodden and the Unit

[99] Dr David Taylor-Robinson was a member of the scientific staff of the MRC Common Cold Unit from 1960 to 1970.

[100] Dr Sheila Howarth (b. 1920) was a principal medical officer in the Medical Research Council head office. She retired in 1980.

invariably got another three years' support. Am I right in thinking that in the terminal stages – I think I had left by that time – problems were arising? The buildings were in need of maintenance; there was an increasing difficulty in recruiting volunteers; there was always a problem in getting a suitable medical superintendent. At one stage, as I recall, the Clare Hall site was mentioned as being a place for re-siting the Common Cold Unit, bringing it nearer to London and that, of course, fell down when the Ministry of Transport decided to construct a large extension to the M1 or one of the big roads. Have I got it right?[101]

Tyrrell: I never disagree with you, Sheila. You see I never lose these relationships, either with my ex-Director [Sir Christopher Booth] or my minder from Park Crescent [Dr Sheila Howarth]. I think you have picked up something which we didn't mention, which was that the original idea was that once the Lister Building was built and functioning at the Clinical Research Centre then the Common Cold Unit work would be transferred to the CRC site. This didn't work out for various reasons. One was that it took an unconscionable time to get the Lister Unit built and functioning. Another was that our expectation that once we could grow the viruses there would be nothing interesting to do with large numbers of volunteers, but we were having repeated requests from pharmaceutical houses. 'You are the only place in Europe where we can test out our very hopeful new drug' or people like John Oxford who wanted to do studies on an interesting variant virus. There was nowhere else you could do it and we had the set up. So there was the pressure to keep it going. We tried therefore to find some alternative site with more capacity than the Lister Unit, such as Clare Hall – and that wasn't the only one – but that would have been nearer the Clinical Research Centre site, but we couldn't find anywhere adequate. The other thing is that you were right about the buildings falling down. That was policy. We were told that we would be moving and therefore the MRC wouldn't put any more money into the buildings. It was a policy that had to be reversed, because at one point we'd spent, and Tom [Keith Thompson] particularly had spent, many years of work designing a permanent site, which had been strongly recommended by an MRC committee, where volunteer work could be continued and the buildings could eventually be converted into an old people's home or flats or something of that sort, and all the designs were there. You and I, Chris, went to the Council meeting, and we were told it was a rubber stamp meeting, that the whole thing was basically agreed; and then someone somewhere said something about 'at a stroke' they were going to save a million pounds. And guess what was chopped.

[101] Dr David Tyrrell wrote: 'It was also proposed to rebuild the Unit with permanent buildings at a site near to the CRC. No site could be found, though we nearly moved to Clare Hall. Detailed plans for rebuilding at Salisbury were completed and agreed but Council approval was cancelled at the last minute.' Letter to Mrs L Reynolds, 4 September 1997.

Booth: I don't really want to get involved in the morale-sapping nature of the discussions that preceded the closure of this Unit. I would like to close our discussion today on a very much more positive note, and that is to say that sitting here – and I am very privileged to Chair this meeting – it's fascinating to see the still youthful exuberance and enthusiasm of all the scientists we have listened to this afternoon and this evening. It really has been fascinating. I think this is the sort of operation that could only have been done in this country and could only have been done under the auspices of the MRC. Universities wouldn't have touched it and never got involved with it. This is the way in which the MRC gives opportunities to people to devote themselves wholeheartedly and fully to research and not to have to attend all those morale-sapping bureaucratic committees so beloved of university professors. Now having said that, I would like to thank David Tyrrell and all those who have come here to contribute to this admirable discussion, and also to Tilli Tansey for having organized it and having set it up. Tilli, thank you very much.

Boon: May I make an appeal? There is one film which is missing, believed lost, which I think was the first official film made about the Common Cold Unit in 1947 by Paul Rother's unit in the COI Newsreel 'Britain Can Make It' – I think Issue 17. This issue has not been preserved for the nation, there's not a copy at the National Film Archive. I can't help thinking there must be a copy out there somewhere, if anybody has any ideas, please let me know.

GLOSSARY*

Cytopathic effect (CPE) – A method of confirming virus infection, where infected cells degenerate or die; recognized microscopically by shrinking from the side of the glass or fusing with each other.

Droplet infection – Spread of disease through the respiratory route, as organisms carried from person to person in droplets of saliva or respiratory mucus (sneeze, cough, speaking loudly).

Enzyme-linked immunosorbent assay (ELISA) – A method for detection of antibody-antigen reaction.

Fomites – Items (crockery, clothes, bedding, carpets, toys, books) retaining infectious material which then spreads the disease to others, until disinfected.

Gradocol membranes [Elford membranes] – Accurately graded collodion membranes used to measure the size of small particles, such as viruses, before the advent of the electron microscope. They had uniform pores from 3 microns or less, were thin and tough enough for steam sterilization but cheap enough to be disposable. The first viruses measured using these filters were from mice. See Andrewes C H. (1952–53) William Joseph Elford, 1900–1952. *Obituary Notices of Fellows of the Royal Society* **8**: 149–158, particularly 151–152.

Interferon – A virus inhibitor; a protein released by infected cells in response to virus infection.

Parker's 199 Medium – A defined nutrient medium which is particularly useful in the maintenance of cells for virus production in vaccine manufacture and in diagnostic work with the enteroviruses.

Roller tube culture – Cultures in test tubes or bottles continuously rotated in a near-horizontal rack within an incubator. See Parker R C. (1961) *Methods of Tissue Culture*. 3rd edn. London: Pitman Medical Publishing Co. Ltd, 158–161, including photograph of a motor driven rack.

Scrub typhus – Caused by *Rickettsiae orientalis*, which is carried by a mite and hosted by small rodents and birds. Rickettsiae are small bacteria, not true viruses.

Slit sampler – An instrument which sucks air through a narrow slit onto the surface of a culture medium, rotated slowly, just below the slit. See Bourdillon R B, Lidwell O M, Thomas J C. (1941) A slit sampler for collecting and counting airborne bacteria. *Journal of Hygiene* **41**: 197–224.

Staphylococcus aureus – Common organism in noses and on skins of healthy people which can cause infections of skin, internal organs and tissue; blood poisoning or food poisoning, especially in hospital conditions. Often resistant to penicillin.

Streptococcus pyogenes – Occurs in the upper respiratory tract of a small number of people; or in the vagina, the perineal skin or the throat. Causes various infections such as sore throats, scarlet fever, meningitis, wound or puerperal sepsis or blood poisoning. It may cause late complications such as rheumatic fever and kidney disease.

Streptococcus salivarius – An organism not easily classified, which is found in the human mouth, throat, and intestine. It is non-haemolytic. Used as an indicator of the presence of droplets of human secretions in air.

Tissue culture – The growth of animal or human cells in the laboratory under controlled conditions. The cells may descend from many tissue components or from a single cell or cell type. The improvement of techniques and availability of suitable media in the 1950s contributed to advances in experimental biology and medicine. See Parker R C. (1961) *Methods of Tissue Culture*. 3rd edn. London: Pitman Medical Publishing Co. Ltd.

Maitland-type tissue culture – Cultures of chopped tissue incubated in medium in a

* We are very grateful to Dr David Tyrrell for his considerable help in compiling this glossary.

flask at 37 °C.

Trypsinization technique – A method to prepare freshly dissociated cells and fragments of tissues and organs for cultivation using enzymes or chelating agents. In 1952, Dulbecco prepared a trypsin-dispersed cell suspension from minced chick embryos and later applied it to monkey-kidney tissue, for which the most efficient trypsinizing procedures have been designed. For a description of the technique, see Parker R C. (1961) *Methods of Tissue Culture*. 3rd edn. London: Pitman Medical Publishing Co. Ltd, 119–126.