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:
E M TANSEY D A CHRISTIE L A REYNOLDS

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CONTENTS

WITNESS SEMINARS IN THE HISTORY OF TWENTIETH CENTURY MEDICINE

E M TANSEY i

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

EDITORS : D A CHRISTIE AND E M TANSEY

TRANSCRIPT 1

GLOSSARY 72

RESEARCH IN GENERAL PRACTICE

EDITORS : L A REYNOLDS AND E M TANSEY

TRANSCRIPT 75

DRUGS IN PSYCHIATRIC PRACTICE

EDITORS: E M TANSEY AND D A CHRISTIE

TRANSCRIPT 133

GLOSSARY 205

THE MRC COMMON COLD UNIT

EDITORS: E M TANSEY AND L A REYNOLDS

TRANSCRIPT 209

GLOSSARY 267

INDEX 269

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**.