ELSEVIER

Progress in Nuclear Magnetic Spectroscopy 28 (1995) 1–9

PROGRESS IN NUCLEAR
MAGNETIC RESONANCE
SPECTROSCOPY

Milestones in the first fifty years of NMR

J.W. Emsley[a], J. Feeney[b,]*

[a]Chemistry Department, University of Southampton Southampton SO17 1BJ, UK
[b]Laboratory of Molecular Structure, National Institute for Medical Research, The Ridgeway, Mill Hill, London NW7 1AA, UK

Received 7 August 1995

1. Introduction

1995 marks the 50th anniversary of the detection of NMR in condensed phases, which started the avalanche of developments that led to the subject as it is known today. This issue of Progress in NMR Spectroscopy contains four articles giving historical perspectives on four of the major areas of NMR. No doubt there will be other attempts to document the history of NMR, some of them much more ambitious, but all will have to recognize that writing about the past is necessarily subjective and never complete, even when done by those who took part in the events. The authors of the four articles have all taken part in the development of NMR, and are still actively involved. We invited them to give an overview of particular, important aspects of the subject and, while this covers a great deal, there will be some major areas of NMR development not included. However these are being written about elsewhere [1].

We have also compiled a list of milestones in NMR. This is history at a glance, and is presented in the Table. We were helped in constructing this by Raymond Andrew, Jack Cohen, Jim Shoolery and Felix Wehrli, but it is essentially our own view of the events which shaped NMR. Omissions from the list reflect our limited knowledge and experience of NMR, and should not be taken as judgements by us of their relative importance.

The first volume of Progress in NMR Spectroscopy was published in 1965, and so we too have an anniversary to celebrate, albeit of 30 rather than 50 years. In the last 30 years we have endeavoured to cover the advances in NMR and its applications, a task which we, and hopefully you, have found a stimulating experience. Here we wish to present our own impressions of the development of NMR and to provide an overview of some of the material in the four articles in this issue of the Journal.

2. Early experiments

The experiments on condensed phases in 1945 were preceded by more than twenty years of investigations which started with the observation of hyperfine splittings in the optical spectra of particular atoms [2], and which led Pauli in 1924 [3] to propose that certain nuclei should possess spin angular momentum. That nuclei had magnetic moments was verified directly in the beam experiments of Gerlach and Stern [4] and these were later refined by Rabi and et al. [5] who first demonstrated the resonance effect produced by applying electromagnetic radiation. It was also realised that NMR should be observable on solid or liquid samples, and attempts to detect NMR signals

---

* Corresponding author.

0079-6565/95/$29.00
SSDI 0079-6565(95)01023-8

from such samples were made, but were initially unsuccessful, probably because the nuclei in the chosen samples had long spin–lattice relaxation times. NMR is an insensitive technique, and the detection of NMR signals from condensed phase samples had to wait for the development of more sophisticated electronic devices. It was achieved eventually in 1945 by groups led by Bloch [6], working at Stanford, and by Purcell [7] at Harvard. This early history of the subject is described in detail in the volume in the Encyclopaedia of NMR [1] devoted to the historical development of NMR, which also contains the biographies of many of those who were witnesses to these pioneering experiments. Andrew and Szczesniak describe some of the early developments in our opening article. Raymond Andrew was one of the first in Europe to become involved in this new, exciting subject. His laboratory at the University of Wales in Bangor hosted the first meeting in 1956 of the British Radiofrequency Spectroscopy Group, and one of us (JWE) was a member of the audience. Four years later he and Raymond met in the rather more formal setting of a Ph.D. viva.

The early years of NMR were dominated by work on solids. These gave spectra of great interest, being dominated by large anisotropic interactions such as the nuclear dipolar coupling, which could give structural information. Perhaps the greatest impact of the value of the method came with the realisation that molecular motion in the solid state could be detected with unprecedented sensitivity and ease. Initially, work on liquids was confined to studies of the factors which affect relaxation, beginning with the classic study by Bloembergen, Purcell and Pound [8], published in 1948. Then came the momentous discoveries of the chemical shift and spin–spin coupling phenomena. Both discoveries are marvellous examples of how the scientific method patiently uncovers what was previously unsuspected.

One of the first applications of the NMR technique was to attempt to measure accurate magnetic moments of different nuclei by comparing their resonance frequencies in the same applied magnetic field. During the course of these measurements it became clear that the measured values depended on the chemical environment of the nucleus under investigation. The phenomenon, known as the chemical shift effect, was first seen by Knight [9] in studies of metals and metal salts and later by Proctor and Yu [10] for ^{14}N and by Dickinson [11] for ^{19}F. Proctor and Yu, working in Bloch's laboratory, were attempting to measure the magnetic moment of the ^{14}N nucleus. They chose to examine NH_4NO_3 in the hope that this sample would give an NMR signal with twice the intensity of that of a molecule containing one nitrogen. They were astonished when they detected not one, but two separate ^{14}N signals. Their initial excitement based on the possibility that the differences might have some nuclear origin soon evaporated when they realised, together with Bloch, that they were probably dealing with some 'nasty chemical effect'.

The discovery of spin–spin coupling was no less dramatic [12–14]. One such observation was made by Proctor and Yu [12], who noted the multiplet structure of the ^{121}Sb resonance in $NaSbF_6$. They thought the spectrum contained five lines, but the two weak outer lines of the septet were discernible, and were pointed out by Gutowsky and McCall [13], who had characterised the phenomenon in more detail by observing the different multiplicities produced by neighbouring groups of spins. It was well known at the time that direct interaction between the nuclear magnetic moments produced splittings in the solid state, but it was also firmly understood that this interaction must vanish in a liquid when the internuclear vector is moving rapidly and randomly with respect to the direction of the applied magnetic field. An explanation of this new phenomenon therefore required the postulation of a new way for two nuclear spins to sense their mutual spin states. Such an explanation was provided by Purcell and Ramsey in 1952 [15].

The effects of spin–spin coupling were also observed independently as a modulation on the newly discovered spin echo. Hahn [16] discovered his amazing echo phenomenon in 1949, and the observation of echo modulation was published in 1951 by Hahn and Maxwell [14]. The discovery of the spin echo phenomenon by Hahn is often presented as one of the great lucky discoveries. However, what is perhaps overlooked is that most scientists observe curious phenomena in their experimental work. Often this is because they do not fully understand what they are doing and not all observations are pursued. The only serendipitous aspect of the spin echo story was that Hahn observed the echoes when he was applying pairs of pulses for an unrelated reason. Fortunately, he quickly realised that the phenomenon he was observing was real and not some uninteresting artifact of the experiment.

Within seven years of the successful detection of NMR, all the important spectral parameters had been discovered and details about the origins of chemical shifts, spin–spin coupling and relaxation had been defined. The power of NMR for measuring the dynamics of inter- and intramolecular exchange processes had also been established.

The discoveries of the chemical shifts and spin–spin interaction, which make NMR such an important technique for chemists, dramatically altered the development of NMR, which became more and more the province of the chemist rather than the physicist. Today, while NMR is thought of as a minor part of physics, sometimes not even appearing in an undergraduate syllabus, it is regarded by chemists as the most important of all spectroscopies.

3. The development of spectrometers

The first generation of NMR spectroscopists had to build their own spectrometers. Present day users of the versatile commercial spectrometers now available should rightly marvel at the accomplishments of the early workers, such as Herbert Gutowsky at the University of Illinois, and Rex Richards at the University of Oxford, who, with their graduate students and postdoctoral workers, built their own spectrometers and then showed how the NMR technique could be used to solve problems in chemistry and physics. Commercial spectrometers began to appear in 1952, and Jim Shoolery, who was an early bird at Varian, chronicles in his article the developments that resulted in today's sophisticated spectrometers. Few, if any, experimental techniques have witnessed such advances in such a short period of time. The development of homogeneous, high field magnets is a fascinating story and has progressed from 0.7 T magnets of the first commercial spectrometer, to the 18.8 T magnets in use today. Over the years, the NMR community has come to expect a steady increase in the highest magnetic fields available, and it will be fascinating to see if this trend will be maintained in the future. At the moment there seems to be a limit of $\lesssim$ 1GHz resonance frequency for protons using the magnets made from currently available superconducting materials. The hope is that the new, high T_c superconductors, which are capable of sustaining higher magnetic flux densities, can be made into sufficiently long wires for the construction of stable magnets. If this is achieved, then the progression to higher fields will continue, and should pass the 1 GHz proton frequency barrier.

Spectrometer developments have not been confined to the magnets. Improvements in the electronics have been equally important, first through the use of solid state devices rather than thermionic valves, and more recently by the use of digital electronics. The early spectroscopists would often use inexpensive, ex-military radio transmitters and receivers. These had the advantage that if your experiment did not work, you could console yourself by tuning in to some music!

Over the years, steady improvements in the signal-to-noise ratio (S/N) have resulted mainly by increasing the field strength, by optimisation of probe design and by using improved pre-amplifiers and receivers. There have been no fundamental changes in the way the NMR signal is detected, which is still predominantly by measuring the emf induced in a coil. There have been some attempts to make dramatic improvements in detection sensitivity, such as by using SQUID devices, or by using cooled detection coils, but these approaches have still not become routine. The advent of equipment for coherently time-averaging signals was a major step forward in the 1960s: the so-called Computer of Average Transients, the CAT, was the forerunner of today's on-line computer. In the early 1960s computers started to be used, at first only as more versatile CATs, and those of us who acquired one of these new wonder machines were eager to implement the Fourier transform (FT) techniques introduced by Anderson and Ernst in 1965 [17]. However, this development was slow in becoming the standard method for recording spectra. On a visit to Southampton in about 1968, Richard Ernst was still somewhat pessimistic about the practicalities of using pulse excitation, followed by Fourier transformation of the response, as the standard way of recording NMR spectra. His doubts were based on the relative difficulty of doing the Fourier transformation. At that time it was not obvious that computers would soon become much faster and that disk storage would become much cheaper, allowing FT processing of data to become a trivial pursuit.

The discovery by Overhauser [18] of how to increase the S/N by transferring polarisation from electrons to nuclei not only made it possible to enhance NMR signals for some rather unusual samples, but also laid the foundation for the more general exploitation of the nuclear–nuclear Overhauser experiments which are now used routinely to improve the S/N of less sensitive nuclei. Sensitivity enhancement is still the Holy Grail for many NMR spectroscopists, who realise that they could solve many more problems if only the signals were not so weak. Perhaps the recent detection of NMR using the principles of the atomic force balance will stimulate the search for improved detection techniques which will be generally applicable.

We have seen that NMR started mainly as a way of studying solids, and then switched its emphasis to liquids with the discovery of chemical shifts and spin–spin couplings. These small effects are usually obscured in solids by the much larger anisotropic interactions, but by the 1960s the balance has been partly re-adjusted by the realisation that the broadening effects in solids could be dramatically reduced by a combination of spin-decoupling and magic angle spinning. It is instructive to note that there was almost a 20 year gap between the initial, and highly original, experiments of Andrew [19], and separately of Lowe [20], of the effects produced by rotating a solid sample, and the realisation by the wider NMR community of the potential of this technique for studying solid samples by NMR. Andrew and Szczesniak in their article give us a unique insight into how this subject developed to become a routine way of studying solids.

NMR appeared to be developing in a steady, but not spectacular way in the 1960s and early 1970s, and then came what can only be described as a revolutionary development, the advent of multidimensional NMR spectroscopy. Following this, there was a breathtaking pace of progress, brought about by the force of original ideas pouring out from many laboratories, but most notably from these working with Richard Ernst in Zurich, Ray Freeman in Oxford, and Alex Pines in Berkeley, combined with the rapid improvements in instrumentation which made the implementation of these ideas a practicality for ordinary NMR spectroscopists.

4. Biological applications

NMR started as the plaything of the physicists, became the favourite toy of the chemists and finally went on to seduce the biochemists. We invited Jack Cohen and his colleagues to provide a broad overview of the development of the biological applications of NMR embracing not only the structural and functional studies of isolated biological macromolecules but also ‘in vivo’ NMR studies.

Pioneering workers such as Mildred Cohn, Oleg Jardetzky and Bob Shulman were convinced of the potential value of the technique in biochemistry even in the days when the problems of low sensitivity and chemical shift dispersion could not be adequately tackled with the available instrumentation. The challenge of being able to study successfully large macromolecules at reasonable concentrations has been one the major driving forces encouraging the remarkable instrumental advances over the last 30 years. From the first, almost featureless, ^{1}H spectrum recorded for a protein in 1957 [21], there have been truly amazing instrumental and methodological advances which now allow essentially complete assignments for proton resonances in proteins with molecular masses up to 30 kDa. The successful harnessing of NOE effects for making signal assignments and for providing distance constraints for subsequent structural work was an important feature in the development of structural biological NMR. Many of the pioneering experiments in this field were made by Wüthrich and his co-workers who, in 1985, reported the first complete NMR structure determination for a globular protein [22]. The extension of this approach to large proteins was only made possible by the subsequent development of multidimensional NMR techniques in combination with ^{13}C and ^{15}N labelled proteins as typified in the work of Bax and Clore and their co-workers. NMR determined structures of comparable quality to 0.20–0.25 nm resolution X-ray structures can now be obtained for protein–ligand complexes in solution.

In the early 1970s, a completely new area of NMR study was opened up by the reports of Moon and Richards [23] and of Hoult and co-workers [24] showing that it was possible to record high resolution ^{31}P NMR spectra on cells and intact organs. There was great excitement at the time at the prospect of eventually being able to study directly the chemistry within living tissue in a non-invasive manner. Since the initial pioneering ^{31}P studies on muscle metabolism and the ^{13}C and ^{31}P studies of cellular metabolism, the technique has progressed to the stage where it can monitor biochemical responses to exercise, stress, and drug therapy in humans. It can also follow metabolic processes using the excellent perfusion methods that have been developed for studying cells and intact isolated organs. The combination of such approaches with improved techniques for localised magnetic resonance imaging in whole body studies present enormous opportunities for the future work. In fact, recent NMR imaging experiments have indicated the possibility of following the chemical changes in the brain accompanying various thought processes [25,26]. There seems to be no limit to the versatility of the NMR technique!

5. Imaging

Surely NMR is unique amongst spectroscopies in its range of applications, and in the areas of science which it affects. Which other spectroscopy can claim to be mentioned in a film by Woody Allen, and a best-selling book, the Bonfire of the Vanities? Of course, these latter indicators of influence are references to the medical imaging technique based on NMR. The article by Felix Wehrli recounts in a non-partisan way the history of the imaging method. We recall the intellectual excitement created in the NMR community by the early experiments demonstrating the physics of how to encode spatial information into an NMR spectrum (Lauterbur [27]; Mansfield and Grannell [28]). In particular, the experiments reported by Paul Lauterbur [27] on water in concentric glass tubes appealed by their simplicity at a time when the majority in the NMR community were thinking only in terms of improving ways of unravelling ever more complex spectra for larger and larger molecules. To point out that spatial resolution is obtained by deliberately applying field gradients, which are normally strenuously sought out and eliminated in high resolution spectroscopy, was a wonderful example of individual lateral thinking. Truly this was one of those thought-liberating experiments of which NMR in its first 50 years has seen so many examples.

The early workers [27,28,119] realised that their non-invasive imaging method could make its greatest contribution in the area of clinical imaging. However, the technique was initially greeted with much scepticism and its performance was compared very unfavourably with X-ray CT scanners which were already well-developed. The situation soon changed as the rapid progress in instrumental development and methodology allowed MRI (magnetic resonance imaging) to show some of its advantages in diagnostic medical imaging of soft tissues [29].These advantages derive from the extraordinary tissue contrast available via relaxation time differences. There are now many applications where MRI has become the diagnostic method of choice over the X-ray CT approach, and nowadays MRI scanners are used routinely in many hospitals. The great impact of MRI as a health care tool and the attendant publicity for the technique has certainly created a public awareness of the nuclear magnetic resonance phenomenon which NMR spectroscopists alone could never have achieved!

Table
Milestones in the development of nuclear magnetic resonance[a]

1924–1939	Early work characterising nuclear magnetic moments and using beam methods [3,4,5].
1936	First attempt (unsuccessful) to detect NMR in solids [45,46]
1938	First NMR experiment using molecular beam method [5]
1945	Detection of NMR signals in bulk materials [6,7]
1948	Bloembergen, Purcell and Pound (BPP) paper on relaxation [8]
1948	Van Vleck expression for 2nd and 4th moments [63]
1949	Knight shift in metals [9]
1949–1950	Discovery of chemical shift [9–11]
	Discovery of spin–spin coupling [12–14]
1950	Hahn spin echoes [16]
1950	Discovery of nuclear quadrupolar resonance [31]
1951	Discovery of ^{1}H chemical shifts [30]
1952	First commercial NMR spectrometer (Varian 30 MHz)
1952	Bloch [6] and Purcell [7] receive Nobel Prize
1953	Bloch equations for NMR relaxation [6,32]
1953	Overhauser effect [18]
1953	Theory for exchange effects on NMR spectra [33,34]
1954	Carr–Purcell spin echoes [35]
1955	Solomon equations for NMR relaxation [36]
1955	Relaxation in the rotating frame [37]
1956	Early NMR studies on body fluids and tissues [120,121]
1953–1958	Sample spinning used for resolution improvement [32]
	Field gradient shimming with electric currents [38]
	Magnetic flux stabilisation (Varian)
	Spin-decoupling [39]
	Variable temperature operation ([40] and Varian).
1957	Redfield theory of relaxation [41]
1957	Analysis of second-order spectra [42,43,92,93]
1957	NMR spectrum shown to be Fourier transform (FT) of Free Induction Decay (FID) [44]
1958	Magic angle spinning for high resolution studies of solids [19,20]
1959	Blood flow measurements in vivo [47]
1959	Vicinal coupling constant dependence on dihedral angle [48]
1961	First 60 MHz field/frequency locked NMR spectrometer (Varian A60)
1962	First superconducting magnet NMR spectrometer (Varian 220 MHz)
1962	Indirect detection of nuclei heteronuclear double resonance (INDOR) [49]
1963	Liquid crystal solvents used [54]
1964	Spectrum accumulation for signal averaging [52]
1965	Nuclear Overhauser enhancements (NOE) used in conformational studies [50]
1965	Deuterium spectrum of a liquid crystal [51]
1965	Fourier transform (FT) techniques introduced [17,52]
1967	Spin multiplets detected in solids [53]
1969	Nuclear ferromagnetism [56]
1969	First commercial FT NMR spectrometer (Bruker 90 MHz)
1969	Computer controlled pulse programmers
1969	Lanthanide paramagnetic shift reagents [57]
1970–1975	^{13}C studies at natural abundance become routine
1970	First commercial FT spectrometer with superconducting magnet (Bruker 270 MHz)
1971	Pulse sequences for solvent signal suppression [58]
1971	T_1 relaxation measurements in FT mode [60]
1971	Two-dimensional (2D) NMR concept suggested [61]
1971	Photo CIDNP (chemically induced dynamic nuclear polarisation) [64,65]
1972	^{13}C studies of cellular metabolism [62]
1973	^{31}P detection of intracellular phosphates [23]
1973	NMR analysis of body fluids [23] and tissues [24]

Table

1973	Spin-imaging methods proposed [27,28,119]
1973	NMR diffraction used for NMR imaging [28]
1973	Zeugmatography: first two-dimensional NMR image [27]
1973	360 MHz superconducting NMR spectrometer (Bruker)
1974	Sensitive point imaging method [66]
1974	2D-NMR techniques developed [67]
1975	Slice selection in imaging by selective excitation [68–70]
1975	Fourier zeugmatography [71]
1976–1979	^{31}P studies of muscle metabolism [72–80]
1976	Cross polarisation/magic angle spinning for solids [81]
1977	First 600 MHz spectrometer (non-persistent) (Mellon Institute)
1977–1980	Spin-imaging of human limbs and organs [82]
1977	Echo-planar imaging [83]
1977–1978	Whole-body scanning
1979	Detection of insensitive nuclei enhanced by polarisation transfer (INEPT) [84]
1979	Detection of heteronuclear multiple quantum coherence (HMQC) [55,85]
1979	500 MHz superconducting spectrometer (Bruker)
1979	Chemical shift imaging [86–89]
1980	Surface coils used for in vivo NMR [90]
1980	Spin warp-imaging [91]
1980	3D-projection reconstruction [94]
1980	Pulse field gradients used for coherence selection [115]
1981	Composite pulse decoupling [98,109]
1981	NMR used to diagnose a medical condition [95]
1981–1983	Perfusion methods used for NMR studies of cell metabolism [96,97]
1982	Full assignments for small protein [99]
1983	First 3D structures of proteins from NMR data [22,100]
1983	Whole body imaging at 1.5 T [101]
1984–1987	Gradient methods used for spatial localisation [102–104]
1984	Combined imaging and spectroscopy (human brain) [105]
1985	FLASH imaging [106]
1985	MR Angiographic images [107]
1986	NMR microscopy imaging on live cell [108]
1987	600 MHz superconducting spectrometer (Bruker; Varian; Oxford Instruments)
1987	Echo-planar imaging at 2 T [110]
1988	2D-NMR combined with isotopically labelled proteins for full assignments [111]
1988	Whole body imaging and spectroscopy at 4 T [112]
1989	3D-NMR on isotopically labelled proteins [113]
1990	4D-NMR on isotopically labelled proteins — assignment and conformation [114]
1990	Pulse field gradients routinely incorporated into pulse sequences [115,116]
1991	Functional MR-detection of cognitive responses [25,26]
1991	Ernst receives Nobel Prize
1992	750 MHz spectrometers (Bruker; Varian; Oxford Instruments)
1993	NMR microscopy using superconducting receiver coil [117]
1994	NMR force detection [118]

[a] Some of the milestones were taken from Feeney [59] and others from discussions with Raymond Andrew, Jack Cohen, Jim Schoolery and Felix Wehrli.

References

[1] Encyclopaedia of NMR, Vol. 1, D.M. Grant and R.K. Harris (Eds.), Wiley, New York, 1995.

[2] S. Tolansky, High Resolution Spectroscopy, Methuen, London, 1947.

[3] W. Pauli, Naturwisschaften, 12 (1924) 741.

[4] W. Gerlach and O. Stern, Ann. Phys. Leipzig., 74 (1924) 673.

[5] I.I. Rabi, S. Millman, P. Kusch and J.R. Zacharias, Phys. Rev., 55 (1939) 526; 53 (1938) 318.

[6] F. Bloch, W.W. Hansen and M.E. Packard, Phys. Rev., 69 (1946) 127.

[7] E.M. Purcell, H.C. Torrey and R.V. Pound, Phys. Rev., 69 (1946) 37.
[8] N. Bloembergen, E.M. Purcell and R.V. Pound, Phys. Rev., 73 (1948) 679.
[9] W.D. Knight, Phys. Rev., 76 (1949) 1259.
[10] W.G. Proctor and F.C. Yu, Phys. Rev., 77 (1950) 717.
[11] W.C. Dickinson, Phys. Rev., 77 (1950) 736.
[12] W.G. Proctor and F.C. Yu, Phys. Rev., 81 (1951) 20.
[13] H.S. Gutowsky and D.W. McCall, Phys. Rev., 82 (1951) 748.
[14] E.L. Hahn and D.E. Maxwell, Phys. Rev., 84 (1951) 1246.
[15] E.M. Purcell and N.F. Ramsey, Phys. Rev., 85 (1952) 142.
[16] E.L. Hahn, Phys. Rev., 80 (1950) 580.
[17] R.R. Ernst and W.A. Anderson, Rev. Sci. Instrum., 37 (1966) 93.
[18] A.W. Overhauser, Phys. Rev., 92 (1953) 411.
[19] E.R. Andrew, A. Bradbury and R.G. Eades, Nature, 182 (1958) 1659; 183 (1959) 1802.
[20] I.J. Lowe, Phys. Rev. Lett., 2 (1959) 285.
[21] M. Saunders, A. Wishnia and J.C. Kirkwood, J. Amer. Soc., 79 (1957) 3289.
[22] M.P. Williamson, T. Havel and K. Wüthrich, J. Mol. Biol., 182 (1985) 195.
[23] R.B. Moon and J.H. Richards, J. Biol. Chem., 248 (1973) 7276.
[24] D.I. Hoult, S.J.W. Busby, D.G. Gadian, G.K. Radda, R.E. Richards and P.J. Seeley, Nature, 252 (1974) 285.
[25] J.W. Belliveau, D.N. Kennedy, R.C. McKinstry, B.R. Buchbinder, R.M. Weisskoff, M.S. Cohen, J.M. Vevea, T.J. Brady and B.R. Rosen, Science, 254 (1991) 716–719.
[26] J. Prichard, D. Rothman, E. Novotny, O. Petroff, T. Kuwabara, M. Avison, A. Howseman, C. Hanstock and R. Shulman, Proc. Natl. Acad. Sci. USA, 88 (1991) 5829.
[27] P.C. Lauterbur, Nature, 242 (1973) 190.
[28] P. Mansfield and P.K. Grannell, J. Phys. C: Solid State Phys., 6 (1973) L422.
[29] P.G. Morris, in R. Budd and S.E. Cozzens (Eds.), Invisible Connections: Instruments, Institutions and Science, SPIE Optical Engineering Press, Chapter 11, 1992.
[30] J.T. Arnold, S.S. Dharmatti and M.E. Packard, J. Chem. Phys., 19 (1951) 507.
[31] H.G. Dehmelt and H. Kruger, Naturwiss, 37 (1950) 111.
[32] F. Bloch, Phys. Rev., 94 (1954) 946.
[33] H.S. Gutowsky, D.W. McCall and C.P. Slichter, J. Chem. Phys., 21 (1953) 279.
[34] H.M. McConnell, J. Chem. Phys., 28 (1958) 430.
[35] H.Y. Carr and E.M. Purcell, Phys. Rev., 94 (1954) 630.
[36] I. Solomon, Phys. Rev., 99 (1955) 559.
[37] A.G. Redfield, Phys. Rev., 98 (1955) 1787.
[38] M.J.E. Golay, Rev. Sci. Instr., 29 (1958) 313.
[39] A.L. Bloom and J.N. Shoolery, Phys. Rev., 97 (1955) 1261.
[40] H.S. Gutowsky, L.H. Meyer and R.E. McClure, Rev. Sci. Instr., 24 (1953) 644.
[41] A.G. Redfield, IBM J. Res. Dev., 1 (1957) 19.
[42] H.S. Gutowsky, C.H. Holm, A. Saika and G.A. Williams, J. Amer. Chem. Soc., 79 (1957) 4596.
[43] H.J. Bernstein, J.A. Pople and W.G. Schneider, Can. J. Chem., 35 (1957) 65; 35 (1957) 1060.
[44] I.J. Lowe and R.E. Norberg, Phys. Rev., 107 (1957) 46.
[45] C.J. Gorter, Physica, 3 (1936) 995.
[46] C.J. Gorter and L.F.J. Broer, Physica, 9 (1942) 591.
[47] J.R. Singer, Science, 130 (1959) 1652.
[48] M. Karplus, J. Chem. Phys., 30 (1959) 11; J. Phys Chem., 64 (1960) 1793.
[49] E.B. Baker, J. Chem. Phys., 37 (1962) 911.
[50] F.A.L. Anet and A.J.R. Bourn, J. Amer. Chem. Soc., 87 (1965) 5250.
[51] W.D. Phillips, J.C. Rowell and L.R. Melby, J. Chem. Phys., 41 (1964) 2551.
[52] R.R. Ernst, Rev. Sci. Instr., 36 (1965) 1689.
[53] E.R. Andrew, L.F. Farnell and T.D. Gledhill, Phys. Rev. Lett., 19 (1967) 6.
[54] A. Saupe and G. Englert, Phys. Rev., 11 (1963) 462.
[55] L. Mueller, J. Amer. Chem. Soc., 101 (1979) 4481.
[56] M. Chapellier, M. Goldman, V.H. Chan and A. Abragam, C.R. Aca. Sci., 268 (1969) 1530.
[57] R.E. Sievers (Ed.), NMR Shift Reagents, Academic Press, New York, 1973.
[58] S.L. Patt and S.B. Sykes, J. Chem. Phys., 54 (1971) 1148.
[59] J. Feeney, in R. Budd and S.E. Cozzens (Eds.), Invisible Connections: Instruments, Institutions and Science, SPIE Optical Engineering Press, Chapter 10, 1992.
[60] R.L. Vold, J.S. Waugh, M.P. Klein and D.E. Phelps, J. Chem. Phys., 48 (1968) 3831.
[61] J. Jeener, Ampere International Summer School, Basko Polje, Yugoslavia, 1971, (unpublished).
[62] N.A. Matwiyoff and T.E. Needham, Biochem. Biophys. Res. Commun., 49 (1972) 1158.
[63] J.H. Van Vleck, Phys. Rev., 74 (1948) 1168.
[64] R. Kaptein, J.C.S. Chem. Commun., 732 (1971).
[65] R. Kaptein, K. Dijkstra and K. Nicolay, Nature, 247 (1978) 293.
[66] W.S. Hinshaw, Phys. Lett., 48 (1974) 87.
[67] W.P. Aue, E. Bartholdi and R.R. Ernst, J. Chem. Phys., 64 (1976) 229.
[68] A.N. Garroway, P.K. Grannell and P. Mansfield, J. Phys. C: Solid State Phys., 7 (1974) L457.
[69] R.J. Sutherland and J.M.S. Hutchison, J. Phys. E., 11 (1978) 79.
[70] D.I. Hoult, J. Magn. Reson., 26 (1977) 165; 35 (1979) 69.
[71] A. Kumar, D. Welti and R.R. Ernst, J. Magn. Reson., 18 (1975) 69.
[72] C.T. Burt, T. Glonek and M. Bárány, J. Biol. Chem., 251 (1976) 2584.
[73] C.T. Burt, T. Glonek and M. Bárány, Science, 195 (1977) 145.
[74] B. Garlick, G.K. Radda and P.J. Seeley, Biochem. Biophys. Res. Commun., 74 (1977) 1256.
[75] E. Jacobus, G.J. Taylor, D.P. Hollis and R.L. Nunnally, Nature, 265 (1977) 756.
[76] P. Hollis and R.L. Nunnally, Biochem. Biophys. Res. Commun., 75 (1977) 1086.
[77] J. Yoshizaki, J. Biochem., 84 (1977) 11.

[78] M. Cohen and C.T. Burt, Proc. Natl. Acad. Sci. USA, 74 (1977) 4271.
[79] A. Sehr and G.K. Radda, Biochem. Biophys. J. Commun., 77 (1977) 195.
[80] C.T. Burt, S.M. Cohen and M. Bárány, Ann. Rev. Biophys. Bioeng. 8 (1979) 1.
[81] J. Schaefer and E.O. Stejskal, J. Amer. Chem. Soc., 98 (1976) 1030.
[82] P.G. Morris, NMR Imaging in Medicine and Biology, Oxford University Press, 1986.
[83] P. Mansfield and I.L. Pykett, J. Magn. Reson., 29 (1978) 355.
[84] G.A. Morris and R. Freeman, J. Amer. Chem. Soc., 101 (1979) 760.
[85] D.P. Burum and R.R. Ernst, J. Magn. Reson., 39 (1980) 163.
[86] J. Cox and P.J. Styles, J. Magn. Res., 40 (1980) 209.
[87] T.R. Brown, P.M. Kincaid and K. Ugurbil, Proc. Natl. Acad. Sci. USA, 79 (1982) 3523.
[88] A.A. Maudsley, S.K. Hilal, W.H. Perman and H.E. Simon, J. Magn. Reson., 51 (1983) 147.
[89] A.A. Maudsley, A. Oppelt and A. Ganssen, Siemens Forsch. Entwickl. Ber, 8 (1979) 326.
[90] J.J.H. Ackerman, T.H. Grove, G.G. Wong, D.G. Gadian and G.K. Radda, Nature, 283 (1980) 167.
[91] W.A. Edelstein, J.M.S. Hutchison, G. Johnson and T. Redpath, Phys. Med. Biol., 25 (1980) 751.
[92] J.T. Arnold, Phys. Rev., 102 (1956) 136.
[93] W.A. Anderson, Phys. Dev., 102 (1956) 151.
[94] C.M. Lai and P.C. Lauterbur, J. Phys. E. Sci. Instr., 13 (1980) 747.
[95] B.D. Ross, G.K. Radda, D.G. Gadian, G. Rocker, M. Esiri and J. Falconer-Smith, J. New Engl. J. Med., 304 (1981) 1338.
[96] K. Ugurbil, D.L. Guernsey, T.R. Brown, P. Glynn, N. Tobkes and I.S. Edelman, Proc. Natl. Acad. Sci. USA, 78 (1981) 4843.
[97] D.L. Foxall and J.S. Cohen, J. Magn. Reson., 52 (1983) 346.
[98] M.H. Levitt and R. Freeman, J. Magn. Reson., 43 (1981) 502.
[99] G. Wagner and K. Wüthrich, J. Mol. Biol., 155 (1982) 347.
[100] W. Braun, G. Wider, K.H. Lee and K. Wüthrich, J. Mol. Biol., 169 (1983) 921.
[101] H.R. Hart, P.A. Bottomley, W.A. Edelstein, S.J. Karr, W.M. Leue, O. Mueller, R.W. Redington, J.F. Schenck, L.S. Smith and D. Vatis, Am. J. Roentgenol, 141 (1983) 1195.
[102] P.A. Bottomley, U.S. Patent, 4 480 228, 1984.
[103] R.J. Ordidge, A. Connelly and J.A.B. Lohman, J. Magn. Reson., 66 (1986) 283.
[104] J. Frahm, K.D. Merboldt and W. Hänicke, J. Magn. Reson., 72 (1987) 502.
[105] P.A. Bottomley, H.R. Hart Jr, W.A. Edelstein, J.F. Schenck, L.S. Smith, W.M. Leue, O.M. Mueller and R.W. Redington, Radiol., 150 (1984) 441.
[106] A. Haase, J. Frahm, D. Matthaei, W. Hänicke and K.D. Merboldt, J. Magn. Res., 67 (1986) 258.
[107] V.J. Wedeen, R.A. Mueli, R.R. Edelman, S. Geller, L. Frank, T. Brady and B. Rosen, Science, 230 (1985) 946.
[108] J. Aguayo, S. Blackband, J. Schoeniger, M. Mattingly and M. Hintermann, Nature, 322 (1986) 190.
[109] J.S. Waugh, J. Magn. Reson., 49 (1982) 517.
[110] I.L. Pykett and R.R. Rzedzian, Magn. Res. Medicine, 5 (1987) 563.
[111] D.H. Torchia, S.W. Sparks and A. Bax, Biochemistry, 27 (1988) 5135.
[112] H. Barfuss, H. Fischer, D. Hentschel, R. Ladebeck and J. Vetter, Radiol., 169 (1988) 811.
[113] D. Marion, P.C. Driscoll, L.E. Kay, P.T. Wingfield, A. Bax, A.M. Gronenborn and G.M. Clore, Biochemistry, 28 (1989) 6150.
[114] L.E. Kay, G.M. Clore, A. Bax and A.M. Gronenborn, Science, 249 (1990) 411.
[115] A. Bax, P.G. De Jong, A.F. Mehlkopf and J. Schmidt, Chem. Phys. Lett., 69 (1980) 567.
[116] R.E. Hurd, J. Magn. Reson., 87 (1990) 422.
[117] R.D. Black, T.A. Early, P.B. Roemer, O.M. Mueller, A. Morgo-Campero, L.G. Turner and G.A. Johnson, Science, 259 (1993) 793.
[118] D. Rugar, O. Zugar, S. Hoen, C.S. Yannoni, H.M. Vieth and R.D. Kendrick, Science, 264 (1994) 1560.
[119] R. Damadian, K. Zaner, D. Hor and R. Dimaio, Proc. Natl. Acad. Sci. U.S.A., 71 (1974) 1471.
[120] O. Jardetzky and J.E. Wertz, Arch. Biochem. Biophys., 65 (1956) 569.
[121] E. Odeblad, N. Bhar and G. Lindstrom, Arch. Biochem. Biophys., 63 (1956) 221.