RAY FREEMAN

6 January 1932 – 1 May 2022

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Elected FRS 1979

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Ray Freeman pioneered many of the important advances in the technique of liquid-state nuclear magnetic resonance spectroscopy: he changed fundamentally the ways in which chemists and structural biologists use NMR. Born in Nottingham, he was an undergraduate chemistry student at Oxford after National Service working with radar, and completed his Part II and doctoral research with Rex Richards FRS. After brief spells with Anatole Abragam in Saclay, France, and at the National Physical Laboratory in Teddington, he worked for ten years in the research department of Varian Associates, Palo Alto, USA. He was appointed as Lecturer in Physical Chemistry and Tutorial Fellow of Magdalen College, Oxford, in 1973, and subsequently promoted to Aldrichian Praelector. In 1987 he was appointed to the John Humphrey Plummer chair at the University of Cambridge, where he remained active in research long after his retirement in 1999, publishing his last paper at the age of 84.

EARLY YEARS 1930-1951

Ray was born in Long Eaton, Derbyshire, in 1932, the only child of Albert and Hilda Freeman. Tragedy hit the Freeman household in 1940 when Albert, a builder and joiner by trade, died as a result of an infection contracted after routine surgery. This had a profound effect on Ray; it perhaps accounts for how intensely he felt about his own children and grandchildren, and also how much he valued the guidance and mentorship of figures such as Sir Rex Richards. Hilda had an interest in art and painting, but at that time this was not considered to be a suitable occupation for a young woman. Ray’s eye for graphic art and his beautiful handwriting were most definitely things he acquired from his mother.

Hilda Freeman supported herself and Ray after the death of Albert. She was immensely proud of Ray’s achievements at school and supported his ambition to carry on with his studies. Ray won a scholarship to Nottingham High School, which had, as Ray recorded, some excellent teachers. Here Ray developed a determination to study science, but the headmaster thought that bright pupils such as Ray should be directed to study the classics. The intervention of his kindly physics master, Dr Somekh, allowed Ray to pursue his passion for science. It is typical of Ray that many decades later he recalled both the incident, and the name of the teacher whose intervention was so critical.

Further academic success followed, with Ray gaining a scholarship to Lincoln College Oxford in 1949. At this time National Service was compulsory, so Ray joined the Royal Air

Force, gaining useful experience of radio-frequency circuits, finally starting university in October 1951.

OXFORD 1951–1957

No doubt Ray learnt a great deal of chemistry from his Tutors at Lincoln College, including the young Rex Richards who was to have such an influence on Ray. However, it was his non-academic activities which led to two of the great loves of his life. The first was his discovery of the exuberant joy and energy of traditional jazz, and the second was meeting a young Frenchwoman, Anne-Marie, who was also studying in Oxford and became his wife.

Then, as now, Oxford undergraduate chemists devoted their fourth year (‘Part II’) to research. Ray chose to work with Rex, who had just completed building an NMR spectrometer – one of the first in the UK. It was a formidable piece of equipment, assembled from ‘war surplus’ electronics with a home-made electromagnet. Ray’s doctoral work with Rex involved spending much of his time developing the spectrometer. His first paper (1), on the proton NMR spectrum of polycrystalline potassium amide, reported the H—H distance in the water of crystallisation. Ray recalled this as painstaking work for little reward. More profitable was searching for the resonances of nuclei such as ^{7}Li, ^{59}Co, ^{71}Ga, ^{115}In, and ^{205}Tl, for which the precise resonance frequencies were not then known. This was greatly aided by Ray’s use of a sensitive super-regenerative detector, popular with amateur radio enthusiasts at the time and adapted for NMR by Robert Pound (the ‘Pound box’). Ray greatly appreciated, and benefitted from, Rex’s light touch when it came to supervising graduate students. Advice was freely given and guidance was gentle, but above all Rex encouraged his students to explore and to be adventurous. Ray’s own style of supervision was much the same, and proved equally effective.

SACLAY 1957–1959

After Ray completed his D.Phil., Rex – knowing that Anne-Marie had returned home to Paris – suggested that he might like to spend a period working at Saclay in the group of Anatole Abragam. Ray leapt at the possibility, and duly arrived in Paris in 1957. Abragam’s group saw NMR very much from a physicist’s point of view, emphasising theory and mathematics. Ray commented of this time that his rather more pragmatic chemist’s approach was regarded with some suspicion. Perhaps this was responsible for Ray’s long-held belief that if you could only explain something with heavy-duty theory and mathematics, you probably had not really understood what was going on. Ray always felt that a physical picture, combined with a good dose of intuition, was the best way of explaining something.

At Saclay, Ray worked with Robert Pound (of the Pound box) on refinements and adaptations of the regenerative detector. It soon dawned on him that it was not suited to high-resolution work, but was an excellent basis for stabilizing the resonance frequency of the spectrometer, anticipating the now ubiquitous use of field-frequency locking. Ray also encountered Ionel Solomon, whom he greatly revered for his insight and advice, including him in the list of six ‘sorcerers’ from whom he learned much as an ‘apprentice’.

In 1958 Ray and Anne-Marie married. The wedding was touch-and-go as French bureaucracy did not look too kindly on an English–French conjunction, but with timely intervention from well-placed friends and relatives all was well.

NATIONAL PHYSICAL LABORATORY, TEDDINGTON 1959–1963

After a stimulating two years at Saclay, Ray moved to the National Physical Laboratory (NPL) in Teddington, Middlesex, living with Anne-Marie and their baby daughter Dominique in New Malden in Surrey. A second daughter, Anne, joined the family the following year. Ray's time as a senior scientific officer at the NPL was highly productive, leading to a string of papers on multiple resonance methods for determining the relative signs of coupling constants and for the analysis of complex spectra. He collaborated with a wide range of scientists, including Ray Abraham, Peter Diehl, Laurie Hall, Keith McLauchlan FRS, Klaus Pachler and David Whiffen.

Ray's work with Pound led to a characteristically elegant method (2) for automatically mapping magnetic field contours in an NMR magnet, using a probe scanned over the pole face by electric motors. The active components used were still thermionic valves, but already Ray's circuit used semiconductor diodes, and within a few years almost all NMR equipment would use solid-state electronics. Sixty years on, automated field mapping ('gradient shimming') is used in virtually all modern high-resolution spectrometers.

Ray had a healthy respect for the role of blind chance in science. In the early 1960s, many British scientists followed a well-trodden path to the USA. Ray had received an invitation to join the group of Britton Chance in Philadelphia, but his boss at the NPL, John Pople FRS (Nobel Laureate 1998) suggested that Ray first look into other possibilities. Ray contacted John Baldeschweiler at Harvard, Paul Lauterbur in Pittsburgh, Britton Chance, and Wes Anderson at Varian Associates. The first to come up with financial support was Wes Anderson; had he delayed just a few hours, Ray would instead have gone to Harvard, and the history of NMR would have been quite different.

VARIAN ASSOCIATES, PALO ALTO, CALIFORNIA 1963–1973

Ray's 1961 sabbatical, the California weather and the warm welcome from Wes Anderson and colleagues led to his moving to Varian in 1963. The family settled very happily – and grew, with the arrivals of Louise, Jean-Marc and Lawrence – in Ladera, close to Palo Alto.

At that time Varian's research was world-leading, eclipsing that of almost all university groups. Initially Ray worked with Wes on double resonance methods. Spin tickling (3), the use of a very weak continuous second radiofrequency (RF) field to reveal connectivities between different transitions, is nowadays little remembered. However, like many of the methods pioneered by Ray at Varian, it had a lasting impact, and was responsible for the joint award to Ray and Wes of the Russell Varian Prize in 2012. It sowed the seeds for later two-dimensional (2D) NMR methods such as COSY and eCOSY (Aue *et al.* 1976, Griesinger *et al.* 1985). Similarly, Ray's and Wes's papers on indirect detection laid the foundations for HSQC and HMBC, the mapping of protein energy landscapes by detecting transient 'dark state' protein conformations, and chemical exchange saturation transfer (CEST) and magnetization transfer contrast (MTC) methods in magnetic resonance imaging (MRI).

As early as 1963, Ray and Wes were using double-quantum transitions for spectral assignment (10). Almost twenty years later, Ray was to these in one of the most powerful structure elucidation methods in organic chemistry, the INADEQUATE (Incredible Natural Abundance DoublE QUAntum Transfer Experiment) technique (41, 45). From 1963 onwards, Ray's attention began to shift towards experiments using RF pulses, as opposed to the constant low-level RF magnetic fields used for almost all NMR work up to that point. This made it possible to study relaxation processes, giving access to a wide range of information about molecular structure and dynamics.

While Ray worked on double resonance and relaxation, another young European researcher at Varian, Richard Ernst ForMemRS (Nobel Laureate 1991) was – also in collaboration with Wes Anderson – doing the first practical experiments using the pulse Fourier transform (FT) method that was to revolutionise the practice of NMR. 'Practical' is perhaps stretching a point; the experiments required the nuclear free induction decay to be recorded, digitised, transferred to punched cards, transported by car to a remote mainframe computer, Fourier transformed by brute force numerical integration, and finally, a day later, plotted out to produce a spectrum. With hindsight, the sensitivity advantage brought by the Fourier transform method made it inevitable that it would supplant the CW method, but at the time Varian's management were slow to appreciate this, not least because the minicomputers that would make such methods practical were only just being developed. Referees were equally slow on the uptake: Ernst and Anderson's paper was rejected twice, before being published (Ernst & Anderson 1966). It took the Nobel Committee for Chemistry another 25 years to recognise the importance of this idea.

The development in 1970 of Varian's first commercial FT NMR spectrometer, the XL100, coincided with the arrival from England of a new collaborator, Howard Hill. This led to a series of classic papers that presaged many of the important developments of the next 20 years. The initial success of the FT method rested on its dramatic sensitivity advantage, but a secondary advantage proved even more important. This was the added flexibility afforded by separating the excitation of the nuclear spins from measurement of the resultant signals. Ray rapidly showed that by controlling the timing of proton irradiation it was possible to measure carbon-13 spectra both with and without Overhauser enhancement and with and without decoupled multiplets.

Ray's collaboration with Iain Campbell FRS on the effects of dipolar cross-relaxation (5) helped lay the foundations for the major impact of NMR on the determination of biomolecular structure in solution, of which Campbell went on to become a pioneer. Experiments combining heteronuclear double resonance with rapid spin echo trains showed that Hartmann-Hahn magnetization transfer, which is mediated by dipolar couplings in solids, could also be seen in liquids, mediated by scalar couplings. This is the basis of TOCSY (Braunschweiler & Ernst 1983), a key tool in modern structure elucidation.

The most far-reaching product of Ray's collaboration with Howard Hill was probably their invention of '*J*-spectroscopy' (4), in which the measurement of a train of spin echoes as a function of time maps out the modulation caused by scalar couplings. Their motivation was to suppress the effect of magnetic field inhomogeneity, enabling both the detection of very small couplings (as low as 0.05 Hz), and the measurement of couplings with unprecedented accuracy. The principle of mapping out signal evolution in a series of measurements using incremented time intervals was proposed independently by Jean Jeener as a key component of 2D NMR spectroscopy. When the first 2D NMR results were published by Richard Ernst, Ray was well-placed to see the power of Jeener's innovation, and rapidly exploited it in 2D analogues of *J*-spectroscopy.

For many years Varian Associates had thrived as a relaxed and creative research community as well as a commercial organisation, but by the early 1970s commercial considerations had begun to dominate. The failure to capitalise on their development of FT NMR opened the door to more agile competition, notably from Bruker. Varian began to lose both its pioneer ethos, and some of its best scientists. When Ray heard from his former NPL colleague David Whiffen of an opening for a physical chemist at Oxford, he initially put the letter straight into the waste bin as the salary looked so poor. When he realised that the university Lectureship was accompanied by a college Fellowship with its own salary, he retrieved the letter, applied, and was appointed. In Ray's words, "It turned out to be a brilliant move."

OXFORD 1973–1987

After over fifteen years working in pure research environments, academic life as a Lecturer in Physical Chemistry and Tutorial Fellow at Magdalen College posed significant challenges for Ray. His first priority was to prepare for the demands of the Oxford teaching system, which required multiple weekly tutorials for groups of 2–3 students. He therefore joined the undergraduate audiences for the lectures on physical chemistry. Somewhat conspicuous in such a young milieu, he was thought by the students to be some sort of government inspector. His second priority was to acquire an NMR spectrometer, which he did by submitting a research proposal on stopped flow kinetics to the Science Research Council. While no kinetic results were ever obtained, the SRC got good value; methods developed using this spectrometer are still in use in almost all Chemistry departments.

The spectrometer Ray purchased, and installed in room 049 of the Physical Chemistry Laboratory, was a Varian CFT-20 (figure 1), as a low-budget instrument for carbon-13 NMR. Varian's decision to economise on parts by using the built-in minicomputer to control as many functions as possible was providential. The instrument was controlled through a keyboard, and a small oscilloscope tube, driven directly by the computer, served both to display small amounts of text and to show spectra. All the key functions for acquiring spectra, generating RF pulses at the ^{13}C and ^{1}H Larmor frequencies, and digitising, recording and averaging free induction decays, were controlled by the computer. As a result, new experiments could be set up and tested in a matter of hours, simply by changing the control software.

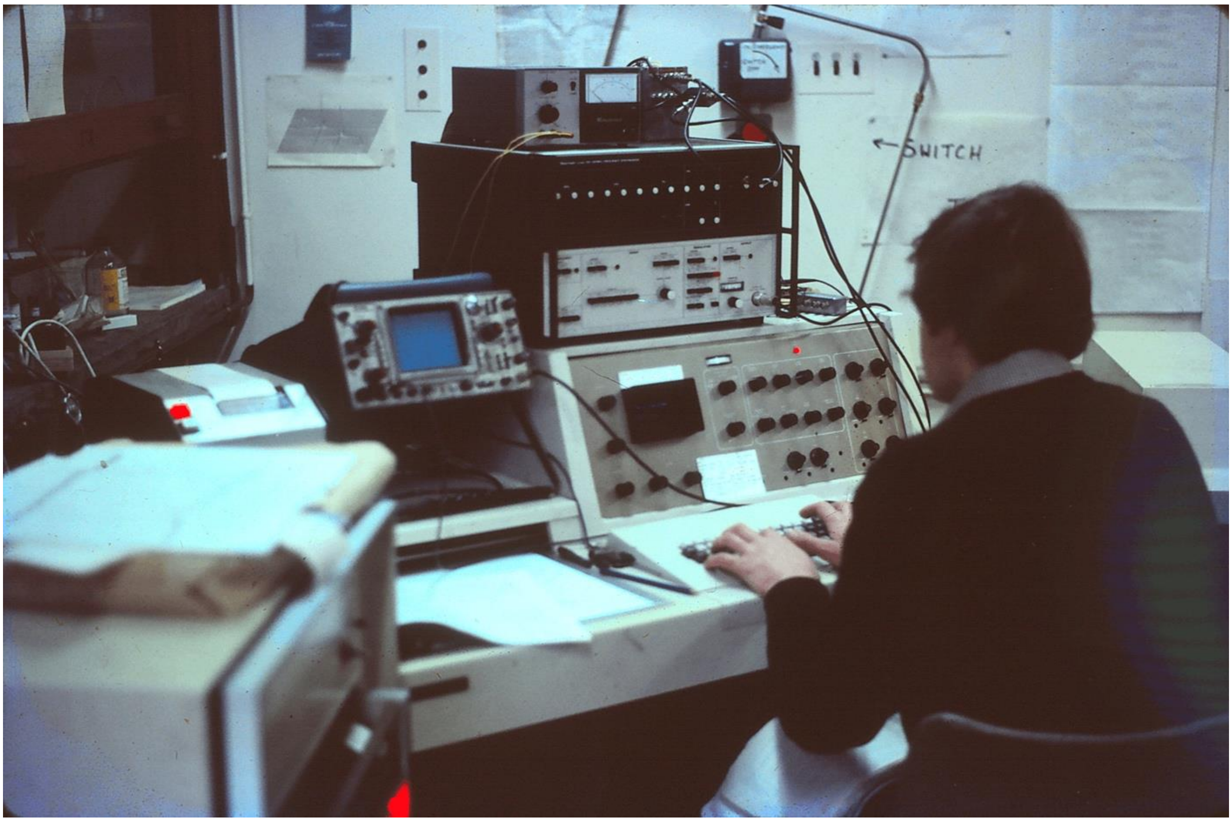


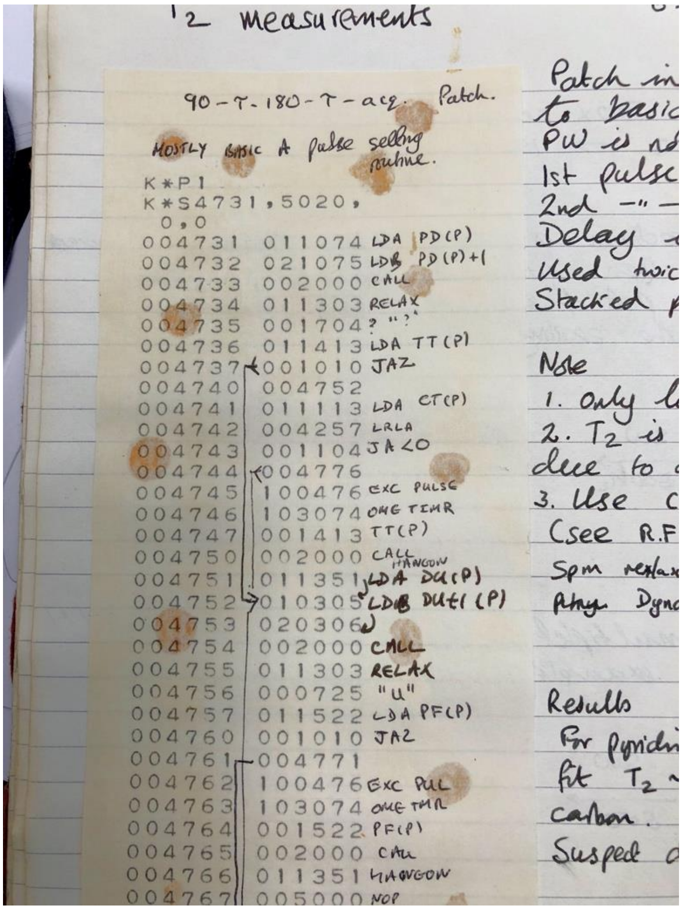
Figure 1. The CFT-20 spectrometer, with an unidentified graduate student (possibly JK or Tom Frenkiel) at the console. Photograph dated August 1982, kindly provided by Professor Peter Barker.

Ray's first two PhD students, David Turner (who began his Part II undergraduate project with Ray in autumn 1974) and Geoffrey Bodenhausen (who arrived in January 1975, having done some undergraduate research with Richard Ernst), set out to explore the possibilities of the new instrument. Initially, David worked on ^{13}C spin-lattice relaxation, and Geoffrey investigated using spin echo trains for T_2 measurement. This both revealed problems with the timer electronics, and required great ingenuity in adapting the machine code control programme to generate arbitrary pulse sequences. The next October they were joined by one of the authors (GAM) as an undergraduate research student, who set out to build a high-power RF amplifier to allow 'spin-locking' measurements of transverse relaxation. Alas the first test of this amplifier was the last, the expensive power transistor in the output stage failing almost immediately. Fortunately, Ray had also suggested looking into an experiment for measuring T_2 using transient nutations, and while this proved impractical the same computer code allowed a completely different experiment to be performed. This was what became known as the DANTE pulse sequence ('Delays Alternating with Nutations for Tailored Excitation'), which allows short, powerful RF pulses to achieve the same sort of frequency-selective excitation as a long, low-power pulse (6, 15; Morris 1996). The name DANTE was suggested by the resemblance between the trajectories of magnetizations subjected to a 90° DANTE sequence and the reverse of the trajectory taken by Dante and his guide Virgil up through Mount Purgatory in the *Divine Comedy*. (The name was given extra resonance by a fancied resemblance, spoilt only by the lack of glasses, between Ray and the portrait of Dante in Domenico di Michelino's depiction of the *Purgatorio* in the cathedral in Florence.)

At first sight it seems counter-intuitive to excite just one peak in a spectrum when the sensitivity advantage of the FT method rests on measuring many resonances at once. However, in FT NMR the excitation of the nuclear signal is separate from its measurement, so it is possible to excite selectively a decoupled ^{13}C signal, then switch of the decoupling and measure a single proton-coupled multiplet. The overlapping multiplets typically observed in proton-coupled ^{13}C NMR can thus be neatly decomposed into a set of individual multiplets, exciting each chemical shift in turn (6,7). Selective excitation proved a very fruitful idea,; while DANTE itself is now rarely used, many more sophisticated methods using amplitude- and phase-modulated RF pulses have been developed, many of them by Ray and his group (28, 31, 40).

Using DANTE to disentangle proton-coupled ^{13}C spectra brought an alternative method (Müller *et al.* 1975), published a few months previously by Richard Ernst and based on an unpublished idea from Jean Jeener, to Ray's attention. Ernst showed that ^{13}C signals could be dispersed in one dimension of a 2D spectrum according to both chemical shifts and couplings, and in the other just according to chemical shift, thus separating the multiplet structures. While the results were less impressive than those obtained with DANTE, and the effort required far greater, the power and potential of the 2D approach were immediately obvious. Ray saw straight away that a much more effective solution to the problem of unravelling ^{13}C multiplet structure was to add a 180° pulse to Ernst's pulse sequence, creating the first 2D *J*-spectroscopy experiment (8). This not only separated the individual multiplets out, dispersing signals according to chemical shifts and scalar couplings in orthogonal frequency dimensions, but also removed the limit imposed by magnetic field inhomogeneity on signal linewidths. The choice of pyridine as the first sample to be analysed was a fortunate one, as it revealed very early on the complications caused by strong coupling, and led to the production of software for the analysis of *J*-spectra (10, 12). Later, the loan of a new FT-80 spectrometer, to enable a 2DFT software package to be developed for other users, gave Ray's group access to proton NMR and allowed similarly detailed analysis of strongly-coupled homonuclear *J*-spectra (16).

Doing 2D NMR on the CFT-20, with its very limited computer memory (just 16k 16-bit words), was a formidable challenge. Geoffrey Bodenhausen, David Turner and Reinhard Niedermeyer (a visiting PhD student from the group of Dieter Leibfritz in Bremen) had to recode the software not only to generate the new pulse sequence required, but also to Fourier transform the free induction decays measured, transpose the resultant data matrix, and FT again, all within 16 kilobytes. Coding had to be done in 16-bit machine code, and the total number of data points in the resultant 2D spectrum was initially limited to 8k. Shortly afterwards a 1 megabyte hard disc was added, enabling much larger spectra to be processed. Figure 2 shows a short segment of code for a pulse sequence, with the instruction addresses and codes in octal and handwritten annotations in assembly language.



T_2 measurements

90-τ-180-τ-acq. Patch.

MOSTLY BASIC A pulse setting routine.

```
K*P1
K*S4731,5020,
 0,0
004731  011074 LDA PD(P)
004732  021075 LDB PD(P)+1
004733  002000 CALL
004734  011303 RELAX
004735  001704 ? "?"
004736  011413 LDA TT(P)
004737  001010 JAZ
004740  004752
004741  011113 LDA CT(P)
004742  004257 LRLA
004743  001104 JA<0
004744  004776
004745  100476 EXC PULSE
004746  103074 ONE TIMR
004747  001413 TT(P)
004750  002000 CALL
004751  011351 HANGON
               LDA DU(P)
004752  010305 LDB DU+1 (P)
004753  020306
004754  002000 CALL
004755  011303 RELAX
004756  000725 "u"
004757  011522 LDA PF(P)
004760  001010 JAZ
004761  004771
004762  100476 EXC PUL
004763  103074 ONE TMR
004764  001522 PF(P)
004765  002000 CALL
004766  011351 HANGON
004767  005000 NOP
```

Patch in
to basic
PW is nd
1st pulse
2nd —"—
Delay
Used twic
Stacked

Note
1. Only l
2. T_2 is
due to
3. Use c
(see R.F
Spm relax
Phys. Dyna

Results
For pyridin
fit T_2
carbon.
Suspect

Figure 2. Annotated octal machine language code from the control programme of the CFT-20 spectrometer, from the laboratory notebook of JK, *ca*. 1980.

Early experiments with 2D *J* spectroscopy showed weak extra copies of the expected signals, slightly displaced; the two families of extra peaks were christened 'ghosts' and 'phantoms'. These artefacts arise because the radiofrequency pulses used are necessarily imperfect, the radiofrequency field B_1 varying slightly across the sample. Fortunately, Geoffrey Bodenhausen had modified the CFT-20 transmitter channel to control phase shifts in multiples of 90°. This allowed the artefacts to be averaged out, leaving the wanted signals unchanged, by cycling through 90° phase shifts of the refocusing pulse while alternately adding and subtracting FIDs (11). The method was given the name ‘EXORCYCLE’, in reflecting its exorcism of unwanted apparitions. ‘Phase cycling’ proved to be a very general principle, now used routinely in almost all multiple pulse experiments.

2D processing on the CFT-20 illuminated some of the practical implications of 2D methods, for example the natural ‘phase-twisted’ lineshape of a signal that is phase modulated in two independent time dimensions (9). Because the CFT-20 was limited to carbon-13 measurements, the next step was to investigate heteronuclear correlation methods (13, 14). These generate 2D spectra plotting carbon-13 chemical shift against proton chemical shift, in their most useful form generating a single peak for each directly-bonded C–H atom pair in a molecule. Because of the wide dispersion of ^{13}C chemical shifts, this gives extremely high resolution, circumventing the limitations imposed by the narrow range of proton chemical shifts. The heteronuclear correlation methods developed by the Freeman and Ernst groups were the prototypes for the highly sophisticated 2D and 3D NMR methods now used in structural biology to provide atomic resolution three-dimensional structures of proteins, DNA and RNA in solution.

An analysis of the sensitivity of heteronuclear correlation methods showed that they benefit both from the greater Boltzmann polarisation of the proton at thermal equilibrium, and its faster spin-lattice relaxation. The same advantages can be obtained in 1D NMR by replacing the evolution period of a 2D heteronuclear correlation experiment with a fixed spin echo. An initial demonstration of the sensitivity enhancement of proton-coupled carbon-13 NMR (17) was carried out in the weeks between GAM completing his thesis and leaving for Canada. This required splicing a crude 90° phase shifter into the CFT-20 decoupler ^{1}H channel, using a switched delay line, while Ray was on holiday and out of contact; fortunately the instrument survived the operation unscathed. The basic experiment was given the name INEPT (Insensitive Nuclei Enhanced by Polarisation Transfer). This gives antiphase signals, so experiments were also carried out using a second spin echo to generate in-phase signals, but there was insufficient time to write these up. The ‘refocused INEPT’ experiment was subsequently published by Ernst’s group (Burum & Ernst 1980). INEPT has since become a standard building block applications from structural biology to quantum computing, and has been cited over 2000 times.

A second paper (18) that had a large and lasting impact NMR arose from the Part II research of Malcolm Levitt (FRS 2007). Malcolm appeared in room 049 one afternoon and diffidently explained that by combining an imperfect 90° pulse, an imperfect phase-shifted 180° pulse, and a second imperfect 90° pulse, one could obtain an almost perfect spin inversion. The group were so impressed with this that they downed tools for the afternoon and took Malcolm out for afternoon tea (Levitt 2011). Over the years that followed, a forest of ‘composite pulses’ grew from this small seed. They include many more from Ray, and a seminal series of papers, first with AJ Shaka and then with Eriks Kupče, exploring the use of phase-permuted cycles of composite pulses for highly efficient heteronuclear decoupling (24-27, 36, 37). Such methods made it possible for the first time to acquire proton spectra with broadband ^{13}C and/or ^{15}N decoupling, and are routinely applied in almost every laboratory that uses NMR.

Some years after the publication of his paper with Malcolm, Ray was touched to receive a postcard from Richard Ernst in which the future Nobel laureate wrote that when he first saw the paper he thought it was merely cute, but that he now realised that this was a profound contribution to NMR. More public recognition of Ray's commanding stature in the field came in 1979 in the form of election to the Royal Society, a distinction that he valued greatly.

Shortly after Malcolm Levitt's inspiration – the first of many – another researcher joined the group who was also to become a dominant figure in NMR (and for some years the world's most cited chemist). Ad Bax, a doctoral student of Toon Mehlkopf in Delft, came to Ray's group as an academic visitor to broaden his horizons. Figure 3 shows many of the group members from this time. One of Ad's first contributions was to collaborate with Stewart Kempsell on determining ^{13}C-^{13}C coupling constants. These can be very difficult to measure at natural abundance, because the signals of di-^{13}C isotopologues are very weak, and swamped by mono-^{13}C signals. The arrival in room 049 of a superconducting spectrometer, the XL200, greatly reduced the first problem, but the second remained. Stewart had been laboriously synthesising ^{13}C-labelled molecules, but Ad realised that this could be avoided if it were possible to suppress the signals of mono-^{13}C isotopologues. He showed that this could be achieved by restricting the spin systems observed to those in which forbidden double quantum transitions could be excited. Careful phase cycling enabled excellent results to be obtained, with the unwanted signals attenuated more than 1000-fold (19). This INADEQUATE (Incredible Natural Abundance DoublE QUAntum Transfer Experiment) transformed the measurement of carbon-carbon coupling constants, both one-bond and long-range, from a niche specialty requiring bespoke synthesis to a routine measurement on unenriched material.

Figure 3. Group photograph from 1980 showing (centre) Gladys, who presided over refreshments for the Physical Chemistry Laboratory, and (rear from left) Ray, Ad Bax, Tom Mareci, GAM, Stewart Kempsell, Regina Schuck, JK and Tom Frenkiel. Photograph kindly provided by Professor T. Mareci.

While the values of carbon-carbon coupling constants are of significant interest, the lasting importance of the INADEQUATE experiment lies in its 2D analogue (23), This yields a 2D spectrum which correlates the 1D spectra of di-^{13}C species with the frequencies of the double quantum coherences excited. The signals of directly-bonded carbon atoms appear at the same F_1 frequency, making it immediately obvious which carbon is bonded to which, tracing out the carbon skeleton of a molecule. Where sample quantity permits, 2D INADEQUATE remains one of the most powerful structure elucidation methods currently available to chemists.

In three very highly-cited papers (20-22), Ray and Ad revisited Jeener's original 2D NMR experiment, later christened 'COSY', that had been analysed in detail by Ernst (Aue *et al.* 1976) but relatively little used. They both that the signs of F_1 frequencies could be distinguished by phase cycling, and that symmetric weighting of experimental data greatly improved lineshapes (21). They went illustrated the power and flexibility of the COSY experiment (22) with 9-hydroxytricyclodecan-2,5-dione, an intermediate in a projected synthesis of dodecahedrane. These developments, coupled with improvements in commercial spectrometers, have made COSY one of the most popular NMR experiments used by synthetic chemists.

Ray's fourteen years in Oxford had a great and lasting impact on science. His intuitive and creative approach to the technical challenges and opportunities of NMR complemented the analytical and theory-based approach of Ernst's group in Zürich. Together they made NMR spectroscopy the single most important structural technique for chemists. The authors' departments run over a quarter of a million spectra every year, many using methods pioneered by Ray. Many group members from this period went on to academic careers, including Geoffrey Bodenhausen, David Turner, Malcolm Levitt FRS, Ad Bax, Tom Mareci, Ole Sørensen, AJ Shaka, Steve Wimperis, Hartmut Oschkinat, Peter Barker and Peter Hore FRS.

In 1987, though, Ray was made an offer that was too good to turn down. Completely unexpectedly, he was offered the John Humphrey Plummer chair at the University of Cambridge, a research post with minimal teaching responsibilities. Although he had been become the Aldrichian Praelector in Chemistry in 1982, there was no prospect of a comparable position in Oxford. With four out of Ray and Anne-Marie's five children having left home this was a good time for a change, so they made the decision to move. For almost 30 years more, Ray's research would be based in the University of Cambridge and Jesus College.

CAMBRIDGE 1987–1999 AND RETIREMENT

The move to Cambridge proved quite disruptive, with new people and new ways of working to adapt to, and, importantly, the supply of talented research students from the Oxford Part II system had no parallel in Cambridge. Nevertheless, the freedom from teaching was welcome, and enabled Ray to focus on research with renewed intensity. He also found Jesus College be a congenial second home, much as he had found Magdalen College, Oxford. Ray continued to explore a wide range of new methods, sometimes in response to the literature and sometimes taking entirely new directions. During this period Ray was joined by a Latvian postdoctoral scientist, Ēriks Kupče. Ēriks was an organometallic chemist by training, but had developed a serious interest in NMR. This blossomed when he started working with Ray, initially supported by a Humboldt Fellowship and subsequently by the Royal Society. Ēriks was a gifted experimentalist, endlessly interested in trying out new ideas and approaches. He and Ray published over 60 papers together in a collaboration that extended beyond Ēriks' time in Cambridge and Ray's retirement.

Ray's works from this period can be grouped into a number of themes. His formal retirement in 1999 had little effect on his output, with more than 40 papers after this point.

Selective pulses and their applications

A selective pulse affects only a subset of resonances in a spectrum. Earlier work in Oxford (28) had shown that a smoothly-shaped pulse gives better selectivity than a traditional 'square' pulse. Ray and Helen Geen (30) used numerical optimisation of shapes based on Fourier series to create 'BURP' (Band-selective, Uniform-Response, Pure-phase) pulses, offering a significant improvement over simpler shapes such as the Gaussian or half-Gaussian. These and similar pulses have been widely used, and his paper with Geen is the most cited of Ray's papers from his Cambridge period. Further work in this area sought to create an arbitrary excitation profile, for example one in which several different parts of the spectrum are excited. Ray and Ēriks used DANTE sequences (6) in which the phase is steadily advanced from pulse to pulse in each separate sequence (31), exploiting the growing ability of commercial spectrometers to generate small phase shifts and complex sequences of pulses.

Adiabatic pulses and broadband decoupling

Ray's work in Oxford with Levitt (24) and Shaka (26) had dramatically improved broadband decoupling, using inversion pulses to greatly reduce the RF power needed. However, work on ^{13}C-labelled proteins required much more efficient decoupling sequences. Ray and Ēriks realised that inversion over a wide frequency range could be achieved by adiabatic passage, in which a radiofrequency field is swept through the resonances. By optimising the sweep rate and amplitude envelope they created inversion pulses which worked over an unprecedented range, giving much greater decoupling efficiency (36). Their name, WURST pulses, reflected both the sausage-like shape of the pulse envelope and the folk wisdom that with sausages one should never enquire too closely as to what they contain. WURST decoupling has been very widely used; while it can introduce 'cycling sidebands' into a spectrum, subsequent papers showed how to suppress these (37, 38).

Pure shift spectra and data reduction

Removing all multiplet structure from a proton NMR spectrum would result in an attractively simple spectrum, with just a single line for each chemically distinct proton. Finding effective ways to generate what is now known as 'pure shift' spectra has long been a goal of NMR spectroscopists. Ray made a number of contributions to this quest, for example using pattern recognition in modified *J*-spectra to find chemical shifts (34, 35).

Alternative approaches to multi-dimensional NMR

Two-dimensional NMR has greatly increased the range and complexity of structural problem that can be addressed by NMR. It can readily be extended to three or more dimensions, giving greater and allowing more complex networks of interacting nuclei to be analysed, for example in structural biology. However, such methods need long experiment times to map out the evolution in each of the indirect dimensions. Ray addressed this issue by exploring alternative ways of recording multi-dimensional spectra that avoid the need to map out the evolution in the indirect dimensions in such a complete way.

One promising approach to this problem is the use of Hadamard data processing (33, 43). A series of spectra is recorded using multiple selective pulses, simultaneously applied to different spectral regions, with different phases for the pulses. The resulting spectra are combined using a Hadamard transform to yield a separate spectrum for each region excited. This confers a similar multiplex advantage to the Fourier transform, but without the need for complete sampling of the data space. The regions of interest to be excited need to be selected in advance, but given prior knowledge of the spectrum this is not a serious drawback.

Ray had always maintained an interest in magnetic resonance imaging, and this led him to explore using projection-reconstruction to generate two- and higher-dimensional NMR spectra. The sparse nature of many multi-dimensional spectra means that only a relatively small number of projections is needed to reconstruct them. Ray and Ēriks applied the method to labelled proteins (44), and also explored related processing methods such as the direct and inverse Radon transforms, and ‘hyperdimensional NMR’ (45).

Exotica

Ray was always intrigued by new ideas in NMR and innovations in instrumentation. With Noah Linden he explored how NMR experiments could be used as models for quantum computing (41). The availability of multiple receivers led to further methods for multi-dimensional NMR (46), and Ray also published on stochastic NMR, oversampling, the PASADENA effect, and radiation damping.

Books

In 1987 Ray published his first book *A handbook of nuclear magnetic resonance* (29), a series of brief essays on a wide range of topics in NMR. The style is typical of Ray: clear and concise, leavened with dry humour and featuring beautifully drawn figures and cartoons adapted from masters such as Thelwell and Halbritter. No other single piece of work so effectively conveys Ray’s view that NMR can be simple if viewed from the right perspective.

In 1998 Ray published *Spin choreography: basic steps in high resolution NMR* (39). This is more didactic and less whimsical than the *Handbook*, leading the reader through the different approaches used to describe and devise NMR experiments. Ray followed it up in 2003 with *Magnetic resonance in chemistry and medicine* (42), aimed at practitioners of MRI wishing to gain a wider understanding of magnetic resonance in chemistry, and *vice versa*.

RAY THE MAN

At this point anyone who actually knew Ray will be saying that all this dry history rather misses the point. There have been many great scientists, but few with Ray's warmth, creativity, dry wit, and powers of communication. His unique style of conference lecturing, often enlivened by his own adaptations of the work of famous cartoonists (a compilation of Ray's humorous slides has been made available by the International Society of Magnetic Resonance (ISMAR, 2022)), meant that he was in demand as a speaker well into his eighth decade. One of the keys to Ray's success was his egalitarian and collaborative approach to research. The most productive place in his Oxford years was not the laboratory, but the tearoom. The many hours spent there discussing ideas for new experiments over morning coffee, lunch and afternoon tea may have bemused his more dirigiste academic colleagues, but they paid great dividends in the creativity of his research group, with everyone contributing ideas and building their understanding. Ray led by example rather than precept; he very rarely told students what to do, but rather gently led them to work things out for themselves.

While science had great importance for Ray, family had even greater. His 64 years of marriage to Anne-Marie produced five children and were the foundation on which his other achievements rested. Away from work he was a great enthusiast for traditional jazz (indeed for some years he had the thankless task of being Senior Member - and carrying the can - for the Oxford University Jazz Club). A strong swimmer, he took up windsurfing in his fifties after trying out the sport at a conference in Sardinia.

In addition to over 300 journal articles, reviews, book chapters and books, Ray left a number of less formal articles describing his career and the influences on it. These are included in the materials accompanying this memoir, and are available online (Keeler, 2022). Ray's distinctive voice speaks clearly through these pieces, and the reader interested to go beyond this present pedestrian account of Ray's achievements is urged to enjoy them. It seems only fitting to give Ray the last word, so here to close are his thoughts on supervising PhD students:

I learned a great deal by simply observing Rex in action - teaching by osmosis. Rex clearly understood the importance of a "hands off" style of supervising research. A neophyte student was allowed the chance to shrug off the doctrine (inherited from the undergraduate courses) that there is always a correct, prescribed way to attack a scientific problem. For the very first time, one could use one's own initiative and perhaps discover new things for oneself. Trial and error, with a large dose of the latter. I suppose it was inevitable that, many years later, I adopted a similar laissez-faire approach to supervising my own students. As an analogy, I am reminded of an almost surreal episode recounted by our youngest daughter Louise. One day, on a visit to Magdalen College, she was passing the old squash courts when "it started to rain ducklings". Together with another girl, Louise tried to catch these fluffy little balls before they hit the hard ground. The ivy-covered walls of the squash courts must have been over 15 feet high, but Mama duck had decided that the time had come to ease the ducklings out of the nest so that they could find their own way to the river Cherwell and learn to fend for themselves. Darwin would have been very pleased. I found that my own research students seemed to fall neatly into two distinct groups (a) highly motivated ones who would have been seriously hindered by any micro-management, and (b) others who were not really interested and who would soon graduate to careers outside of chemistry.

MAJOR AWARDS

1978	Chemical Society Award in Theoretical Chemistry and Spectroscopy
1988	Honorary DSc, Durham University
1990	Leverhulme Medal, Royal Society
1999	Longstaff Medal, Royal Society of Chemistry
2002	Queen’s Medal, Royal Society
2006	Günther Laukien Prize
2008	Fellow of the International Society of Magnetic Resonance
2012	Russell Varian Prize

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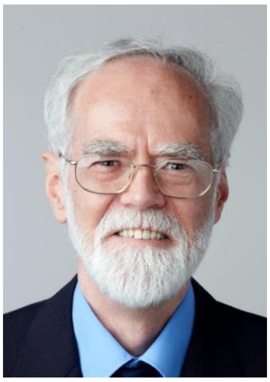
AUTHOR PROFILES

Gareth A. Morris FRS



Gareth Morris is Professor of Physical Chemistry at the University of Manchester and continues to work on the development of novel techniques in liquid-state NMR and their application to problems in chemistry, biology and medicine. He was a Part II and D.Phil. student of Ray Freeman from 1975 to 1978, a Fellow by Examination of Magdalen College, Oxford from 1978 to 1981, and an Izaak Walton Killam Postodoctoral Fellow (on leave from Oxford) with Laurie Hall at the University of British Columbia 1978-79. From 1982 he was successively Lecturer, Reader and Professor at Manchester, and was elected FRS in 2014.

James Keeler

James Keeler is Professor of Chemistry in the Yusuf Hamied Department of Chemistry, University of Cambridge, and a Fellow of Selwyn College Cambridge. He was a Part II and D.Phil. student of Ray Freeman from 1979 to 1984. In 1984 he moved to Cambridge as a University Demonstrator in Chemistry under the New Blood scheme. As well as running a small research group in NMR (now defunct) he has been Admissions Tutor and Senior Tutor at Selwyn College, and Director of Undergraduate Teaching in the Department of Chemistry. He is presently Head of Department.

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