Ian Pykett ***[rev September 12 2021]***

Biography

PYKETT, Ian Lewis

b 11.1.1953, m Gwen Andrea Brown 1977. 1s, (Alexander Ian b 1993), 1d, (Andrea Christine b 1997). ed: London University Sir John Cass College of Science & Technology (BSc, physics, 1974), Birmingham University (MSc, radiobiology, 1975), Nottingham University (PhD, physics, 1978 'Biological and Medical Imaging by NMR'). empl: Nottingham University: Postdoc Fellow '78-'80; Technicare Corp: Principal Physicist, and Harvard University: Asst Prof Radiology, and Massachusetts General Hospital: Research Fellow, '80-'83; Advanced NMR Systems: Founding Director, Pres & CEO '83-'90; Intermagnetics General Corp: VP Tech Devt '91-'00, Chief Tech Officer '00-'02; Independent Adviser '04-'11; Phasefocus Ltd: Founding Director & CEO '06-'16, CFO '16-'18, Exec Consultant '18-'19. Awards: Colleague, American Guild of Organists '91; FInstP '95; FIPEM '96; R&D100 Award '96; Rank Prize in Optoelectronics '97; Microscopy Today Innovation Awards '13 & '17. pub: about 29 peer-reviewed papers; about 25 reviews/chapters; local history book '21; rec: local history, choral & organ music.

In Memoriam:

Richard Rzedzian (1950-1997)

Jack Belliveau (1959-2014)

Andy Hurst (1982-2011)

Does anyone really know what they want to do when they graduate with their physics degree?

All I knew was that I thought I might like to work in some kind of medical application of physics. I looked at the various masters degree programmes in that area, and enrolled in the 1974-1975 Radiobiology MSc class at Birmingham University.

My collaborator on the concluding summer project was fellow student, Dr Richard Greathead. Our supervisor, Dr David Reece – then Principal Physicist at the Regional Radiation Physics & Protection Service at Queen's Medical Centre – showed us Raymond Damadian's paper on the detection of cancerous tissue by NMR[1], suggesting that we might attempt to reproduce his results. Given the *ad hoc* technical resources at hand (a teaching pulsed NMR spectrometer; a 'kit-of-parts' (a 0.9T electromagnet; a pulse generator; an RF amplifier); limited access to a 100MHz continuous-wave spectrometer; and occasional tissue specimens from consultant surgeons), it was less of a research project, and more of an excellent hands-on introduction to NMR.

By the end of the project, I had concluded that NMR could most decidedly be that sought-for link between physics and medicine, noting in my Master's thesis that 'imaging of biological

[1] R Damadian. Tumour Detection by Nuclear Magnetic Resonance. Science. 171. 1971, 1151.

systems by nuclear magnetic resonance is now possible', and citing the publications of Peter Grannell and Peter Mansfield.[2]

Nottingham (1975-1980)

I wrote to Peter Mansfield, asking whether further information was available, and a package containing a preprint and some reprints arrived. Shortly afterwards, my mother sent me a scoop from the *Nottingham Evening Post & News*[3] that contained the first published selective irradiation line-scan images from the Mansfield group.[4] (A description of the method and data did not appear in the scientific literature until the following year.)[5] Alongside was a photo of Peter and his PhD student, Andrew Maudsley, and the departmental master electronics technician, Terry Baines. Requiring some considerable imagination to interpret, the images were of a turkey leg bone in mineral oil, and several plants from Peter's garden: a lupin stalk, a stem of pampas grass, and a balsam poplar twig.

I was, of course, completely hooked. I became Peter's next PhD student, and – subsequently – a post-doctoral fellow at Nottingham.

At that time, Peter's system acquired and processed data using a Honeywell 316 computer with 8k of 16-bit memory. Amusingly, Honeywell and the Neiman-Marcus department store had attempted to sell this very same processor as a kitchen computer, with the outrageous tag-line, 'If she can only cook as well as Honeywell can compute'. How they expected a housewife (or a househusband) to use this was unclear, as the only i/o supplied was the front panel bank of binary switches. We at least had the luxury of punched paper tape and a teletype (although quite a lot of data entry was, in fact, via those switches).

The Honeywell/Neiman-Marcus Kitchen Computer, 1969.

At $10,600 in 1969 money (around £55k today) there is no record that any 316 kitchen computers were sold, notwithstanding the fact that potential customers were tempted with a free apron and recipe book.

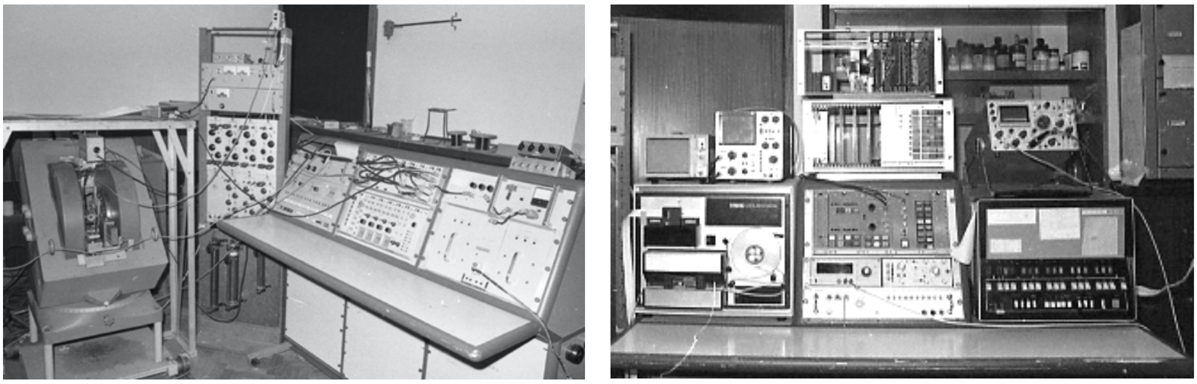
In addtion to the Honeywell computer, the Mansfield lab's NMR system consisted essentially of a 3-inch bore 0.35T Varian electromagnet; an RF console; and a digital control and data display console.

[2] Grannell PK and Mansfield P. Microscopy in vivo by nuclear magnetic resonance. Phys Med Biol. 20. 1975, 477-482.

[3] In Focus: The Pacemakers. Images that Blaze a Trail. Nottingham Evening Post, September 25, 1975.

[4] Maudsley A. Early development of line-scan NMR imaging. Mag Res Mtls in Phys, Biol & Med. 9. 1999, 100.

[5] Mansfield P, Maudsley AA, and Baines T. Fast scan proton density imaging by NMR. J Phys E: Sci Instrum 9 1976, 271



The Mansfield group MRI system, ca. 1976: Left: 0.35T electromagnet and RF console. Right: Honeywell 316 computer, digital data control & display console, and paper tape punch and reader.

The specimen had to fit within a 2cm internal diameter probe and gradient coil assembly, positioned between the pole pieces of the magnet.

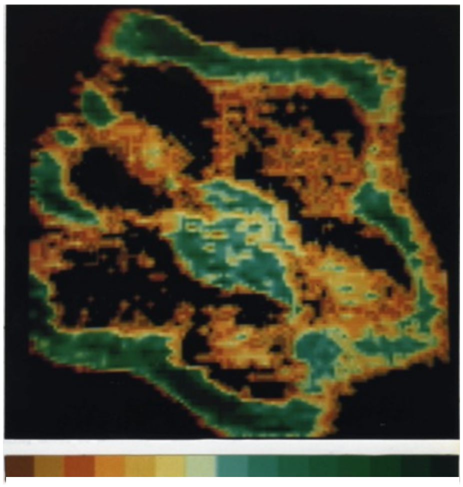
At the time I arrived Andrew had just obtained some images of his finger, with a 64 x 64 matrix and an acquisition time of 23 minutes,[6] that, for the first time, bore a very creditable resemblance to reality.

I learned the ropes by imaging my own fingers. Then, like Peter and Andrew before me, I scoured the local grocery establishments for vegetables of an appropriate maximum diameter, and with good cylindrical symmetry. (Slice selection was then achieved via the inherent sensitivity profile of a simple loop RF coil). I came upon what seemed to me – unencumbered by adventurous culinary ambitions – to be a very exotic plant: the okra seed pod.[7] This specimen was far more patient, and could remain motionless for much longer, than could I and my fingers.

Peter's constant passion to improve imaging speed[8] is reflected in our paper that presented – along with an image of that okra seedpod – our first echo planar (EPI) image:[9]

- *'Standing in some awkward stance with one's hand in the NMR probe for 20 mins or so gives time for reflection on just how imaging can be speeded up without impairing signal-noise ratios.'*

The EPI image was crude, to say the least – as had been the group's first line-scan images 18 months earlier. But Peter's parallel passion was to obtain a whole body image – to the extent that he presented in the same paper a hand-generated impression of what such an image might look like, based on the differential water distribution in the tissues. Another of my efforts was therefore directed towards obtaining the first whole-body line-scan[10] on a four-coil air-cored and water-cooled 0.1T resistive magnet (Oxford Instruments, Ltd) that was delivered in December 1977.



Line-scan imaging of an okra seed pod. See refs 7, 9.

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[6] Mansfield P and Maudsley AA. Medical Imaging by NMR. Br J Radiol 1977; 50:188

[7] Pykett I. Pioneering veggie MRIs. Phys World. 26. 2013, 23.

[8] Mansfield P. The Long Road to Stockholm. Oxford University Press. 2013, p 114.

[9] Mansfield P, Pykett IL. Biological and Medical Imaging by NMR. J Mag Res. 29. 1978, 355-373.

[10] Mansfield P, Pykett IL, Morris PG. Human whole-body line-scan imaging by NMR. Brit J Radiol. 51. 1987, 921-922.

Delivery of the 0.1T resistive magnet, December 1977. Peter Mansfield (far left); Ian Pykett (far right).
Photo credit: Waldo Hinshaw.

Peter has described the story of his volunteering for the first whole-body MRI line-scan in April 1978, including his concerns about the risk of cardiac fibrillation, and his ongoing health anxieties over the next few days and weeks.[11] The event was re-enacted on October 19th 1978 on BBC's *Tomorrow's World*, with Peter dramatically holding back a steel chain from being consumed by the hungry magnet (obviously pre-health and safety), and with me and Peter Morris (who had just completed his PhD on multi-pulse NMR) at the controls.[12]

Imaging system at the time of the first whole-body line scan image (1978).
Left to right: Ian Pykett; Peter Mansfield; Peter Morris. See ref 12.

[11] Mansfield P. The Long Road to Stockholm. Oxford University Press. 2013, p 125 et seq.

[12] An archive video of the Tomorrow's World segment is available in an online press release from the University of Nottingham: The future of MRI in Nottingham unveiled. Jan 13 2017.

At about the time that I was to leave Nottingham in 1980, the group (now also including Richard Rzedzian, Roger Ordidge and Volker Bangert) had to decide whether to concentrate on developing further the EPI method, with its manifold concomitant system design challenges; or whether to focus on improving the whole-body imaging technology and exploring its clinical potential – using either the line-scanning method, or a projection reconstruction approach that had been implemented via mechanical rotation of the gradient coil.[13] The team opted for EPI.[14]

The Mansfield Group, 1980. Left to right: Peter Morris, Ian Pykett, Peter Mansfield, Volker Bangert, Richard Rzedzian, Roger Ordidge. The 'patient' is the lab technician, Barry Hill.

Nottingham Evening Post, May 1st 1980.

Postscript

Sir Peter Mansfield's 0.1T four-coil resistive magnet is now in the London Science Museum (Object No. 1988-186 Pt8), transformed from red to yellow, and looking somewhat the worse for wear. On September 22nd 2004 the University of Nottingham hosted a celebration at the Museum (*The Magic Inside*), to which I and my wife were invited, to celebrate the culmination of a year which Peter was awarded – jointly with Paul Lauterbur – the 2003 Nobel Prize in Physiology or Medicine.

The 0.1T resistive magnet at the Science Musem, London, 2004. With (left to right): Jean Mansfield, Peter Mansfield, Ian Pykett, Gwen Pykett.

[13] Bangert V, Mansfield P, and Coupland, RE. Whole-body tomographic imaging by NMR. Brit J Radiol. 54. 152-154.

[14] Mansfield P. The Long Road to Stockholm. Oxford University Press. 2013, 135-136.

Massachusetts General Hospital/Harvard/Technicare Corp (1980-1983)

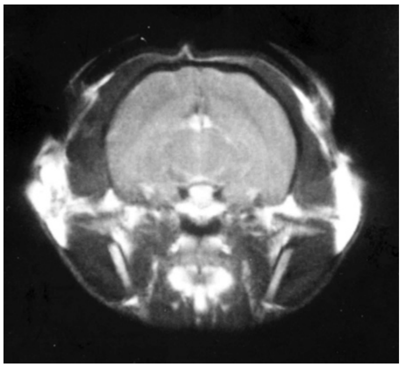
In the mid-1970s there was little interest from either the UK medical or business community in the few reasonable images that had so far been obtained. There were some notable exceptions, however, including – on the medical side – Brian Worthington and Rex Coupland from Nottingham, and Frank Smith from Aberdeen, and – on the commercial side – EMI, for whom Peter became a consultant.

But there was substantial commercial interest developing in the United States and in continental Europe. After my post-doc in 1980 I was tempted with an employment offer from Jack McConnell, Corporate Director for Advanced Technology for the American company, Johnson & Johnson. An introduction had been mediated by J&J's consultant, the diagnostic ultrasound pioneer, Peter Wells of Bristol.

Two years earlier, J&J had acquired Technicare Corp of Solon, OH, the successor firm to Ohio Nuclear – a manufacturer of nuclear medicine scanners. Technicare, which had added X-Ray CT technology to its product line, now wanted to add MRI as well, and had already hired Waldo Hinshaw as its Vice President of Engineering. Waldo, the developer of the steady-state-free-precession (SSFP) sensitive point/line MRI method,[15] had been a postdoc at Nottingham working variously with Raymond Andrew, Paul Bottomley, Neil Holland, and Bill Moore, so he and I were already acquainted.

The plan was that I would be ensconced at Massachusetts General Hospital (MGH), which was to receive Technicare's first MRI systems: a 1.4T, 8cm-bore, superconducting system; and a 0.14T resistive system for human head scanning. Both used Waldo's SSFP-based pulse sequence approach, along with either 2D (in the case of the superconducting system) or 3D (head system) projection reconstruction imaging. The former system provided exquisite (for that time) images of anaesthetised small animals, human arms, etc., and a key advantage of the latter system was its capability to reconstruct images in any chosen plane after the 3D acquisition was complete.

Nuclear Medicine clinician Tom Brady and cardiologist Gerry Pohost were the leaders of the MGH program, under the aegis of the Chief of Radiology, Juan Taveras. A large number of clinicians were involved, but my closest colleagues on a day-to-day basis – in addition to Waldo, Gerry, and Tom – were Phil Kistler and Ferdy Buonnano (neurology);[16,17] Jeff



Top: Paul Beaulieu with MGH's 1.4T, 8cm-bore superconducting magnet (Technicare Corp). Bottom: SSFP image of the head of an anesthetised cat (see ref 16). 1982.

[15] Hinshaw WJ Image formation by nuclear magnetic resonance: The sensitive-point method. Appl Phys. 47, 1976, 3709.

[16] Buonanno FS, Pykett IL, Kistler JP, Vielma J, Hinshaw WS, Goldman MR, Newhouse JH, Pohost GM. Cranial anatomy and detection of ischemic stroke in the cat by nuclear magnetic resonance imaging. Radiology. 143. 1982, 187-193.

[17] Pykett IL, Buonanno FS, Brady TJ, Kistler JP. True three-dimensional nuclear magnetic resonance neuro-imaging in ischemic stroke: Correlation of NMR, X-ray CT and pathology. Stroke. 14. 1983, 173-177

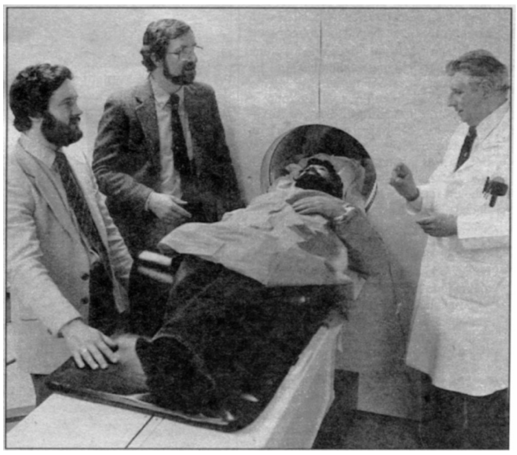
Newhouse Radiology);[18] and Mark Goldman (cardiology).[19] Paul Beaulieu was perhaps the first hospital MRI technician, who became expert in filling the cryogen-hungry superconducting magnet; explaining the MRI procedure to patients; and running and archiving scans.

I was privileged when I was asked to mentor a PhD student – Bruce Rosen from MIT, already with an MD degree from Hahnemann Medical College. With Bruce I published research on the measurement of relaxation times[20] and proton chemical shift imaging,[21] among other things. Bruce is now the Director of MGH's Athinoula A. Martinos Center for Biomedical Imaging.

A recurring theme underlying much of the MGH research was the correlation of MRI scans with images obtained using other methods (X-Ray CT; Nuclear Medicine; Positron Emission Tomography (PET)), and with 'gold standard' anatomic and pathological information; and how pulse sequences might be altered to optimise contrast and differentiate disease states. Other early projects centred on the potential applicability of paramagnetic contrast agents.[19]

Another major thrust of the MGH programme was education. We published several 'primers' on MRI,[22,23] and I was invited to write an article for *Scientific American*,[24] and, with Jack Correia, a review for *Encyclopaedia Britannica* of PET, MRI and Digital Subtraction Angiography.[25]

The MGH programme generated significant press interest. I spent the best part of one particular day with a reporter from a national magazine who, when she saw the imaging systems, was a little underwhelmed: there were no flashing lights; no people in white lab coats; no flasks of mysterious bubbling chemicals. I said, 'yes – pretty dull, isn't it'. And that was the only quote from me that I remember appearing in the resulting multi-page article.



The Technicare 0.14T MRI system, with (left to right) Ian Pykett and Tom Brady, and (far right) neuroradiologist, Paul New.
Boston Globe Magazine, April 10 1983.

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18 Newhouse JH, Pykett IL, Brady TJ, Burt CT, Goldman MR, Buonanno FS, Kistler JP, Pohost GM. NMR scanning of the abdomen: Preliminary results in small animals. In: Witcofski RL, Karstaedt N, Partain CL, eds. NMR Imaging. Winston-Salem: Bowman Gray School of Medicine of Wake Forest University Press. 1982, 121-124

19 Goldman MR, Brady TJ, Pykett IL, Burt CT, Buonanno FS, Kistler JP, Newhouse JH, Hinshaw WS, Pohost GM. Quantification of experimental myocardial infarction using nuclear magnetic resonance imaging and paramagnetic ion contrast enhancement. Circulation. 66, 1982, 1012-1016.

20 Pykett IL, Rosen BR, Buonanno FS, Brady TJ. Measurement of spin-lattice relaxation times in nuclear magnetic resonance imaging. Phys Med Biol. 28. 1983, 723-729.

21 Pykett IL, Rosen BR. Nuclear magnetic resonance: In-vivo proton chemical shift imaging. Radiology. 149. 1983, 197-201. (Presented at the 68th Scientific Meeting of the RSNA, Chicago, IL, Nov 28-Dec 3, 1982).

22 Pykett IL, Newhouse JH, Buonanno FS, Brady TJ, Goldman MR, Kistler JP, Pohost GM. Principles of NMR imaging. Radiology 143. 1982, 157-168.

23 Pykett IL, Buonanno FS, Brady TJ, Kistler JP. Techniques and approaches to proton NMR imaging of the head. Comput Radiol. 7. 1983, 1-17

24 Pykett IL. NMR imaging in medicine. Scientific American. 246. 1982, 78-88.

25 Correia JA, Pykett IL. CAT's kin: New windows on the body. Medical and Health Annual. Encyclopaedia Britannica, Inc. Chicago. 1984, 142–159.

In 1983, Juan Taveras offered me the position of Director of Magnetic Resonance Research at MGH, with Tom taking the role of Director of Clinical Magnetic Resonance; and at the same time, Technicare had requested that I relocate to the company's headquarters in Ohio. However, I wanted to further develop the EPI concept that was being progressed at Nottingham, notably by Peter's PhD students, Richard Rzedzian and Roger Ordidge. For perfectly rational commercial and technical reasons, Technicare did not want to entertain such a plan, and there was clearly not the right mix of resources at MGH to embark on such a venture.

Advanced NMR Systems, Inc. (1983-1990)

I had met Charles Haar, a Professor of Law at Harvard and a Trustee of MGH, on several occasions. He introduced me in 1983 to Philip David, a Professor of Urban Development at MIT and private investor. Together, they were in a position to enable the financing of a new company. I therefore jumped from the relatively safe environment (from a career point of view) of MGH and Harvard, into the unknown environment of a high-risk start-up. Advanced NMR Systems, Inc. was therefore born, and financed by August of that year.

I was delighted to be successful in recruiting Richard Rzedzian from Peter's lab at Nottingham, shortly after he had obtained the group's first human EPI images, of infants and young children.[26] Andrew Maudsley also worked with us in the early years. I had naïvely envisioned a system that could perform both EPI and multinuclear applications, the latter being one of Andrew's particular interests. Whilst not theoretically impossible, such a parallel technical development effort, in the context of real-world budget constraints and milestone expectations, was bound to be unsustainable. It was necessary to set priorities, and the focus was to be on a variant of Peter's original EPI method, which Advanced NMR trademarked as 'Instascan'.[27]

Advanced NMR Systems, Inc's facility, under construction at Sonar Drive, Woburn, MA, ca. 1984. Left to right: Andrew Maudsley, Richard Rzedzian, Ian Pykett.

The company's first home was 2,800 sq ft office and laboratory facility in Woburn, MA, about 12 miles north of Boston, but within a year, we had negotiated an agreement with a local developer to have them build for us a purpose-designed 9,400 sq ft facility. The price was reasonable – perhaps because the building was sited beneath a vertical cliff face that, together with children throwing rocks from the top edge, presented potential dangers that were more concrete than the perceived risks of start-ups and exposure to high magnetic fields.

It is important to recognise what the MRI community felt about EPI at the time. I believe it is true to say that, in 1983, EPI was mostly thought to be a really neat idea that would be far too technically difficult to work in practice, with anything approaching the signal-to-noise and spatial resolution that would be required for useful clinical work. Even Peter Mansfield felt that,

- *'[EPI] is by no means a simple technique to implement, particularly for matrix sizes in excess of 32 x 32 … the broad bandwidth and large-gradient requirements present a major challenge which is likely to limit the*

[26] Rzedzian RR, Mansfield P, Doyle M, Guilfoyle D, Chapman b, Coupland RE, Chrispin A, Small P. Real-time NMR Clinical Imaging in Paediatrics. The Lancet. 1983, 1281.

[27] Cohen MS and Weisskoff RM. Ultra-Fast Imaging. Mag Res Imaging. 9. 1991, 1-37.

matrix size to ~64 x 64'.[28]

Michael Stehling, Bob Turner and Franz Schmitt held a similar view:

- *'Until the end of the 1980s few people believed that EPI would be clinically useful, since its complexity was far greater than that of 'conventional' methods.'* [29]

Delivery of 2.0T magnet to Advanced NMR Systems, Inc, ca. 1985.

It is also interesting to recall that, before ca. 1980, it was perceived that whole-body MRI would be viable only at what would now be considered a low field:

- *'…the cost of producing large-volume static magnetic fields in excess of 0.1T becomes inordinately high and suggests a cost limit in operating frequency for protons of about 4.0MHz…'* [30]
- *'…[for] proton NMR imaging of the whole human body the laboratory magnetic field should … not exceed 0.2T…'* [31]

Even by 1984, following the introduction of superconducting whole-body magnets, the pragmatic 'maximum' field strength (limited mainly by cost and siting considerations) was still expected to be below about 1T:

- *'… an MR unit will be able to achieve full clinical potential in proton imaging in the range between 0.3 and 0.6T …'* [32]
- *'… the average hospital will settle in the 0.3 to 1T range as a reasonable compromise …'* [33]

It was therefore a quite audacious decision to commission Oxford Instruments to build us a 2T whole-body magnet, with a non-conducting room-temperature bore in order to reduce eddy currents. (I believe that Magnex was building the only other whole-body-sized 2 tesla magnet at that time, for Elscint).

The magnet was un-shielded: the building had been designed such that it could be placed in the centre of a large, otherwise empty, room. The necessary pair of heavy exterior air conditioning units were placed exactly symmetrically about its projected centreline, to help avoid field distortions.

To provide the unusually fast gradient switching times, a resonant circuit was created by connecting the inductive gradient coils (designed and made by Richard) in a series configuration with large capacitors. This generated high, constant amplitude, sinusoidally-modulated readout gradient fields. Resistive losses in the circuit were topped up by Techron power amplifiers. Since

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[28] Mansfield P and Morris PG. NMR Imaging in Biomedicine. Academic Press. London. 154. 1982, 333.

[29] Schmitt F, Stehling MK, and Turner R. Echo-Planar Imaging: Theory, Technique and Application. Springer-Verlag. Berlin. 1998, Preface.

[30] Mansfield P, Pykett IL. J Mag Res. 29, 1978, 370.

[31] Andrew ER. NMR Imaging of intact biological systems. Proc Roy Soc. 1980, B289: 477.

[32] Kaufman L, Crooks LE and Margulis A. Siting and Operation. In: James TL and Margulis AR (eds). Biomedical Magnetic Resonance. Radiology Research & Education Foundation. San Francisco, CA. 1984, 443-447.

[33] Hoult DI. Field, Contrast, and Sensitivity in Imaging. In: James TL and Margulis AR (eds). Biomedical Magnetic Resonance. Radiology Research & Education Foundation. San Francisco, CA. 1984, 35-45.

the gradient strength was continually varying, a non-linear scheme for sampling of the NMR signal was necessary.

The computer, a 32-bit Concept 32/67 (Gould Inc., Computer Systems Division), was selected mainly because of its unmatched bus bandwidth, and a benchmarked processing speed 50% faster than similarly-configured competing machines. However, Gould's focus on high performance hardware at the expense of software resulted in a distinctly non-user friendly programming environment.

Richard Rzedzian and Ian Pykett, determining the placement of air conditioning units at Advanced NMR Systems, Inc, ca. 1984.

Working in tandem with the Gould computer was a dedicated real-time digital function generator (nicknamed 'The Box') that was designed and made by Randal Briggs.

Peter Mansfield reports an occasion when I 'insisted that [Advanced NMR Systems] was not doing EPI experiments, but something quite different'; whereas Richard had commented some time later that 'strictly speaking, [the Advanced NMR Systems] machine was indeed producing EPI data'. Peter is correct when he says, 'in fact, [the Advanced NMR Systems] machine was an improved variant of EPI'.[34] He was aware, of course, that I could not disclose any details of the Instascan method before the relevant patents had been filed. He had learned this the hard way:

- *'The first invention on MRI filed by us was in 1974. I was a bit naïve, and not terribly street-wise, so our very first paper on imaging[35] just went into the public domain without patent cover.'* [36]

The Instascan method, and its own variants, as developed by Richard, are presented in a review by Mark Cohen and Robert Weisskoff.[27] This approach to EPI resolved several problems associated with Peter Mansfield's original method, firstly, by scanning the entirety of k-space, from -z to +z (*vs* only half); and, secondly, by filling k-space data in a rectilinear (*vs* zig-zag) pattern.

In addition, the data were collected under the Hahn spin-echo envelope created by a 90°-180° RF pulse pair, producing images with conventional T1 and T2 contrast. (In fact, a single-shot Instascan image generated an intensity distribution that was independent of T1, because just one 90°-180° pule pair was required. Consequently, the T2 contrast was 'uncontaminated' by T1 contrast, which was distinctly helpful in certain clinical situations.[37] However, T1 contrast could easily be re-introduced by simply by repeating the imaging sequence, or adding another RF pulse before the imaging sequence).

In the original implementations of Instascan the 180° RF pulse was frequency-selective, to generate separate chemically-resolved 'lipid' and 'water' images.

I was about to appreciate Peter Mansfield's anxiety when he had volunteered for the first whole-

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[34] Mansfield P. The Long Road to Stockholm. Oxford University Press. 2013, p 142.

[35] Mansfield P and Grannell PK. NMR 'diffraction' in solids? J. Phys C: Solid State Phys. C6. 1973, L422-L426.

[36] Tansey EM, Christie DA, Reynolds LA. Making the Human Body Transparent: The Impact of NMR and MRI. Wellcome Witnesses to Twentieth Century Medicine: Vol 2. Wellcome Trust. 1998, 66.

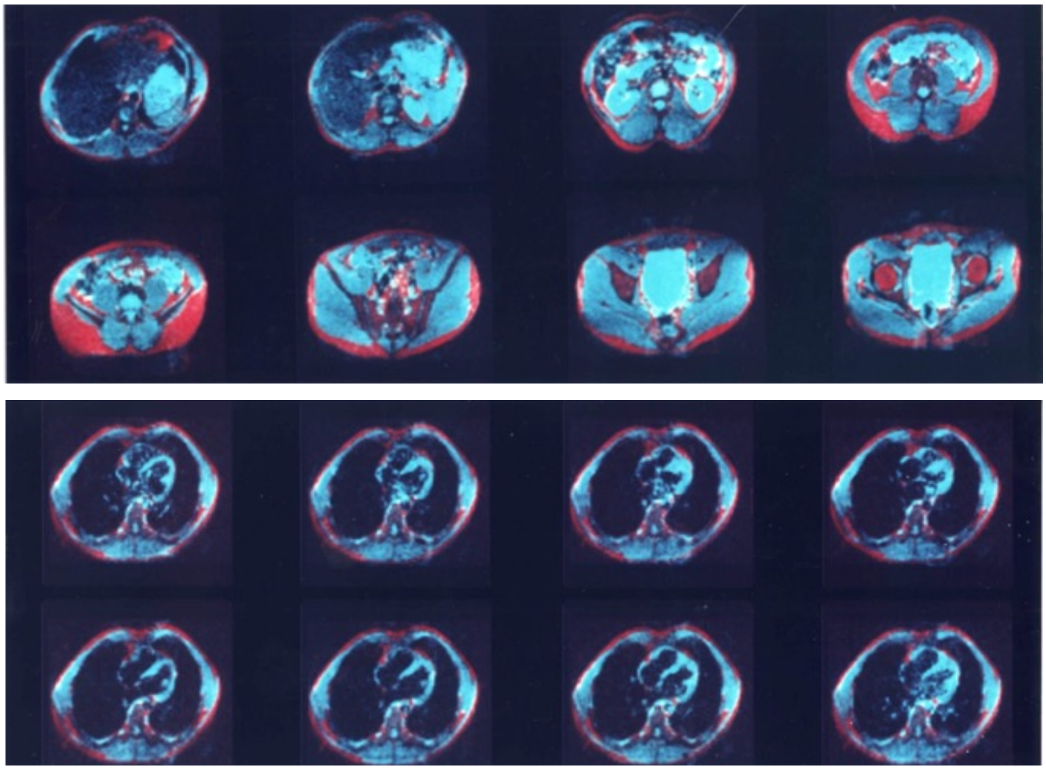
[37] Saini S, Stark DD, Rzedzian RR, Pykett IL, Rummeny E, Hahn PF, Wittenberg J, Ferruci JT. 40ms Imaging of the Abdomen at 2.0 T. Radiology 173. 1989, 111-116.

body MRI line scan at 0.1T, when I did exactly the same for the first adult EPI whole-body images, at 20 times that field strength. In fact, though, we understood that the main risk factor was not the field strength, but at what db/dt threshold nerve stimulation might occur; and whether such stimulation might affect the heart. So I asked my MGH colleague, cardiologist Mark Goldman, to stand by with a defibrillator kit, whilst Richard gradually increased the gradient fields to their maximum strength.

I felt nothing, and had no adverse effect, neither on that occasion, nor during many subsequent imaging sessions. However, the concern was not without basis: peripheral nerve stimulation was perceived some years later by other volunteers,[38] and this became one of the main constraints on the use of large switched gradient fields for EPI.

Other key technical staff in those first few years included physicists Michael Rohan and the afore-mentioned Robert Weisskoff, and the director of software engineering was Tim Bowe. Mark Cohen joined the team in 1988 to lead the clinical applications effort; he has provided elsewhere his own reminiscences of his time at the company.[39] Chuck Martin – there from almost the beginning – was one of those rare individuals with a 'can-do' attitude, who baulked at nothing, and who had the broad experience and skills to build or fix almost anything.

Richard and I first published the company's images in 1987.[40,41] Lipid and water protons are shown as red and blue, respectively, with an acquisition time of 40ms each.



Advanced NMR Systems, Inc's first-published EPI images, 1987. See refs 40, 41.

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[38] Cohen MS, Weiskoff RM, Rzedzian RR, Kantor HL. Sensory Stimulation by Time-Varying Magnetic Fields. Magn Res Med. 14. 1990, 409-414.

[39] Cohen M and Schmitt F. Echo Planar Imaging before and after fMRI: A personal history. Neuroimage. 2. 2012, 652-659.

[40] Rzedzian RR and Pykett IL. Instant Images of the Heart Using a New, Whole-Body MR Imaging System. Am J Radiol. 149. 1987, 245-250.

[41] Pykett IL and Rzedzian RR. Instant Images of the Body by Magnetic Resonance. Mag Res Med. 5. 1987, 563-571.

The image quality far surpassed the forecasts of a few years earlier: the 128 x 64 (0.08 cm^3 voxel size) single-shot images had a signal-to-noise ratio of about 30:1.

This work stimulated the mainstream MRI companies to commence or accelerate their own EPI research activities:

- *'For sure, the formation of the ANMR company and their first EPI results caused us to speed up with our efforts significantly.'* [39]

Peter Mansfield commented that it was,

- *'not without the enthusiasm and dedication of a group of people at Nottingham and two of my former students, Ian Pykett and Richard Rzedzian, who went to the United States to set up their own company to make EPI machines, that the topic took off in a way which convinced far-sighted radiologists that there was something to the method'.* [42]

It was not difficult to encourage my erstwhile MGH colleagues to become involved with us. An early interest was abdominal imaging, where the single-shot Instascan method had the advantages of no motion artifacts, and – as mentioned above – very high and uncontaminated T2 contrast.[37] However, Advanced NMR Systems and other early commercial EPI research groups (e.g.: Siemens[39]), had always felt that the primary applications of EPI would be cardiac, because it was so difficult to obtain high quality images of the beating heart with ECG-gated conventional MRI scanning methods – not least because the sinus rhythm was irregular in many cardiac pathologies, and even in normal volunteers.

But not harbouring any such preconceptions, and stimulated by their individual and institutional dual interests in dynamic magnetic contrast susceptibility effects in the brain, and measurements of regional brain activation by positron emission tomography, Bruce Rosen and his student Jack Belliveau worked with Advanced NMR to confirm that the high temporal resolution of dynamic contrast-enhanced EPI could be used for the in vivo measurement of cerebral physiology in the canine brain.[43] Subsequently, functional human brain activation studies using, first, an exogenous contrast agent,[44] and then, the intrinsic paramagnetic properties of deoxygenated haemoglobin ('BOLD' imaging),[45] led to the development of a 'killer app' for EPI: functional brain imaging.

It is clear that this put EPI on the map. And, as Kenneth Kwong has said,

- *'the critical enabling technology of BOLD fMRI was the introduction of single-shot echo planar imaging.'* [46]

I took responsibility for the operations and administration of Advanced NMR, including legal, regulatory affairs, accounting, and (as staff were added) human resources matters, and I was the primary liaison with investors.

On the commercial front, in December 1987 a joint development agreement was signed with

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[42] Mansfield P. In: Schmitt F, Stehling MK, and Turner R. Echo-Planar Imaging: Theory, Technique and Application. Springer-Verlag. Berlin. 1998, Foreword.

[43] Belliveau JW, Rosen BR, Kantor HL, Rzedzian RR, Kennedy DN, KcKinstry RC, Vevera JM, Cohen MS, Pykett IL, Brady TJ. Functional Cerebral Imaging by Susceptibility-Contrast NMR. Mag Res Med. 14. 1990, 538-546.

[44] Belliveau JW, Kennedy DN, McKinstry RC, Buchbinder BR, Weisskoff RM, Cohen MS, Vevea JM, Brady TJ, Rosen BR. Science. 254. 1991, 716–719.

[45] Kwong KK, Belliveau JW, Chesler DA, Goldberg IE, Weiskoff RM, Poncelet BP, Kennedy DN, Hoppel BE, Cohen MS, Turner R. Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. Proc Nat Acad Sci USA. 89. 1992, 5675-5679.

[46] Kwong KK. Record of a Single fMRI Experiment in May of 1991. Neuroimage. 2. 2012, 610-612.

GE Medical Systems to integrate our Instascan technology on the GE Signa MRI system. In 1989, we entered into a second, longer-term, agreement to sell EPI retrofits to GE's customers. The first such retrofit (a principal component of which was a replacement EPI-capable gradient coil set) was delivered to GE itself, and the second to MGH in 1990.

First EPI-capable gradient coil retrofit, ready for delivery to GE, with staff of Advanced NMR Systems, ca. 1990.

Our application to the FDA to reclassify our Instascan system as a Class II device, *vs* the default Class III category (reserved for the most risk-laden devices), was part of a major industry-wide technical and legal effort to enable marketing of future MRI products on the basis that their safety and effectiveness could be assured via adherence to specific technical performance standards.[47] Advanced NMR's significant contribution was to ensure that the approved performance standard for gradient switching rates was sufficient to enable implementation of EPI pulse sequences.

In March 1990 I resigned as CEO of Advanced NMR Systems. Paul Bullinger (previously of Analogic Corporation and Picker International) – who at that time had been working as General Manager for the company for three months – took over the reins as CEO, and moved the company to a 34,000 sq ft facility in Wilmington, MA. The team went on to manufacture the Signa retrofits for GE's customers; and to develop a dedicated MRI breast imaging system, 'Aurora', via a new subsidiary, Advanced Mammography Systems.

Postscript

In 1997 (by which time I was at Intermagnetics – see below) I was thrilled to be awarded a Rank Prize in Optoelectronics, along with Peter Mansfield and Richard Rzedzian, 'in recognition of significant contributions to the development and commercial exploitation of echo planar imaging, not least in the development of novel pulse sequences.'[48]

Peter had been scheduled to give the acceptance address at the Royal College of Medicine, but, at the last minute, became ill; and, by that time, Richard was incapacitated with cancer. I therefore gave the talk on behalf of the three of us, and delivered Richard's citation to him at his home in Lexington, MA.

Richard was to die two months later, aged only 46 – a tragedy and a tremendous loss to the MRI community and, of course, to his wife Jane and his two young children.

Richard and I had joked on many occasions whilst we were at Nottingham about his long list of 'ex-friends' and, indeed, he was not always easy to work with, as Mark Cohen has attested.[39] Notwithstanding, as I mentioned in his Obituary,[49] he was, in my opinion, unmatched in his tenacity, stamina, and intellectual rigour.

I was humbled when he had called me to visit him in hospital not long after his diagnosis, to talk about his illness and his concern for his family and personal affairs. I find it very sad that I can

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[47] Kahan JS. Medical Device Reclassification: The Evolution of FDA Policy. Food, Drug, Cosmetic Law Journal. 42. 1987, 288-306.

[48] Mansfield P. The Long Road to Stockholm. Oxford University Press. 2013, 142.

[49] Pykett, IL. Richard R Rzedzian (1951-1997). MR Pulse. 4(2). 1997, 15.

not now be reminiscing with him about the times we spent together at Nottingham and Advanced NMR Systems.

Intermagnetics General Corp (1991-2002)

I started to work for Intermagnetics General Corporation (IGC) in Albany, upstate New York, in 1991. The company was founded 20 years earlier by Carl Rosner, as a spin-off from General Electric's Corporate R&D department in Schenectady, NY.[50] By the 1980s its main commercial products were low-temperature superconducting wire (sold mainly for MRI magnets, but also for high-energy physics applications); and superconducting magnets for MRI. With the acquisition of the refrigeration company, APD Cryogenics, in 1987, Intermagnetics became vertically integrated in all the principal technologies required for superconducting magnets.

The company sold its first MRI magnet in 1983 to a Philips-sponsored programme at Columbia-Presbyterian Medical Centre, where Andrew Maudsley had managed its installation.[51] At the then relatively high field of 1.5 tesla, this product became a catalyst for orders from Technicare, who, for a while, became Intermagnetics' largest customer, to be superseded ultimately by Philips.

After a few months working with Intermagnetics' Vice President of Marketing, Dick Mullen, in 1991 I became Vice President, Technology Development Operations, with responsibility for a three-person high-temperature superconducting (HTS) materials and devices R&D group (Mike Walker, Drew Hazelton and Pradeep Haldar); and the Field Effects permanent magnet division in Acton, MA, that had been acquired in 1986. Field Effects was led by Ron Holsinger, and also employed a pioneer of superconducting materials and magnet design, Zdenek JJ ('John') Stekly. (John had co-founded Magnetic Corporation of America, which had been acquired in 1982 by Johnson & Johnson to build a superconducting magnet for the Technicare MRI programme). Several other extremely talented researchers were assigned to my division, including Mike Hennessy, who acted as Chief Scientist.

Carl had a vision that Intermagnetics should make complete MRI systems, because he felt that, by selling only components (magnets, LTS wire and refrigerators) to the OEM MRI vendors, he was unable to capture the true value of his enabling technologies. I therefore established in 1996 a joint venture (IMiG MRI Systems) with Surrey Medical Imaging Systems of Guildford, to develop low-cost permanent magnet-based MRI systems. Led by David Taylor, SMIS had developed a software and electronics platform for magnetic resonance systems for a wide variety of NMR and MRI applications. Their products sold mainly to academic research groups, who would typically purchase their magnets separately.

As Ron Holsinger began to contemplate retirement, Paul Domigan became the General Manager of Field Effects. He transformed the division into an FDA QSR and ISO 9001-compliant manufacturing organisation that, as well as developing permanent magnets for MRI, won multiple government contracts, including an order to build an earthquake-proof world-record field-strength (2.04T) permanent magnet wiggler for Stanford Synchrotron Radiation Laboratory.[52]

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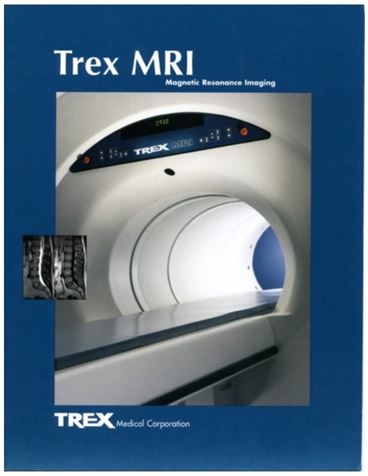
[50] Rosner C. Intermagnetics Remembered: From Superconductor-Based GE Spin-Off to Billion Dollar Valuation. IEEE/CSC & ESAS European Superconductivity News Forum. 19. 2012.

[51] Einstein SG, Maudsley AA, Mun SK, Simon HE, Hilal SK, Sano RM, Roeschmann, P. Installation of High-Field NMR Systems into Existing Clinical Facilities: Special Considerations. Proc. 14th Annual Symposium on 'Sharing of Computer Programs and Technology: Technology of Nuclear Magnetic Resonance'. Orlando, FL. Soc Nucl Med Inc. NY. 1984, 217-231.

[52] Stekly Z, Gardner C, Baker J, Domigan P, Hass M, McDonald C, and Wu C. Design and performance of a 2T permanent magnet wiggler for the Stanford Synchrotron Radiation Laboratory. Rev Sci Instrum. 67. 1996, 3347.

Field Effects' 0.15T whole-body MRI ferrite magnets had the advantage that they were ceramic (hence eddy current-free), and had a transverse field direction that improved the inherent SNR performance of RF coils.

I also appointed Paul as General Manager of the SMIS Joint Venture, where he developed an elliptical-bore version of the ferrite magnet. The product was to be distributed in the clinical marketplace by Trex Medical Systems, then a highly-profitable ca. $100 mill/yr (1996) division of Thermo Electron Corporation. Unfortunately, for completely unrelated reasons, Trex imploded: it lost one of its key customers; its application to the US FDA for authorisation to market its digital mammography system was rejected; and its CEO resigned. Without adequate attention from Trex, the IMiG MRI System failed to gain traction.



Product literature developed by Trex Medical Systems for the IMiG MRI Systems' clinical product, RSNA, Chicago, IL, 1997.

However, the product was customised by the Intermagnetics and SMIS team, in collaboration with Barry Dauber and Tim Schenz of the Ross Products Division of Abbott Laboratories, to enable the successful, factory-integrated, 100% MRI detection of bacterial spoilage in aseptically-packaged liquid foods (typically nutraceuticals, such as baby milk).[53] The fully-automated rate of inspection was 10-16 cartons per minute, each carton containing 12-24 stacked packages.

Another Field Effects 0.15T whole-body MRI ferrite magnet made its way to Nottingham in 1996 for use by John Owers Bradley, Mike Barlow, and colleagues, in hyperpolarised gas imaging. In January 2021, this same magnet moved to start a new life with Simon Duckett at the University of York.

Adventures in high-temperature superconductivity

In 1997, Intermagnetics hired Glenn Epstein (previously of Oxford Instruments) as a successor to Carl Rosner. Glenn brought a strong commercial- (*vs* technology-) orientated strategy that focussed primarily on the company's MRI-related products. However, as a long-term growth opportunity, we also decided to invest in and accelerate our development of high-temperature superconducting materials and devices for energy technology applications. This became a segment of the organisation that was highly valued by Wall Street, alongside the increasingly profitable development and sale of the mainstream magnets, materials and cryogenics products.

By winning numerous collaborative R&D grants from the US Department of Energy and other agencies, together with increased corporate investment, my three-person HTS group was able to gradually expand to about 50 staff by 2000, under the day-to-day management of Pradeep Haldar. Notable among our early hires was Venkat ('Selva') Selvamanickam, who led the design and construction of a pilot manufacturing line for 'second generation' thin-film high temperature superconductor (HTS) wire; whilst Drew Hazelton led the HTS device design and fabrication effort.

We established business relationships with several electric power device companies, and became a world leader in the manufacture of HTS transformers, fault current limiters, current leads and high-voltage transmission cables.

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[53] Pykett IL. NMR: A Powerful Tool for Industrial Process Control and Quality Assurance. IEEE Trans. Applied Superconductivity. 10. 2000, 721-723.

In 2000 I was appointed Intermagnetics' Chief Technology Officer, at which time we spun out the HTS group as a separate subsidiary – SuperPower LLC – under the management of power-industry veteran, Phil Pelligrino.

I left Intermagnetics when I and my family relocated back to the UK in 2002.

Postscript

In 2009, SuperPower, in partnership with Sumitomo Electric Industries, demonstrated the world's first thin film HTS device in the US power grid, when a superconducting transmission cable was installed in Albany, NY to provide power to 25,000 homes and businesses.[54] In 2006 Intermagnetics was acquired by Philips for €1 billion, and SuperPower was acquired from Philips by Furukawa Electric Company Ltd. in 2011, by which time it had more than 130 customers worldwide.

Phasefocus (2006-2018)

Back in the UK I worked as an adviser to several clients and, most particularly, with the University of Sheffield, on identifying, protecting, and commercialising intellectual property. A direct outgrowth of this work was my co-founding of Phasefocus in 2006 with John Rodenburg – the inventor of a computational imaging method known as ptychography.[55]

In this approach the task of image formation is performed by an iterative phase retrieval algorithm, which eliminates the requirement for the customary focussing lenses with their associated aberrations. The technique works equally well in transmitted light and reflected light applications and, given suitable illumination sources and detectors, it can operate using any wavelength in the electromagnetic spectrum, as well with electron and other particle waves.

The technology was initially demonstrated and developed by John in collaboration with his PhD student, Andy Hurst, and Phasefocus's early recruits, Martin Humphry and Andrew Maiden. The first reduction to practice of the method by Andy Hurst[56] was achieved at optical wavelengths, as were a number of important methodological improvements, but further proofs of concept were soon published at X-ray[57] and electron[58] wavelengths.

A second major benefit of ptychography is that the algorithm recovers with great accuracy and high contrast the phase of the wave that has travelled through, or been reflected by, the specimen. This means that it can visualise, and morphologically characterise, very weakly absorbing specimens, including essentially transparent biological cells, without the need to introduce damaging stains or dyes. Consequently, Phasefocus' current principal product line

[54] Yumura H, Ashibe Y, Ohya M, Watanabe M, Takigawa H, Masuda T, Hirose M, Yatsuka K, Itoh H and Hata R. In-Grid Demonstration of Long-length '3-in-One' HTS Cable (Albany Project) SEI Technical Review. 68. 2009.

[55] Rodenburg JM. Ptychography and Related Diffractive Imaging Methods. In: Advances in Imaging and Electron Physics. Elsevier. 2008, 87-184.

[56] Rodenburg JM, Hurst AC, Cullis AG. Transmission microscopy without lenses for objects of unlimited size. Ultramicroscopy. 107. 2007, 227-231.

[57] Rodenburg JM, Hurst AC, Cullis AG, Dobson BR, Pfeiffer F, Bunk O, David C, Jefimovs K, Johnson I. Hard-X-Ray Lensless Imaging of Extended Objects. Phys Rev Lett. 98, 034801, 2007.

[58] Humphry MJ, Kraus B, Hurst AC, Maiden AM, and Rodenburg JM. Ptychographic electron microscopy using high-angle dark-field scattering for sub-nanometre resolution imaging. Nature Communications. 3. 730, 2012.

(Livecyte) uses ptychography, along with single-cell tracking algorithms, to automatically characterise the growth, morphology, and motility of large cell populations in multi-well plates.

After 10 years as CEO of Phasefocus I initiated a three-year management succession plan, handing over the reins to Martin Humphry, and retiring fully three years later, in 2019.

The Phasefocus Livecyte kinetic cytometer.

Postscript

A wide variety of applications of ptychography have been developed in the X-ray, extreme ultraviolet, electron and visible domains. The method has recently achieved atomic-scale resolution, limited by the thermal fluctuations of the atoms themselves,[59] as had been forecast by John Rodenburg and Andy Hurst in their paper that presented the first practical demonstration of the method in 2007.[56] Tragically, Andy Hurst was killed in 2011 while hang-gliding at a competition in Australia, and so did not live to see this prediction come true.

Reflections

I am very privileged to have worked with some exceptional individuals in every one of my roles. As my career has been focussed on the commercialisation of academic inventions, I have been thrilled to see MRI, ptychography, and HTS innovations make it into the marketplace. In every case, the technical performance expectations of the inventors have been achieved or – in most cases – far exceeded. This is, of course, due, not least, to the long-term creativity and effort of the inventors themselves. But it is also due in a very substantial part to – firstly – the funding provided by a variety of 'deep tech' investors: venture capital organisations and 'angel' investors, government agencies, individual investors, and strategic partners, and – secondly – to the remarkable technical advances that have been achieved by the scientists, engineers and technicians in the firms commercialising these innovations, who have worked to make the products meet what appeared at the outset to be impossible market requirements and expectations. Sometimes, their names have appeared on patents and in publications, but, frequently, they are unsung heroes.

I am especially indebted for their love and support to my late wife, Gwen Pykett (1955-2011), and my two children, Alexander and Andrea – the most important collaborators on my life journey.

In my retirement I am focussing on my long-time avocations of choral singing and organ playing, and my first local history book is in press.[60]

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[59] Chen Z, Jiang Y, Shao Y-T, Holtz ME, Odstrčil M, Guizar-Sicairos M, Hanke I, Ganschow S, Schlom DG, Muller DA. Electron ptychography achieves atomic-resolution limits set by lattice vibrations. Science. 372. 2021, 826-831.

[60] Pykett, I. The Life and Times of Revd John Redaway Luxmoore (1829-1917). Country Books. 2021, in press.