MRIS History UK

THE DEVELOPMENT OF MAGNETIC RESONANCE IMAGING AND SPECTROSCOPY

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Graeme Bydder

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Biography

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1. Computed Tomography (CT) at the Medical Research Council (MRC) Clinical Research Centre (CRC) at Northwick Park Hospital (NPH), London

The history of radiology (medical imaging) can be understood in many different ways, but a common approach is to divide it into a classical era beginning with Wilhelm Roentgen's discovery of x-rays in 1895 and characterised by an image of his wife's hand obtained on the 18th December 1895 as well as a modern era beginning with the development of x-ray computed tomography (CT) by Godfrey Hounsfield beginning in 1967 and characterised by an image of a 41 year old woman's frontal lobe glioma produced from data obtained on the 1st October 1971.(1)

Roentgen and Hounsfield were very different men. Roentgen was an established 50 year old professor of physics with a longstanding interest in electricity and magnetism, and a significant reputation in this field. He had deliberately set aside time to investigate cathode rays in his laboratory later in the year 1895 so he could avoid distractions. On 8th November he saw a sheet of barium platinocyanide impregnated cardboard glowing in the dark at a distance from his energised cathode ray tube and deduced that this could not be due to light or cathode rays, and that therefore there must be a new type of ray emanating from the tube. He used photographic paper to obtain images of objects in his laboratory, and established that the new rays penetrated some solids, and the soft tissues of his wife's hand with ease, but only penetrated her bones with difficulty.

His paper on the subject was published on 28th December 1895, and on 1st January 1896 he sent off 12 letters each containing nine photographic prints of his wife's hand and objects in his laboratory as well as a copy of his paper to Lord Kelvin (Glasgow), Arthur Schuster (Manchester), Franz Exener (Vienna), Henri Poncaré (Paris) and other eminent European scientists. His discovery became an international sensation. Over 500 articles were published on the subject in 1896 and the field of radiology was established.

Godfrey Hounsfield was a high school dropout who left without a qualification; he never went to university. He worked as a wireless mechanic while serving in the Royal Air Force during World War

II and some time after he was de-mobbed, joined Electric and Musical Industries (EMI) at their Central Research Laboratory (CRL) in Hayes, Middlesex. The company had considerable expertise in electrical and electronic engineering, dating back to Alan Blumlein in the 1930s and early 1940s, and had applied this to the development of recorded music, TV and radar. However Godfrey worked on a computer, the EMI DEC1000 and when this failed to progress commercially he was at a loose end, and was encouraged to find something else to do. As an abstract exercise, he started thinking about how to determine what was inside a closed box without opening it and thought of projecting x-rays through the box in many different directions and detecting them on the other side. He then thought of using a computerised reconstruction to deduce the size and shape of the object inside the box based on differences in the absorption of the x-rays which had passed through it.

It was a new concept for EMI. The company scientists at the CRL had had no previous experience in designing or manufacturing medical devices or x-ray equipment. Godfrey assembled a prototype using a lathe, and acquired data using a radioactive source over nine days and then used a computer algorithm to produce images in 1969.

The company sought advice and financial assistance from the Scientific and Technical Services Branch of the Department of Health and Social Security (DHSS) (Fig. 1). Gordon Higson of the DHSS showed interest and set up a meeting with three London radiologists: James Ambrose, Louis Kreel and Frank Doyle. They later brought along test objects (brain slices, pig abdomens and small bone samples) and Godfrey successfully imaged them. The radiologists wrote a report strongly supporting further development of the technique in March 1970.(2)

Fig. 1. Gordon Higson (1981).

EMI constructed a prototype scanner for head use (the CT 1000) and this was installed at Atkinson Morley's Hospital in London in 1971, where it produced the dramatic image of a glioma in the brain of the first patient. It was a transformation in medical imaging. Previously the brain was imaged indirectly by injecting an iodinated contrast agent into arteries in order to show its blood vessels, or

by replacing the cerebrospinal fluid (CSF) in and around the brain with air, so that its internal and external surfaces could be seen using conventional x-rays.

With the head CT system, James Ambrose examined 650 patients, used intravenous iodinated contrast agents to highlight tumours including meningiomas and gliomas, and described how to interpret the images.(3) Godfrey's invention suddenly placed Britain at the forefront of modern radiology.

Head CT became a sine qua non for large radiology departments doing neurological and neuro-surgical work. A more advanced head system, the CT 1010 was produced. This showed more detail, but the technique had only been applied to the head, and the question soon arose as to whether a whole body system would work. This would require not only a much larger machine, but a much faster one to allow imaging during a comfortable breathhold (i.e. about 20 secs) so that blurring due to respiratory motion could be eliminated. EMI produced a prototype of such a machine (the CT 5000) in 1975. This was installed at Northwick Park Hospital (NPH) and operated under Louis Kreel's direction (Fig. 2).

Fig. 2. Godfrey Hounsfield, Louis Kreel and Lady Barbara Castle (Oxford, St Hugh's) Secretary of State for Health and Social Services at the opening of the CT5000 scanner at NPH in 1975.

NPH was very different from Atkinson Morley's which was a dedicated neurological and neurosurgical hospital. NPH was the site of the UK Medical Research Council's (MRC's) Clinical Research Centre (CRC), and was designed to bring advanced biological and medical science to a district general hospital. It was operated in 16 divisions which were each supported by the MRC,

including one of medical imaging. The director of the CRC was Christopher Booth, a gastroenterologist who had been head of the Department of Medicine at the Royal Postgraduate Medical School, Hammersmith Hospital in London and the scientific side was directed by Sir Peter Medawar FRS (Oxford, Magdalen, immunologist, Royal Medallist 1959, Copley Medallist 1969, Faraday Medallist 1987) who was the doyen of British science. He had received a Nobel Prize in 1960 for his work on immunology but had suffered a stroke in 1969 while reading the lesson in Exeter Catherdral during the Annual Meeting of the British Association for the Advancement of Science (BAAS), but remained active following this despite suffering a partial left hemiplegia and left hemianopia. His scientific interests included cancer vaccines and xenotransplantation. He was revered as a scientific philosopher (4,5) and for his writings including his book "Advice to a Young Scientist" (6) which was prescribed reading for trainees within the CRC (Fig. 3). He was subsequently described by Richard Dawkins FRS (Oxford, Balliol) as the "wittiest of all scientific writers".(7)

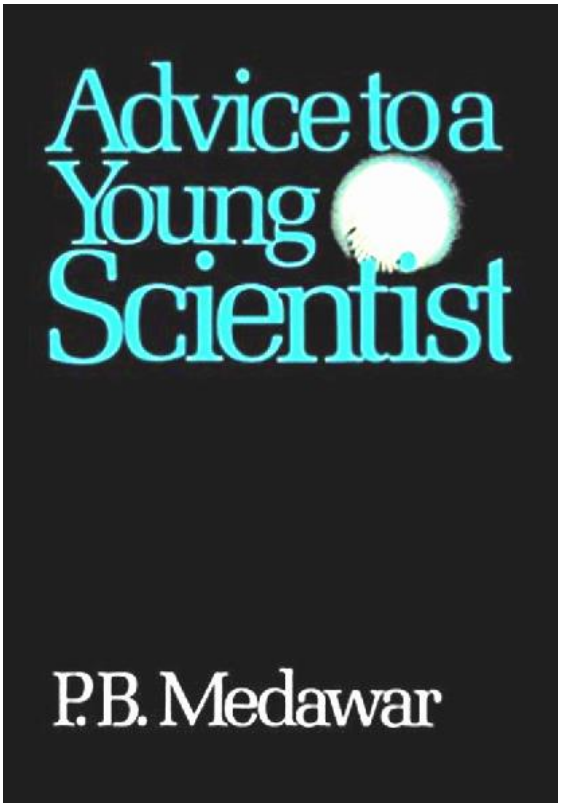


Fig. 3. Cover of "Advice to a Young Scientist" by P B Medawar.

Sir Peter had also championed the MRC's position in a recent controversy. In 1971 the government had commissioned the Rothschild report which had proposed the transfer of funds for research from the Research Councils to government departments so that research could be conducted by them on a "customer/contractor" basis. This approach was based on the belief that the users of the end-products of research were the best people to determine the nature and scope of the research that needed to be done to create them.

The Research Councils had taken a very different point of view, namely that research was a unified activity that could not logically be divided into, among other things, pure and applied forms, and that they should administer government funded scientific and medical research for the benefit of the nation as a whole. Sir Peter had provided the intellectual justification for this position but, in spite of his efforts, the government adopted the Rothschild report's recommendations in 1972 and implemented them in 1974 when government departments set up administrative structures to commission and supervise research in accordance with their needs. Sir Peter was undeterred and continued to support pure curiosity-driven research. He remained adamantly opposed to "the apparent logic of the customer-contractor principle".(8,9)

When the first patient was examined with the new whole body CT scanner Louis Kreel correctly diagnosed cancer in the patient's pancreas and it looked as though the body CT would follow the same pattern as for head CT. However there were a series of radiographic problems that needed to be overcome. Bowel peristalsis could blur the images, loops of bowel could simulate tumours and needed to be labelled with oral contrast agents to avoid confusion, contrast enhancement was necessary to see some tumours, and streak artefacts at air-tissue interfaces often degraded the images. These, and other problems, were directly addressed and whole body CT visibly came of age (Fig. 4).

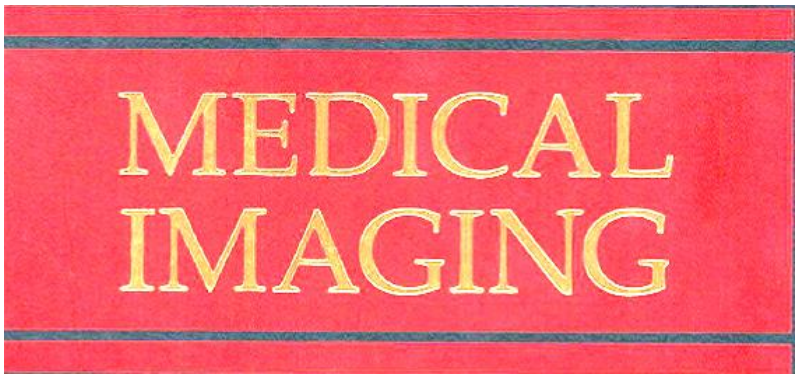
Fig. 4. The CT5005 scanner at NPH seen in the convex mirror used by the radiographers outside the scanner room to observe patients during examinations (1978). (It superceded the CT5000 system.)

There were many things Louis Kreel did:

(i) He spent a lot of time with Godfrey Hounsfield and other members of the EMI staff and regularly worked with them to resolve machine problems.

(ii) He remained in close contact with Gordon Higson who helped fund the clinical CT team.

(iii) He ran a course on medical imaging beginning in 1977. This was entitled "CT, U/S (ultrasound), IS (isotope scanning i.e. nuclear medicine) and NMR (nuclear magnetic resonance)". He edited the presentations in a book published in 1979 (Fig. 5).(10) It was a prescient description of the future of radiology including an NMR section that was published long before a single patient was scanned in the UK, and the prediction that there would be systems that combined different forms of imaging e.g. CT and IS.



Medical Imaging

CT U/S IS NMR

Edited by

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Fig. 5. Cover (upper) and title page (lower) of Louis Kreel's book: Medical Imaging CT, U/S, IS, NMR, published in 1979.

(iv) His tactical judgment on CT was excellent. He concentrated on oncological disease including lymph nodes in malignancy (Jenny Ellert), lung disease (David Katz), attenuation values in the three areas where they were most useful (bone, fat and iron deposition) and even studied psychiatric disease beginning with the first functional CT studies of the brain in conjunction with Eve Johnstone (11) although others had had brain CT available to them for five years before he had.

(v) He asked the Bowlby brothers (Richard, a photographer in the MRC Department of Illustration and Robert, a businessman) to construct a "Vidicam" which was a device that could produce 8x6 inch photographic prints ("bromides") of CT images in large numbers using two feet six inch diameter rolls of photographic paper. The images were developed and fixed using radiographic film processors. Using a Vidicam it was easy to produce 50-100 prints during, and at the end of, a CT examination in time to return them with the patient. The prints could also be submited with papers for publication.

(vi) Louis reported cases at three levels: one for the radiologist, one for the referring clinician and one for the patient so that all three could know what the findings were (this was at a time when patients were not even meant to see their own medical records). He also provided annotated prints so that the images could be understood at the three different levels. His reports were accompanied by personal letters to the clinician, often with hand-drawn diagrams as well as a relevant CT paper of his to clinicians referring patients for the first time. It followed the pattern Wilhelm Roentgen had used to announce the discovery of x-rays, but this time it was to announce the advent of body CT. It was an unheard of level of service and education at the time, and engendered strong support from clinicians.

(vii) He placed a great deal of emphasis on radiological education and ran seminars that attracted trainees from all around London. His technique followed the pattern described in another of his books "Outline of Radiology" (12) (Fig. 6) which emphasised being able to produce a detailed line drawing of the relevant anatomy and pathology of a disease. He said that if you could not do this, you did not understand the condition. It would be described later as "feature extraction" when artificial intelligence (AI) came into radiology.

osteolytic type (*Fig. 6.80*)

destructive lesions merging with normal bone (a)

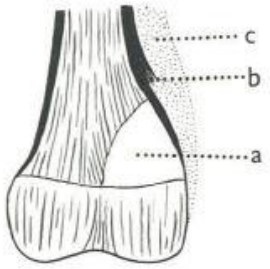


Fig. 6.80

in long bones provoked periosteal reaction (b) and adjacent soft tissue mass (c)

mixed sclerotic and osteolytic type (*Fig. 6.81*)

sclerosis at margin and extending into lytic region (a)

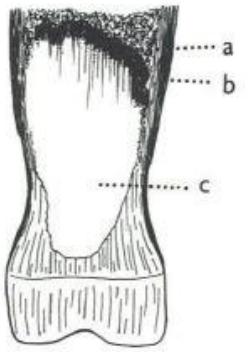


Fig. 6.81

periosteal reaction (b)

slight expansion of bone

osteolytic area (c)

(b) sclerosing osteosarcomatosis (*Fig. 6.82*)

age 5–10 years

rapidly fatal

multiple long bones

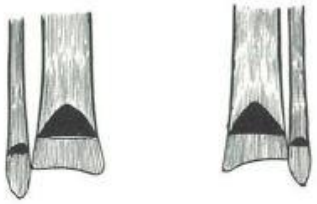


Fig. 6.82

bilateral and symmetrical

metastases in lung contain dense new bone

dense irregular opacities in metaphyses

(c) parosteal sarcoma

age 30–40 years

rare

usually painless mass

slow growing

dense exuberant new bone formation around bone (*Fig. 6.83a*)

early lesion shows lucent line between exuberant new bone and shaft (*Fig. 6.83b*)

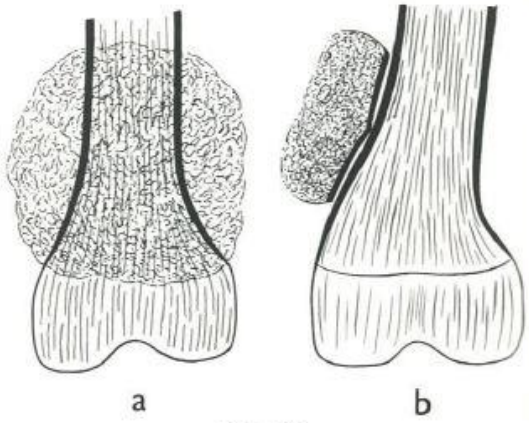


Fig. 6.83

CHONDROSARCOMA

age 30–60 years

about half as common as osteosarcoma

Fig. 6. Cover (upper) and page 338 (lower) from Louis Kreel's book "Outline of Radiology" published in 1971 showing in the lower figures line diagrams of different types of lesion in bone.

(viii) He ran special seminars with the radiation therapists to teach them therapy planning with CT, and helped EMI develop their RAD 8 system to acquire and use CT images for therapy planning.

(ix) The radiology department was run on police department principles with a uniform branch (i.e. the hospital clinical staff who dressed in white coats/uniforms) and a plainclothes branch (i.e. the MRC staff), and there were greater or lesser degrees of friction between the two groups. Although a member of the plainclothes branch, Louis wore a white coat and enjoyed mixing with the uniform branch in clinical meetings. He had a wide-ranging medical knowledge and could often contribute very usefully at clinico-radiologic meetings. The end result, after five years work, was that body CT was a clear-cut success with over 1000 machines placed worldwide. Louis developed an international reputation, clinicians strongly supported his work, and there appeared to be much more to come.

However, it did not last. After a disastrous commercial venture with CT in the US, and problems with the entertainment side of the company, EMI decided to merge with Thorn in October/November 1979 and the merged company (Thorn-EMI) very soon decided to divest itself of its CT interests. These were sold off at a knock-down price to General Electric (GE) of the US in April 1980. EMI scanner production, including their new third generation CT 7070 machine, was discontinued. Godfrey Hounsfield, who had plans to develop spiral and multi-detector row CT stayed on at Thorn-EMI, but with nothing specific to do.

The situation was complicated further when Godfrey was jointly awarded the Nobel Prize for his CT work in December 1979. We initially thought this was something to be celebrated, but quickly found out from the MRC that it was to be deplored. We were told that Sweden was a small Scandinavian country with no worthwhile scientific tradition and that it could not run a decent royal family. Nobel was just an armaments' manufacturer, and the country had backed both sides in World War II; its scientific judgment could not be trusted.

What was good science, and worthy of reward, could only be properly determined by the "the Royal". This was not a local pub, but was the Royal Society of London which had been established in 1660 following the restoration of the monarchy. It was the repository of a vast amount of knowledge and had had enormous experience, acquired over centuries, in determining what was good science and what was not. Any one of its medals was worth much more than anything emanating from Sweden.

This was a disappointment to some of us, because we had been told that Sir Peter Medawar's Nobel Prize awarded in 1960 was a good thing. It was now clear that there were good and bad British Nobel Prizes. When the Swedes did what the Royal Society told them to do it was good; otherwise it could be bad.

It got worse. When the newly elected Prime Minister Margaret Thatcher (Oxford, Somerville) had been appointed Secretary of State for Education and Science by Edward Heath (Oxford, Balliol) in 1970, she had strongly supported the Royal Society as the principal source of advice on government research policy, but after she became leader of the opposition Conservative party in 1975, she had taken a turn for the worse, and now believed that market needs should be the primary determinant of government funded research directions.(13,14) This had been blamed on a reversion back to her past when she had worked as an industrial chemist doing research for three years following her graduation from Oxford University. With CT, the original research had been performed by industry, and this had been supported by the Department of Health without Royal Society or MRC involvement or control. It was an example of how she now thought government funded research should be performed but was the antithesis of the way that the Royal Society and the MRC thought it should proceed. By this time we knew that the game was up.

The Director of the CRC, Christopher Booth (to be Sir Christopher, 1982) informed us that CT was "merely anatomical" and that there was nothing of significance about it since everything that we had seen had been described during the Renaissance. He explained to us that this had occurred 400-500 years ago, and had taken place in Italy.

We might have been more impressed if he had said that CT was "merely mathematical" which could have meant that he had read Louis Kreel's book on Medical Imaging. He might then have recollected that Leonardo da Vinci had not written a great deal about filtered back projection or Fourier transformation in his sketch books, and nor had his contemporaries. Neither had they written much in Fortran, COBOL or "C", using mirror writing or the reverse of it.

And, if he had opened Louis Kreel's other book ("Outlines") he might have observed that all the illustrations inside it were drawings not vastly different from those of Leonardo da Vinci's, but extending his work on normal anatomy and the abnormal appearances seen in different diseases to cover the whole body.

He might also have noted that, as a general rule, we tended to eschew the use of cadaveric dissection as the technique of choice when it was thought necessary to determine the state of a patient's internal anatomy (normal or abnormal) in order to best manage his or her clinical condition.

To console us, should we have felt disappointed in any way at all, we could study some of Sir Peter Medawar's famous aphorisms from "Advice" which was dedicated to the Royal Society, his Presidential lecture to the BAAS titled: On "The Effecting of All Things Possible" and his other works (6,15,16). These included:

(i) "Any scientist of any age who wants to make important discoveries must study important problems. Dull or piffling problems yield dull or piffling answers."

(ii) "A certain class of explanations in science are analgesics that dull the ache of incomprehension without removing the cause".

(iii) "Just as compulsory primary education created a market catered for by cheap dailies and weeklies, so the spread of secondary and, latterly, of tertiary education has created a large population of people, often with well-developed literary and scholarly tastes, who have been educated far beyond their capacity to undertake analytical thought."

(iv) "It is one thing to fall into step with a great concerted movement of thought such as molecular genetics or cellular immunology, but quite another to fall in with prevailing fashion for, say, some new histochemical procedure, or technical gimmick."

(v) "Humility is not a state of mind conducive to the advancement of learning", and

(vi) "For some people, even the smell of telegraph poles is nostalgic, though creosote has a pretty technological smell."

His last aphorism left some of us wondering, sometimes over a lifetime, whether the problem was that Godfrey Hounsfield as an industrial scientist should never have indulged himself by doing

curiosity-driven research, but should have stayed with EMI's basic culture and added to this his computing expertise to invent the iPhone rather than the CT scanner. Or, alternatively, wondering whether we should only breathe in the early morning if we wanted to avoid senescence.

Anyway, the CT unit was closed down in June 1980, and soon after, so was the highly successful MRC Ultrasound unit. After this Louis Kreel started work as a general radiologist at a very run down London hospital, Queen Mary for the East End, and took some of his staff with him. The hospital was delighted to have them. It had tried to exist on locum radiologists for many years and was now very pleased to have permanent radiologists. I was left unemployed with a wife and three young children to support.

2. The Hammersmith Hospital Nuclear Magnetic Resonance Unit

A job was advertised in the British Medical Journal for a one year registrar position (post FRCR) doing NMR imaging at Hammersmith Hospital London and I applied for this. Imaging research was at a low ebb following the sale of EMI's CT interests and the closure of CT at NPH. The job was working with Thorn-EMI's orphan NMR machine which was due to be sold. There were no obvious career prospects. The other short-listed candidate pulled out on the morning of the interviews and I was appointed by default, although I was not qualified for the post since I had not passed the final FRCR examination.

When I joined on 1 January 1981, I was clearly the odd one out among five (Frank Doyle, Richard Greenspan on sabbatical leave from Yale University, John Gore, physicist at Hammersmith Hospital, and Jackie Pennock, radiographer). Three of the other four had worked with the EMI group at the CRL for about two years, and had imaged animals and tested contrast agents.

I began working with the new Siemens Somatom II CT scanner since no one else at Hammersmith had had extended CT experience. There was no neuroradiologist or paediatric radiologist in the department either. The machine was funded by the Bernard Sunley Trust after GE had cancelled the order for an EMI CT 7070 system. The Siemens CT scanner had formidable advantages over the NMR system including a scan time of 5-10 sec (vs 4.2 mins for NMR), and far higher spatial resolution (up to 512x512 matrix size vs 128x128), as well as much better depiction of calcified tissues and push button operation.

However, the CT scans showed quite marked beam hardening artefacts in the posterior fossa and I sought the help of Gunter Dombrowe (Manager, Siemens UK) to see if his company scientists could reduce them. He informed me that no German radiologist had ever asked for this to be done, and that there was therefore no need to pursue the matter. He also enquired of me, as a non-FRCR, what I had been doing during the time when I should have been acquiring a training in radiology. It did not seem the right time or place to tell him that I suffered from nyctophobia, and that this had interfered with my radiological training, so I ignored his enquiry and explained further that the posterior fossa could become the focus of comparative studies with the new Thorn-EMI NMR system in which the Siemens system might well be disadvantaged, and that this could put the historic scientific relationship between Germany and the UK in jeopardy.

It was just conceivable that Sir William Siemens (Göttingen, [founded by King George II in 1734, "Extra Gottingam non est vita"], FRS 1862, Bakerian Medallist, 1871, knighted 1883 by Queen

Victoria for services to science) who had established the London office of his company in 1850 might not have been impressed by his company employee's lack of responsiveness to the apparent need of a fellow British subject, and might have suggested the use of scatter kernel superposition (17) to address the problem of excessive beam hardening artifact. However, Gunter probably knew that we were going to need German help then, and later on, if MRI was to progress, and was kind enough to leave us the beam hardening loophole to exploit in the near future.

In January 1981 Ian Young from EMI shifted to Hammersmith Hospital and brought to it: (i) An experienced team of physicists and engineers that he had built up over five years working at EMI's CRL. (ii) The World's first commercial whole body (large bore) cryomagnet built by Oxford Instruments headed by Martin Wood (Cambridge, Trinity; to be Mullard Medallist 1982, Sir Martin 1986, and FRS 1987). Ian's decision to ask Oxford Instruments to build the large bore cryomagnet had been a leap in the dark since all his previous NMR imaging had been done using a Walker resistive magnet. A properly functioning cryomagnet would provide much better static magnetic field stability than a resistive magnet, but such a magnet could quench and suffer irreparable damage. (iii) An inversion-recovery (IR) pulse sequence which had produced high contrast images of gray and white matter in his normal brain in Autumn 1979. (iv) A Multi Sequence Approach (MSA) which included other pulse sequences such as spin echo (SE) and partial saturation (PS) which he had developed, and (v) a desire to achieve a "decisive clinical advantage" over other imaging and/or medical techniques including, in the first instance, CT (Fig. 7).

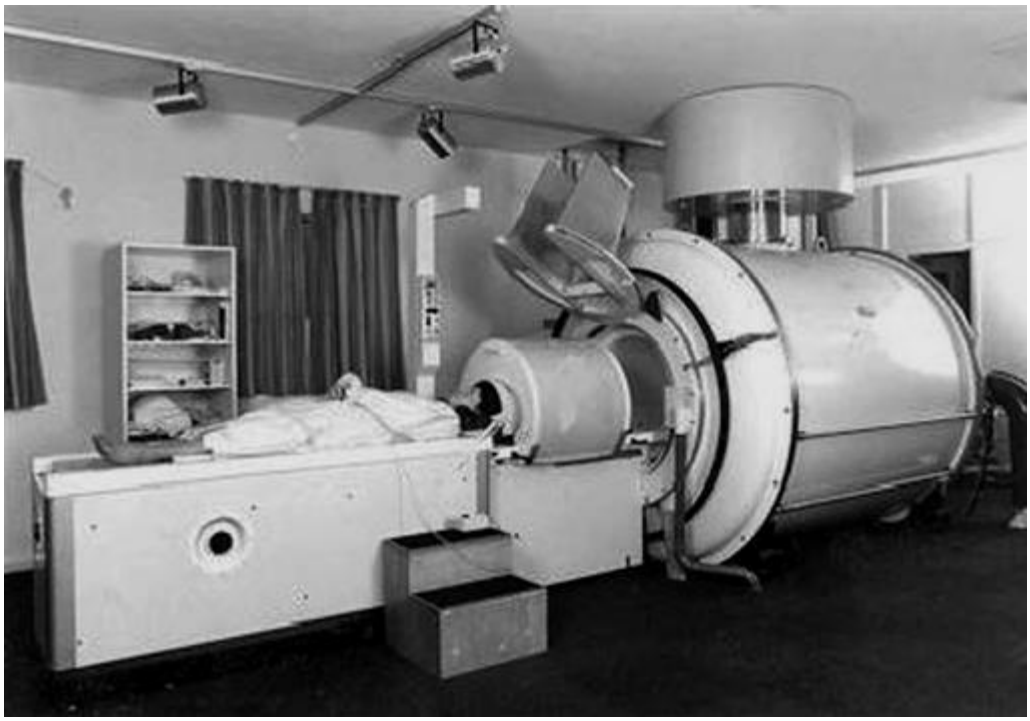


Fig. 7. View of the Thorn-EMI cryogenic magnet (Neptune) at Hammersmith Hospital, 1981. The subject is on the patient bed with her head just outside the head (receiver) and body (transmitter) coils. She is holding the emergency alarm bell.

The NMR system itself was awkward. It had to be licensed as a boiler to obtain insurance, and the motorised patient handling was uncomfortable. The operating manual Ian had written disappeared shortly after the machine was installed and was never found again. The gradient amplifiers required regular top-ups with de-ionised water (carried in buckets from the physics department half-way across the campus) in order to keep the machine operating when it was used to scan volunteers or patients.

In comparative terms CT was a mature technology with one disadvantage (the beam hardening artefacts in the posterior fossa) while MR was an immature technology with one advantage (its soft tissue contrast). However at that time this advantage could only be achieved with one sequence - IR - and this needed with it acceptable spatial resolution and a good signal-to-noise ratio (SNR), which both took time. Achieving both took 25 times longer per slice than with CT. Reductions in NMR scan time just led to loss of contrast, unacceptably low spatial resolution and/or poor SNR. The long scan times also meant that the soft tissue contrast which was developed could easily be degraded or lost by blurring and motion artifacts. NMR scan times would only be improved later when multislice and volume imaging became available.

The first three cases I examined on 25 March 1981 using the IR sequence (multiple sclerosis [MS], posterior fossa disease, and iron deposition in the liver) were all failures. This was unlike the experience of James Ambrose and Louis Kreel with head and body CT respectively where, in both instances, their first cases had been striking successes.

Things got worse. Frank Doyle suffered a major stroke with severe Broca's (non-fluent) aphasia and a right hemiplegia; he was never to work again. Richard Greenspan decided to cut short his sabbatical leave and returned to Yale University. John Gore resigned at the end of June 1981 to later take up a post at Yale with Richard. This left only two of the original five people on the clinical side - Jackie Pennock (radiographer) and me - and I was doing CT half of the time.

We then began implementing Louis Kreel's principles beginning with the purchase of a second-hand, old model Vidicam for £800, and started examining more patients with Jackie functioning as General Manager and me as machine operator, Vidicam service engineer and dark room technician. In addition, my wife Patricia started as secretary (initially unpaid) with a mandate to quickly and accurately prepare patient reports, papers and grant applications.

However, the NMR machine then quenched and became unusable for an undefined period. We retrieved from Frank Doyle's flat the paper that we had drafted in our first few months of operation, and the Lancet was kind enough to publish it as a memorial to Frank (courtesy Ian Munro) in July 1981.(18) It recorded the fact that we had got the machine going even if it never worked again. There was very little clinical content, but the paper did describe the high gray white matter contrast that we could see in the brain with the IR sequence.

During this time the Oxford spectroscopy group had published a paper on the use of MR spectroscopy (MRS) in McArdle's disease in the New England Medical Journal and there was an accompanying editorial (April 1981).(19,20) It described the first clinical use of MRS. Frank Smith of Aberdeen had described the clinical use of MRI to diagnose a haemangioma of the liver using the Spin-warp pulse sequence (21,22) and the use of MRI in the liver in a more comprehensive paper in the Lancet.(23) Brian Worthington in Nottingham had also described the first sagittal and coronal

MR images in 1980 (24) as well as imaging results in six patients with different conditions later in that year.(25)

While the magnet was down we regrouped. No-one had yet shown a decisive clinical advantage for MRI over CT, and there was likely to be a problem obtaining funding for everyone in the field if someone did not do so soon. Of more immediate concern to us was the fact that it might be very difficult to find a manufacturer prepared to buy our MR system and help support Ian Young's physics and engineering group if the machine could not do something of clinical significance.

There was also a meeting scheduled in the US for October 1-3 in Winston-Salem, North Carolina in about two and a half months time to which most of the World's medical MRI and MRS groups had been invited. On our performance to date it looked as though we would be completely outclassed there.

We decided to again try and exploit the high gray white matter contrast seen in the brain with MRI in normal subjects relative to CT in a logical clinical application, namely the study of MS, which is primarily a disease of white matter. The hope was that, even if we had not been able to make the first patient a success, we could at least make the first homogeneous series of brain patients a success.

3. Multiple Sclerosis

In our study the MRI findings in ten patients with relapsing and remitting MS were compared with state of the art contrast enhanced CT obtained with the Siemens Somatom II system on a slice by slice basis, using a single IR pulse sequence. In total there were 112 lesions (plaques) seen with MRI, while only 19 were seen with CT. MRI demonstrated abnormalities on a scale not previously seen except at post mortem.(26) It was a quantified decisive clinical advantage for MRI over CT (Fig. 8).

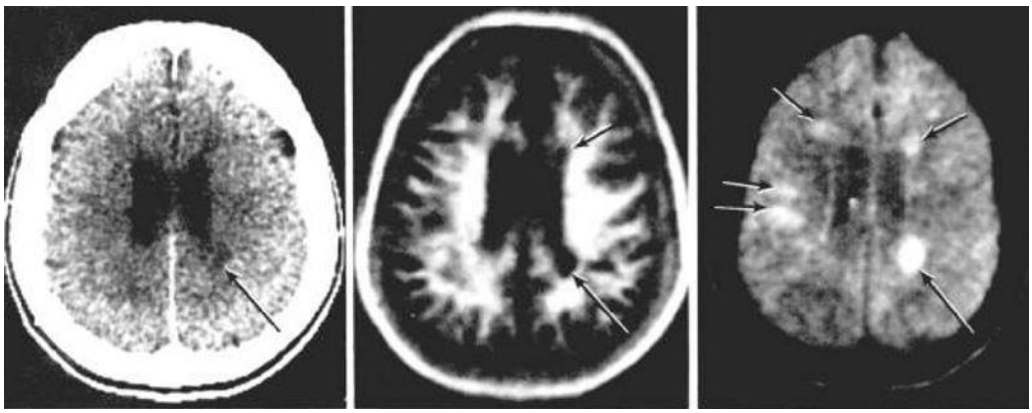


Fig. 8. Multiple Sclerosis: CT (left), IR (centre) and SE (right) images. One lesion (plaque) is seen as a low signal (dark) region on the CT scan (arrow), several are seen as dark regions on the IR image (e.g. arrows) and at least five are seen as high signal (light) regions (e.g. arrows) on the SE image.

In radiological terms, the increase in water and loss of myelin in plaques resulted in an increase in their T_1 with MRI. This produced a dark appearance within the highlighted (white) normal white matter making the plaques easy to recognise on IR images. With CT, normal white matter had a low signal (dark) appearance due to its lower x-ray attenuation. The increase in water and loss of myelin in

plaques produced a decrease in the already low x-ray attenuation white matter which resulted in a limited degree of additional darkening. This was often difficult or impossible to recognise with CT.

The paper was published as the lead article in the Lancet (14 November 1981) with Ian Young (industrial scientist) as first author, the name of his company (Thorn-EMI) in the next line down on the title page, and acknowledgments to Gordon Higson and John Williams of the DHSS at the end of the paper. It was the consequence of market-driven industrial research supported by a government department. There was no mention of the MRC.

The paper also provided an opportunity to compare the opening shots from MRS and MRI. Oxford University had a long history of success in the study of electricity and magnetism. The standard university text on the subject (Bleaney and Bleaney) was from Oxford, the major text on NMR was from Anatole Abragam also of Oxford, and our magnet had been made by Oxford Instruments, a spin-off company from the University. The University also had great strengths in biochemistry including the work of Sir Hans Krebs FRS (Nobel prize winner, 1953, Royal Medallist, 1954, Copley Medallist, 1961) who worked at Oxford from 1954 until his death in 1981.

George Radda FRS (Oxford, Merton, biochemist, to be Buchanan Medallist 1987, to be Sir, 2000) had shown Sir John McMichael FRS that ATP could be observed in the beating mouse heart with MRS and that its level was reduced in ischaemia. Sir John had then facilitated British Heart Foundation (BHF) support for George's unit.(27) A revolution in in vivo biochemistry was anticipated, and the case of McArdle's disease was seen as the first human example of what might be possible.(19,20)

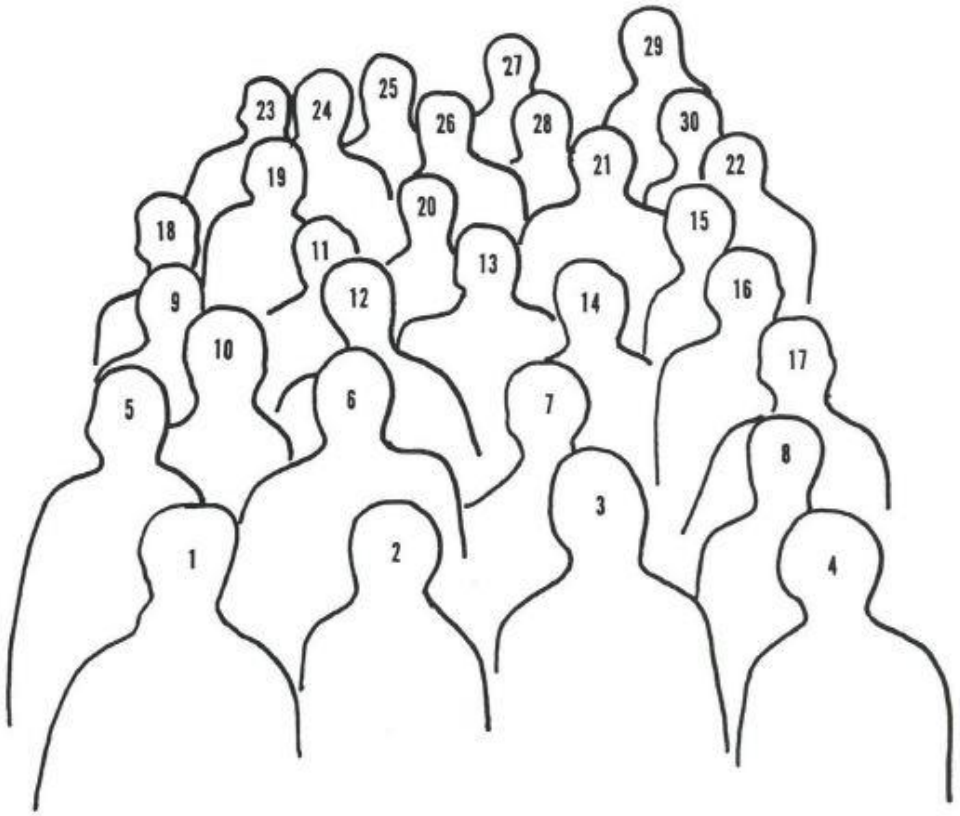
From a clinical point of view McArdle's disease was very rare, and a condition that could be diagnosed at the bedside with a ten minute ischaemic lactate test. It could be confirmed, if necessary, with a muscle biopsy. The disease did not usually affect life expectancy and care with exercise to avoid cramps was adequate treatment in most cases. In contrast, MS was common, potentially disabling and presented diagnostic difficulties with some patients not meeting criteria for dissemination of lesions in time and space leaving them in a diagnostic no-man's land. Previously, imaging in any shape or form had little or nothing to contribute, but now it appeared that imaging could have a major role in diagnosis, and that clinically silent MS lesions could be detected using MRI. This could be very useful in establishing the diagnosis by demonstrating previously unrecognised dissemination of the disease in space, and repeat MRI examinations could also be used to demonstrate dissemination in time.

In terms of future trajectories for MRS and MRI, it looked as though MRS could help in biochemical understanding and this might require a few research machines in the UK, but MRI looked as though it might replace CT and therefore be needed in the several hundred medium or large-sized hospitals in the country. The value of orders for large bore magnets worldwide increased from £1M in 1981 to £25M in 1982 with Oxford Instruments taking 90% of the market share.(28) This caused some astonishment within the company. The vast majority of orders were for magnets to be used for MRI, not MRS.(27,29)

4. The Winston-Salem NMR Meeting October 1-3, 1981: Changing of the Guard

A meeting on the use of NMR in medicine had been held in Nashville on 26-27 October 1980.(30) The only human imaging results at this meeting were from Bill Moore and Brian Worthington of Nottingham (24) and the general conclusion was that radiologists preferred CT. The future of MR was therefore thought likely to be in spectroscopy and Oxford Instruments had proceeded during the following year on this expectation.(27,29)

At Winston-Salem six groups presented clinical MR images: (i) Aberdeen (Frank Smith) who showed extensive body studies, (ii) Nottingham (Brian Worthington) who showed brain and body Steady State Free Precession (SSFP) images, (iii) ourselves, including our MS work, (iv) Massachusetts General Hospital (MGH) (Fernando Buonanno) with brain images using SSFP, (v) FONAR (Raymond Damadian) who showed breast work which was not competitive with mammography,(31) and (vi) Philips (Andre Luiten) who showed images of two meningiomas and a glioma. The results were later published in the proceedings of the meeting (32) which included a well known photograph of the meeting faculty (Fig. 9).



1. HOULT, 2. ORDIDGE, 3. HANLEY, 4. HUTCHISON, 5. FOSSEL, 6. BURT, 7. PARTAIN, 8. BUONANNO, 9. NUNNALLY, 10. GOLDMAN, 11. KUNDEL, 12. WILLCOTT, 13. RADDA, 14. WORTHINGTON, 15. GORE, 16. HINSHAW, 17. MANSFIELD, 18. CROOKS, 19. SAUNDERS, 20. BYDDER, 21. LAUTERBUR, 22. BUDINGER, 23. SMITH, 24. YOUNG, 25. MOORE, 26. DAMADIAN, 27. LUITEN, 28. KARSTAEDT, 29. EDELSTEIN, 30. BOTTOMLEY

Fig. 9. The Old and the New – Faculty at the Winston Salem Meeting Oct 1-3, 1981 (upper) and key with surnames (lower). Most of the groups active in Medical MR at that time were represented at the meeting.

At that time it was possible to assess the impact of a particular image on the audience by the loudness of the shower of camera clicks that followed display of the image on the screen at the front of the lecture theatre. On this measure, our MS study was the most important clinical work shown at the meeting, and the UK groups were ahead of the US groups. It was the first time Ian Young had spoken at an NMR meeting and some of the US attendees were more familiar with his name in print and addressed him as "Iron" using an American pronunciation of his Christian name.

It was an opportunity to meet Frank Smith and Brian Worthington. Frank was imaging single-handedly and doing his own portering. He had no access to CT. Brian said that most of the Nottingham physicists had left, or were planning to leave. He was also single-handed, and only had access to Bill Moore's SSFP system. This was not showing meningiomas, infarcts and other disease

of the brain and did not appear to have a clinical future.(27) Peter Mansfield's EPI was of low spatial resolution and was only available on a small bore system. It was not competitive.

We agreed that with the large US groups now rapidly coming on stream, the UK physics effort in previous years was likely to be forgotten unless we could maintain a connection to it with a significant clinical presence, and we decided to coordinate our work to try and achieve this. Frank said that he would concentrate on the body, I would study the adult brain for 6-8 months and follow this with the paediatric brain, and Brian and I would pool our brain results at the Symposium Neuroradiologicum meeting scheduled for October 1982 in Washington. Brian also said that he would approach Gordon Higson to try and obtain funding for a new more effective clinical machine. Frank, Brian and I would meet again at most Radiological Society of North America (RSNA) annual meetings for the next 20 years (courtesy Bill Bradley).

During the period from 1980 to 1982 the field of MRI shifted from a few people working in laboratories doing occasional volunteer studies to a much larger number working in hospitals and doing patient studies. Over this time:

1) Clinical groups were formed. These usually consisted of radiologists, cardiologists, neurologists and/or oncologists, almost all of whom were new to the technique of NMR but who often had considerable experience in clinical medicine and other methods of imaging.

2) Industry became much more involved and provided investment on a far larger scale than had been done previously. This included support for physicists and engineers at hospital sites as well as in factories. As a consequence the field was now divided into those who had industrial collaborators and support, and those who did not. The latter included:

(i) Paul Lauterbur. He was to contemplate building a 10T system with Tom Budinger, and then bought a 4T magnet which quenched while being energised at 2.5T and was irreparably damaged. He had an unsatisfactory relationship with Morton Meyers head of radiology at Stony Brook,(33) (see also Morton Meyer's account [34]) and moved to Urbana-Champaign in 1987. Paul only made a small contribution to clinical MRI after this meeting.

(ii) Peter Mansfield (to be Wellcome Medallist 1984, FRS 1987, Mullard Medallist 1990, Sir 1993). He had a resistive magnet operating at 0.1T which could only do adult limbs and small children. Five years later he got a 0.5T whole body cryomagnet. He worked exclusively with EPI on both systems.

(iii) Bill Moore (Cambridge, Caius). He went from Nottingham to the Massachusetts Institute of Technology but died after a game of squash in 1984.

(iv) David Hoult (Oxford, St Catherine's). He left Oxford and worked on a prototype spherical resistive magnet for infants at the National Institutes of Health (NIH) Bethesda for many years as well as shimming techniques, selective 180° pulses and theoretical formulations of the NMR experiment. Very much later he developed a per-operative system with IMRIS.

(v) Tom Budinger. He was at the University of California, Berkeley and had a lot of equipment, but now devoted himself to MR safety issues and establishing the Society of Magnetic Resonance in Medicine (SMRM). This society aimed to involve both those who had worked in MR over the

previous eight to ten years as well as newcomers. Another society, the Society of Magnetic Resonance Imaging (SMRI) was also established around this time. It catered much more for newcomers to MR and for those doing MRI.

(vi) Raymond Andrew (Cambridge, Christ's, to be FRS 1984, Wellcome Medallist 1984) head of the the department of physics at Nottingham. He went to Gainesville, Florida, and became the first active editor of Magnetic Resonance in Medicine. He did very little further clinical imaging research.

(vii) Al Macovski at Stanford. He built his own systems but others at Stanford (e.g. Gary Glover, John Pauly) subsequently worked closely with GE and became well known.

3) There was also movement on the magnet front in terms of magnet type, field strength and bore size:

(i) Previously most of the volunteer and patient work had been done with resistive magnets, but there was a sharp shift towards cryomagnets now that Oxford Instruments had shown it was possible to build a successful large bore version. There was only one large bore permanent magnet clinical system available, namely that from FONAR.

(ii) There was also a major shift in field strength with most groups increasing their static field (B_0), or entering at a higher field strength e.g. Aberdeen increased from 0.04 to 0.08T, FONAR increased from 0.045 to 0.3T, GE increased from 0.12T to higher fields, and Diasonics came in at 0.35T.

(iii) There was also a move to whole body rather than small bore imaging systems.

(iv) As yet, high field systems (e.g. 1.9T systems) were only available in small bore form e.g. 32 cm diameter, not in whole body form. The high field strength was necessary for MRS. At this stage this limited human MRS to the study of adult limbs and infants.

4) Pulse sequences. There were major changes here too: Spin-warp quickly began to take over for data acquisition. FONAR completely dropped focused NMR which had given the company its name, and shifted to Spin-warp.(35) Philips also dropped its two back projection techniques, and used Spin-warp exclusively. EMI changed from filtered back projection to Spin-warp in 1982 for most conditions. GE had hired Bill Edelstein and continued his work using Spin-warp. Diasonics changed from line scanning to Spin-warp. SSFP became much less used although it was later used as a rapid high SNR acquisition technique and for diagnosis in situations where intrinsic tissue contrast was high.

In writing a review of the meeting, Bill Oldendorf, a Los Angeles based CT pioneer, lamented the poor performance of the US groups relative to the UK and blamed this on too many physicists working in defence at the expense of medical research.(36) It was fairly widely believed that Bill's name had been on the list of Nobel Prize names for CT in 1979 but was deleted in the last hour before the announcement.(37) (All may be revealed in 2029!) In the near future the US would make amends for any failings (real or imagined) at this meeting. MRI technical development up until this time was summarised by Paul Bottomley in an article submitted in February 1982.(38)

5. Clinico-Industrial Groups: Clinical and Commercial Realities

The field became structured with the formation of 20 or more clinico-industrial groups usually based at well known hospitals and mostly having company scientists on site. They included:

(i) Massachusetts General Hospital (MGH) with in-depth clinical strengths in neuroradiology (Juan Taveras), cardiology (Gerald Pohost), neurology (Fernando Buonanno), and Nuclear Medicine (Tom Brady) working with Technicare (Waldo Hinshaw et al).

(ii) Cleveland Clinic (Meredith Weinstein, Michael Modic) working with Technicare.

(iii) Case Western Reserve, Cleveland (John Haaga, Ralf Alfidi) also with Technicare.

(iv) University of California, San Francisco (UCSF) with their own physicists (Larry Crooks, Leon Kaufman) and about 20 radiologists (Alex Margulis, Michael Brant-Zawadski, David Norman, Hedvig Hricak, Peter Davis etc) working with Diasonics.

(v) University of Pennsylvania (U Penn) (Bob Grossman, Herbert Kressel) working with GE (Paul Bottomley, Bill Edelstein).

(vi) Yale (Richard Greenspan, John Gore) also with GE.

(vii) University of California, Los Angeles (UCLA) (Bob Lufkin) with FONAR,

(viii) Cleveland Institute Inc (Ronald Ross) also with FONAR.

(ix, x) Gröningen (Ad van Voorthuisen) and Leiden (Theo Falke) both with Philips (Andre Luiten, Rob Locher).

(xi) Wiesbaden (Peter Rinck) with Bruker (Bertold Knuttel, Dieter Ratzel, Hans Post).

(xii) Freiburg (Jürgen Hennig) also with Bruker.

(xiii, xiv) Erlangen (Erhard Zeitler), Berlin (Roland Felix) both with Siemens (Anulf Oppelt, Wilfried Loeffler, Andrew Maudsley).

(xv) Gottingen (Axel Haase, Jens Frahm) also with Siemens.

(xvi-xviii) Aberdeen (Frank Smith), St Bartholomews, London (Ian Kelsey Fry and Judith Webb), Edinburgh (Jonathan Best, David Kean, Michael Smith) with M&D Technology (John Mallard, Jim Hutchison) and Asahi.

(xix) Instrumentarium (Raimo Sepponen, Jorma Sipponen).

(xx) Hammersmith Hospital (Graeme Bydder) with Picker/GEC (Ian Young). Picker/GEC had bought the EMI system (Neptune) in October 1981.

Certain clinical realities became obvious too: (i) Some of the groups had up to about 20 radiologists working on their MR system divided by sections within the department of radiology (e.g. UCSF) whereas the three UK groups each had only a single radiologist covering all specialities. (ii) Safety was critical. A single mistake could lead to the injury or death of a volunteer or patient. It could also stall MR development for everyone involved. (iii) There was very active clinical competition to define the appearances of important diseases as seen with MR for the first time and to present and publish these findings. (iv) Comparative studies typically compared CT results obtained from state of the art systems with MRI results from one-off research prototypes. An early discovery was that CT and other imaging techniques were often much better than was generally thought. (v) There were vested interests in CT, US, Nuclear Medicine etc who had something to lose if MRI was successful.

On the commercial side there were also new realities: (i) The companies expected a return on their research expenditure in the forseeable future, often conducted regular reviews and were frequently insistent about their needs. (ii) There was a major advantage in having physicists on site. Unlike CT, the MR properties of tissues in health and disease were only partially understood and experience with patients was necessary to develop useful clinical techniques and exploit them. With CT there had been no equivalent to pulse sequence development, but this was a major feature of MRI, with optimisation on volunteers and patients essential. (iii) There was also strong technical competition between companies. Often customers wanted particular sequences or capabilities as a condition for buying a system and these usually had to be demonstrated at clinical sites. (iv) Customers also wanted clinical training and support afterwards, much of which could only be provided by experienced radiographers and radiologists. (v) There was also a world of marketing, some of which was counter-intuitive. Aspects of this would later be formalised in a book entitled "The 22 Immutable Laws of Marketing" written by Al Ries and Jack Trout (39) following in the footsteps/standing on the shoulders of Sir Isaac Newton PRS (Cambridge, Trinity) (Fig. 10).

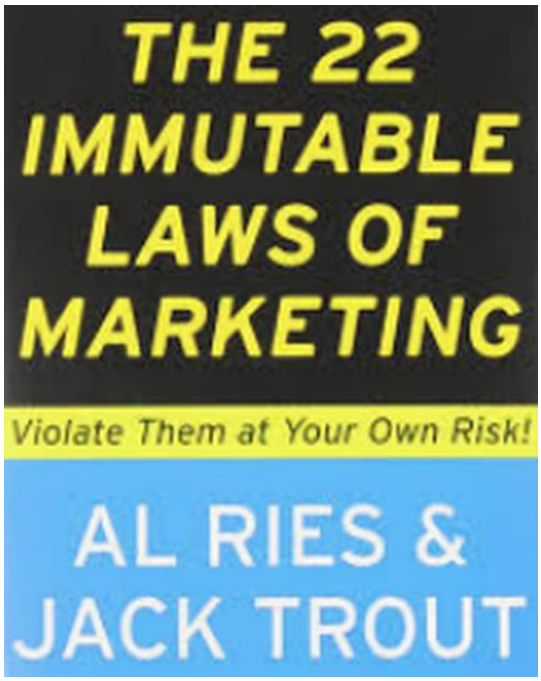


Fig. 10. Cover of the book "The 22 Immutable Laws of Marketing" by Al Ries and Jack Trout.

With Picker we found Bill Doran and Ric Hullihen (Sr) very pleasant, but bereft of MR knowledge. The attempt by Picker to establish a prestige site at the Mayo Clinic was a failure – the Picker system was scrapped and the Mayo bought a GE system. It was not till Surya Mohapatra became Picker manager of MR seven to eight years later that the commercial interests of the company and our own became better aligned.

6. The Long Echo Time (TE) Heavily T_2 Weighted Spin Echo Pulse Sequence

While at EMI Ian Young and his team had produced a short echo time (TE) spin echo (SE) sequence which we described in November 1981.(40) It showed little contrast between normal and abnormal tissue in disease and we did not use it clinically. However, David Bailes increased the TE to 40, 80 and then 120 msec, and increased the repetition time (TR) to 1000 and then 1500 ms, and disease of the brain was highlighted with spectacular T_2 dependent contrast (Fig. 11). The TR could be adjusted to keep the CSF signal just below that of white matter to avoid confusion of lesions with partial volume effects. Measurements of T_2 showed an increase in disease of 20-100% (or more). A T_1 weighted IR sequence could also be used to show brain anatomy and this could be paired with the SE sequence which highlighted pathology. Thirty-two patients were described in the first paper on this subject which was published in July 1982.(41)

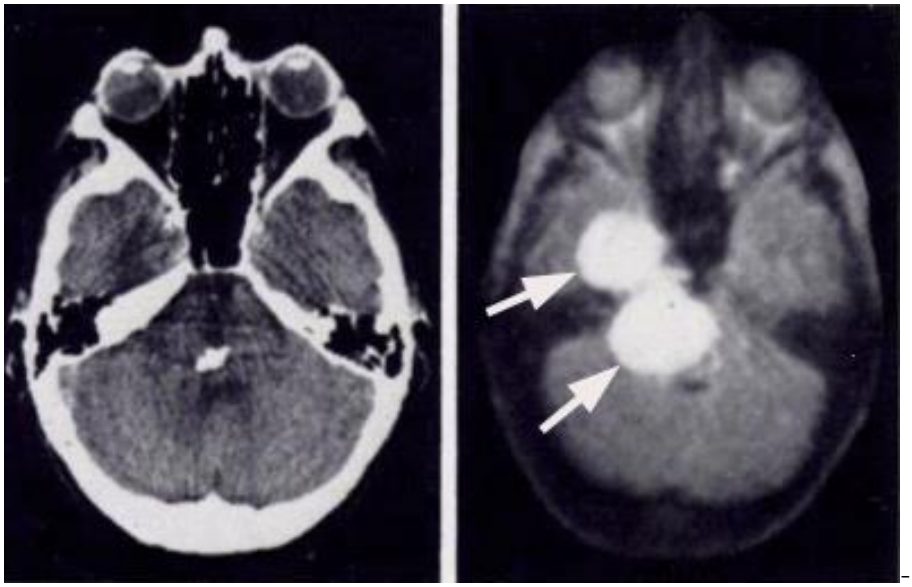


Fig. 11. Chondroma in the posterior and middle cranial fossae: CT (left) and heavily T_2 weighted SE scan (right). Calcification is seen as high signal (light) in the region of the pons on the CT scan but the tumour is much better seen on the SE scan (arrows). The calcification appears dark on the MR scan.

The clinical consequences followed quickly: (i) the SE sequences tolerated inhomogeneous B_0 fields better than the free induction decay (FID) based sequences we had used previously and SE sequences became the preferred option particularly at longer TEs. (ii) We had seen an increase in T_1 in disease previously. Now we had shown a concurrent increase in T_2 so it was clear that the ratio T_2/T_1 probably changed little in most diseases where both relaxation times were increased, and this could

account for the failure of the SSFP sequence (whose contrast was dependent on the ratio T_2/T_1) to show contrast in disease. (iii) The heavily T_2 weighted SE sequence became the single best method for detecting parenchymal disease in a wide range of clinical applications.(e.g. 42,43) It rapidly became a general clinical workhorse, but it was not as useful as the IR sequence for showing brain anatomy and so it quickly became common practice for us to use the two sequences together.

7. Spin-warp and K-space

We were still unable to obtain useful sagittal and coronal images using filtered back-projection even with a SE sequence but, after David Bailes installed sequences with Spin-warp data acquisitions on our system, images in these planes were obtainable and of high quality. In 1996 Sir Godfrey Hounsfield FRS (Mullard Medallist, 1977) said:

"For quite a long time people had been using my CT reconstruction – the r-theta system which of course introduced very bad phase issues when it was used on NMR. It was only when the 2-D Fourier transformation was used that pictures were 100 per cent correct. This was a great step forward."(27)

An IR preparation with Spin-warp produced classic high gray-white contrast midline sagittal images of the brain which had not otherwise been seen except at post mortem, and were not directly obtainable with CT (Fig. 12). From this time on the majority of our images were acquired with Spin-warp.

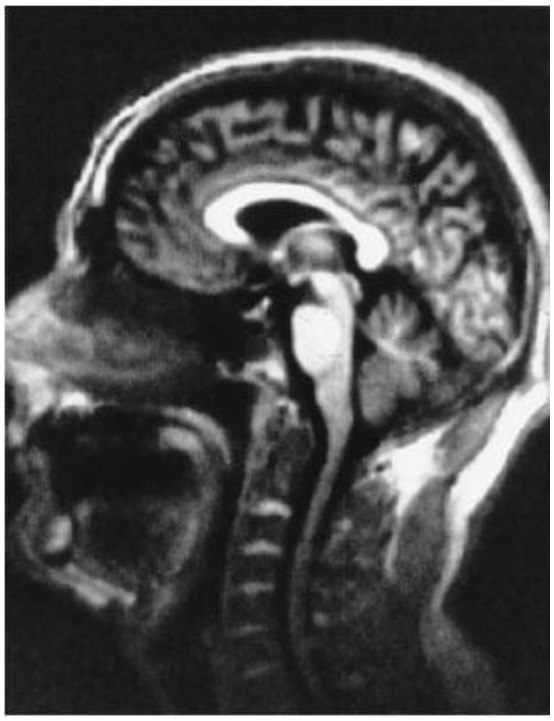


Fig. 12. Sagittal anatomy IR scan using Spin-warp (1982). There is high contrast between white matter which is white, and gray matter which is grey. The sagittal plane could not be directly imaged with CT at this time.

Because our Data General S/250 computer had relatively little random access memory David Bailes had had to use the computer display memory to store image data as it was acquired. A consequence of this was that we saw the acquisition of the images in k-space in real time on the display screen. K-space was the Fourier transformation of the image. Conceptually it was a major advance in understanding data acquisition. This included r-theta which used radial mapping, Spin-warp which used Cartesian mapping, and EPI which used single shot rectangular mapping. David Tweig (44) and Sven Ljunggren (45) published the concept in 1983 although it had been described earlier in a patent. David Bailes and David Bryant also described it in 1984.(46)

8. The Multi Sequence Approach (MSA)

In the initial studies we (and other clinical groups) had used a single sequence or data acquisition, namely a PS/IR sequence to produce a proton density image and a T_1 map in Aberdeen, SSFP in Nottingham and an IR sequence alone for us in MS. We now had IR and PS preparations as well as three types of acquisition (FID, gradient echo, SE). We also had radial and Cartesian k-space mapping. As a result we could acquire images whose main contrast depended on each of mobile proton density (ρm), T_1, T_2 and flow (Table), and do this in multiple planes. This was a multi sequence approach (MSA) as opposed to the previous single sequence approach (SSA). In its favour the MSA provided access to more of the many tissue properties accessible with MR, but against it were: (i) the increase in scan time to do the different pulse sequences, and (ii) an increase in complexity. It was not sufficient just to know one or two patterns of normal and abnormal MRI for each disease as was the case with CT (including contrast enhancement), but perhaps five or six different patterns for each variant of the PS, SE and IR sequences.

Table. The Multi Sequence Approach (MSA) (1982)

Sequence	Preparation			Data Collection	
	TR	TI	TE	Signal type	K-space mapping
Proton density weighted	Long		Short	Free Induction Decay (FID)	Radial (r, θ)
T_1 weighted	Short		Short	Gradient Echo	Spin-warp, Cartesian (X,Y)
T_1 weighted and/or T_2 weighted	Long	Inversion pulse: short TI and medium TI	Short and medium	Spin Echo (SE)	
T_2 weighted	Long		Long		

TR = repetition time, TI = inversion time, TE = echo time (= 2τ in original papers)

We now had an array of options assembled and needed to show how they could be used in clinical diagnosis.

9. The Brain

After the Winston-Salem meeting we examined patients with brain disease and used new options (SE, Spin-warp) as soon as they became available. The largest patient series in clinical MRI published before we began our extended brain study had been our 10 MS cases, and we initially aimed to do 100 cases but later increased this to 140 in order to include patients scanned with recently developed sequences.(47)

The Spin-warp IR sagittal sequence allowed us to show brain anatomy with white matter white and gray matter grey as it was seen in life and at post mortem (unlike CT where gray matter was white and white matter was grey). In addition the heavily T_2 weighted SE sequence highlighted disease with greater contrast than CT in many situations. With CT most disease (except, for example, calcification and early haemorrhage) was lower signal than normal brain and did not "stand out" as it did with MRI. (An exception was contrast enhancement which highlighted meningiomas, and usually part or all of gliomas and metastases so that they "stood out".) The heavily T_1 weighted IR sequence was superior to CT for anatomy and the heavily T_2 weighted SE sequence was generally superior for pathology which gave MRI a double advantage over CT. The combination provided parallel iconic signatures for MRI.

The paper covered the main categories of neurological disease and provided a system for image interpretation based on changes in ρm, T_1, T_2 and flow. There were complex patterns in haemorrhage, but the main disadvantage of MRI was in meningiomas and gliomas where contrast enhancement gave CT a pronounced advantage. The paper was published at the beginning of August 1982 before the first SMRM meeting in Boston on 16-18 August. The first UCSF patient brain series was of six cases and was published in September 1982.(48) They published 70 cases in 1983,(49) Bill Bradley described 400 cases in 1984 (50) and Roland Felix described 1200 cases in 1985.(51) Steven Lukes of UCSF published very similar results to ours in MS in June 1983.(52) Unfortunately he died of a subarachnoid haemorrhage while his paper was in press. By this stage the MSA with a T_1 weighted sequence for anatomy and a heavily T_2 weighted SE sequence for pathology had become common practice. Our paper remained the most cited one in clinical MRI for about the next 15 years.

We were receiving many clinical requests for MRI examinations, but because of the lack of an MR contrast agent the only conditions in which we could consistently deliver a decisive clinical advantage over CT were MS and posterior fossa disease.(53,54) We accepted cases in these categories from all-comers providing that they had previously had a good quality contrast enhanced CT to make sure we were not caught out by meningiomas. We then followed the Louis Kreel practice of sending back to the referring clinicians a three level report, with annotated prints to advertise the advent of clinical MRI - albeit restricted at that time to one disease, and one region of the body.

Gordon Higson was supporting us in the short term although he thought he had received a promise from Sir James Gowans FRS (Oxford, Exeter, immunologist, Royal Medallist, 1976), Secretary of the MRC that the MRC would support the clinical side while Gordon continued to help fund the physics and engineering.(27) Now that we had made some progress Robert Steiner, outstanding head of the Department of Radiology at Hammersmith Hospital (55) (Fig. 13), thought it was time to approach

the MRC again and managed to obtain an appointment to see Sir James. However, about ten minutes into our interview with him, Sir James said that the appointment had been a mistake and asked his secretary to escort us out of his office. True to the thinking of his fellow Oxford immunologist Sir Peter Medawar, Sir James did not have much time for the dull and piffling or technical gimmicks.

Fig. 13. Gertie Steiner, Robert Steiner, Ian Young and Gordon Higson (1982).

Robert then sought help from Sir Frederick Dainton (Oxford and Cambridge, St Johns and Emmanuel, Professor of Chemistry at Oxford, Chairman of the University Grants Committee, Chairman of the National Radiological Protection Board, author of the Dainton report [which had supported Research Councils retaining their own budgets in 1971], FRS, Davy Medallist 1969, Faraday Medallist 1974) hoping that he would have the credentials necessary to qualify for a full length audience with Sir James, and would therefore have time to put the case for supporting MRI research to the MRC. Although he did get to see Sir James, it was to no avail from our point of view, and we had to continue working with what clinical funding Gordon Higson could find.

We presented results from our work at RSNA in November 1982. We showed a substantial advantage for MRI over CT in the posterior fossa using our 0.15T system, but this was not the highlight of the meeting. That was the GE announcement of brain images obtained at 1.5T with higher spatial resolution than ours, and a SNR that was greater than any seen previously. It was a sensation. Their success was aggressively marketed and GE rapidly took ownership of the concept "high field", and made it synonymous with "high quality". The company became the market leader even though it had no product to sell. This did not seem to matter - it was "more important to be first in the mind than first in the marketplace" (Immutable Law 3) and "marketing is not a battle of products, it's a battle of perceptions" (Immutable Law 4).

Their results, showing an 11-fold increase in SNR over operation at 0.12T, were published in the Lancet in July 1983 together with 31P and 13C spectra.(56) The latter created an issue for

spectroscopists. It simultaneously challenged both small bore systems and large bore Topical MR (TMR) systems which were designed specifically for spectroscopy and did not have advanced imaging capabilities. As new forms of spectral localisation became available using imaging techniques it would became possible to do MRS on large bore high field machines primarily designed for MRI at relatively little extra cost.

10. High Field versus Low Field

With GE now established as the market leader, all the other companies and their associated clinical groups either had to match them with 1.5T systems, or show that they could perform just as well, or nearly as well, at lower field strengths. Competing at 1.5T was likely to be difficult because GE was putting large scale resources into its single 1.5T product and already had the lead. We had remained at 0.15T because we did not have the money to buy another system at any field strength. GE scientists published theoretical arguments strongly supporting their view that 1.5T was best,(57) while others such as Leon Kaufman (UCSF with Diasonics) (58) argued that the benefit of increased field strength could be achieved at the much lower strengths such as 0.7T. There were also serious cost arguments because high field systems were more expensive than lower field systems - sometimes very much more so when magnetic shielding was included in the price.

The first showdown between the high and low field groups was scheduled for the SMRM meeting in San Francisco with Ian Young presenting in a morning session, and Bill Edelstein (GE) and Leon Kaufman presenting in an afternoon session on 16 August 1983.

We had a few months to prepare before the meeting and did several things: (i) under the direction of Reg Harman and David Gilderdale we made spherical head coils of many different sizes which closely fitted patients.(59) They produced an obvious increase in the SNR of brain images and were known as "Jedis" after Princess Leia (played by Carrie Fisher) in the film "The Return of the Jedi" released in May 1983 (Fig. 14). (ii) We had seen in the GE figure in their letter to the Lancet (56) that their normal image had reduced grey white matter contrast compared with the images published by us in our Lancet paper two years previously.(18) This was due to the convergence of T_1s at higher field and their use of a T_1-weighted SE sequence rather than the more T_1-weighted IR sequence. GE did not use the "British" IR sequence, so we produced a lot of images at 0.15T showing high gray white matter contrast that was not seen as well at their higher field. (iii) The increase in the T_1 of the brain at 1.5T also meant that it was much more difficult to get high T_2 contrast with the CSF signal less than that of brain at high field so we produced plenty of examples of this which could be done easily at low field. (iv) We also had unusual clinical material (e.g. posterior fossa cases from around the UK and Continental Europe) to interest clinicians rather than just images of normal volunteers.

Fig. 14. Jedi spherical head receiver coil. These were made in 8-10 sizes to closely fit both adults and children.

When the showdown came Bill Edelstein only showed normal images and presented a lot of theory. When asked at the end of his talk why his 1.5T images were no better than the 0.15T ones shown by Ian Young in the morning session, he regarded this as a fatuous question that did not need a serious answer. We found that we now had friends from clinical groups and companies who, like us, were worried that they were going to be quickly put out of business by GE's 1.5T systems.

The first showdown had generated quite a lot of excitement. A second one was scheduled a year later in a single session with David Hoult (Oxford, St Catherine's, Merton), Ian Young, Bill Edelstein and Leon Kaufman at the SMRM meeting in New York on 15 August 1984 and was expected to be the highlight of the meeting.

This time we had: (i) the contrast agent Gadolinium-DTPA (Gd-DTPA) which worked particularly well with IR images which GE still did not have (the US would not obtain FDA approval for Gd-DTPA until 1988); (ii) more coils, including cervical spine (Fig. 15) and body coils (Fig. 16) made by Walter Curati and others with notable images; and (iii) artefact free body images (artefacts were a greater problem at high field) including 384x256 matrix pelvic images obtained using a dedicated coil.

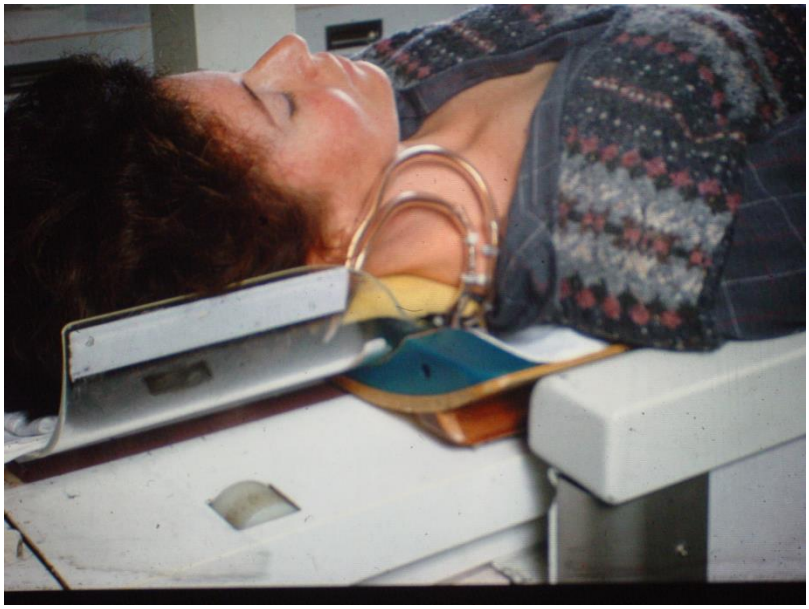


Fig. 15. Patricia Hamilton showing a cervical spine receiver coil. These provided high SNR images of the cervical and upper thoracic spinal cord and column.

Fig. 16. Jedi, planar loop, butterfly, body saddle, and limb saddle receiver coils of different sizes.

After Bill Edelstein's presentation at the New York meeting, he was asked essentially the same question that he had been asked the previous year i.e. why aren't your images any better than Ian

Young's? He replied that he thought Ian Young was being economical with the truth, and that the time taken to acquire his images was much longer than Ian had said. In response Ian drew himself up to his full height (6' 4" at the time), and demanded satisfaction – something that might easily be misunderstood. They were both overshadowed by a heated shouting match later in the session between Leon Kaufman and Paul Bottomley, with the chairman eventually threatening to have them both evicted by security if they did not desist. It was bread and circuses for the masses, but again we acquired new friends, many of whom I had barely known previously.

The GE 1.5T product was still not available and those who, like Yale University, had sat on the sidelines for two years or longer waiting for it to be produced, had allowed other groups who had bought different manufacturers' machines to start their clinical work and take substantial leads in different areas.

11. Paediatric Brain

We started paediatric brain studies promptly after finishing the 140 adult brain cases in 1982. There were several reasons: (i) The ionising radiation associated with CT was a much bigger issue in children than it was in adults and effectively precluded the use of CT for minor conditions, many research studies, and studies of normal children. Just doing as well, or nearly as well, as CT would therefore be a decisive advantage for MRI in many situations. (ii) The older small bore MRI systems e.g. 30-34 cm were not usable for adult head and body studies but could be used for head and body studies in infants and were therefore competitive. (iii) Likewise, the high field 1.9T small bore systems produced for MRS could be used for paediatric brain and body studies, and (iv) specialist paediatric hospitals, and those with large paediatric departments were likely to be interested. Though there were significant technical difficulties e.g. patient monitoring, life support and the need for small coils, paediatric MR was likely be useful and competitive with other techniques, and we wanted to make our mark (Fig. 17).

Fig. 17. Patricia Hamilton and our three children Megan, Mark and Merrin (central) prior to their MR scans as normal paediatric controls (1982), together with two of their friends (Jenny and Gillian Salvage) (left and right).

On the imaging side: (i) We published the first brain study of 18 cases in September 1982 (60) (Fig. 18) and followed this up with a larger series of 52 cases in November 1983.(61) (ii) Frank Smith published his first paediatric body studies in May 1983 with 28 children.(62,63) (iii) The UCSF group followed with ten cases in February 1984 (64) and 14 cases in April 1984.(65) (iv) Peter Mansfield published on the use of EPI in three paediatric cases in December 1983.(66) (v) A specialised hospital became involved in bone marrow studies in 1984.(67) (vi) Hans Ringertz working at UCSF (later to be Chairman of the Nobel Assembly for Physiology or Medicine in 2003) published ten cases in 1984 (68) and 123 cases in 1985.(69) In the historical section of a review of MRI published by him in 1986 (70), he showed that he was aware of the early British clinical work. Four of his first six references were to our work, and two later references were to Frank Smith's work.

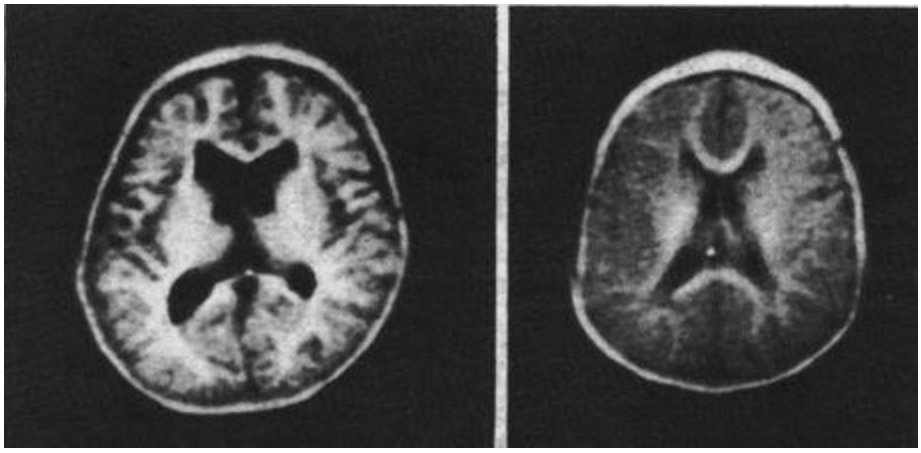


Fig. 18. Normal IR scan (left) at 17 months and delayed myelination (right) showing less obvious white matter at the same age in a child with Down's syndrome.

On the spectroscopy side: (i) Ossie Reynolds used his 1.9T system at University College London (UCL) to do an initial study on birth asphyxia in May 1983 (71) and a later study in August 1984.(72) He found that PCr and ATP were depleted but that there was a delay in this developing which provided an opportunity for intervention. (ii) Britton Chase in Philadelphia published similar results later in November 1984.(73)

Overall it was significant progress. MRI work in the brain was competitive with CT. There was also quality work in the abdomen where ultrasound/CT were the competition. Cardiac MRI was tough because echocardiography was genuinely real time, and congenital paediatric studies would generally require angiography. MRS showed improved in vivo biochemical understanding of disease and supported early intervention in birth asphyxia.

Paediatric hospitals could proceed with MR with confidence, and other hospitals with large paediatric practices now had enough results to make informed decisions about buying systems. We later received support for Frances Cowan to do further paediatric studies courtesy of Sir Rex Richards FRS, (Oxford, St Johns, Warden Merton, Davy Medallist 1976, Royal Medallist 1986) through the Leverhulme Trust.

12. Contrast Agents

Hanns-Joachim Weinmann of Schering in Berlin developed the paramagnetic contrast agent Gd-DTPA for clinical use and took out patents for it and similar agents in 1981.(74) Denis Carr (uniform branch, radiology department, Hammersmith Hospital) established a liaison with Hanns, Peter Neindorf and others in Schering in 1982, and arranged to do patient studies with us. The first study of 12 patients with intracerebral tumours began on 17 December 1983. The paper was published in the Lancet on 3 March 1984.(75) It was the first clinical use of the agent and was an outstanding success (Fig. 19) with the effect of Gd-DTPA greater or equal to that of CT in every case. Roland Felix of Berlin published a similar study with similar results two months later in May 1984.(76) There had been a misunderstanding about the starting dates for the two parallel studies. In addition the company supplied the agent in 20 ml vials and we used any remaining agent for additional half or a quarter dose studies which were usually quite effective. When one ampoule was used others would

appear and this resulted in a surprisingly large clinical experience from the 12 vials of the agent that the company had supplied. The agent proved to be far more effective than anyone could have guessed. Brot und Fische! Diese Fische stinken! Das perfide Albion!

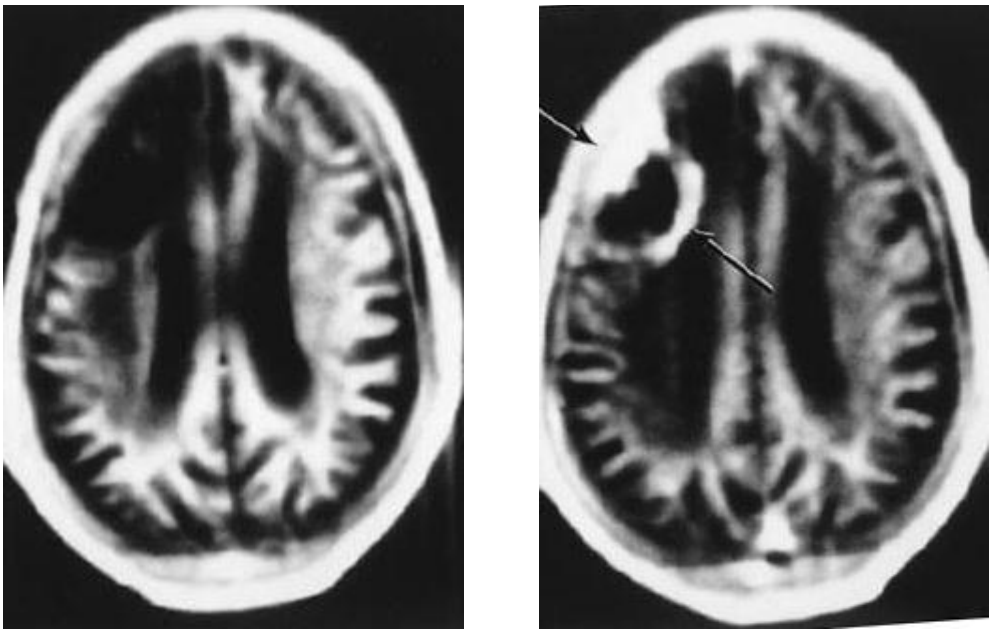


Fig. 19. Frontal metastasis before (left) and after (right) injection of Gd-DTPA, 1984. The lesion shows a ring of increased signal at its margin (arrows) in (b) after enhancement.

The events that occurred during this time would require continued explanation for many years afterwards in forlorn attempts to repair German UK scientific relations.

The new contrast agent changed the clinical scene and was the biggest advance in MRI since T_2 weighted SE sequences, and (for us) Spin-warp in 1982: (i) We could now expect to see meningiomas, gliomas and meningeal disease as well as, or better, than CT, and could now do whole brain examinations using MR alone with confidence (not just MS and the posterior fossa after contrast enhanced CT as we had been doing previously). For the same reasons we could also study the spinal cord with confidence. (ii) It was also a clear cut case for the MSA since the enhancement was only seen with T_1-weighted sequences and not with T_2-weighted sequences which were however generally better than T_1-weighted sequences for detecting abnormalities. Both types of sequences were needed. (iii) The rules for use of Gd-DTPA could be predicted from the parallel with iodinated agents used in CT subject to caveats about the choice of pulse sequence, avoidance of excessive concentrations of Gd-DPTA which shortened T_2 etc. (iv) Application to perfusion as well as body, angiography, cardiac and musculoskeletal imaging would follow. Useful breast MRI only became possible with the advent of Gd-DTPA. However the use of Gd-DTPA made the examination longer and the agent had side effects.

Although it had transformed MRI, the study was not a career-enhancing move for Denis as far as the uniform branch was concerned, and soon after he moved to the Brompton Hospital.

13. Blood Flow and Cardiac Imaging

David Bryant and David Firmin from Donald Longmore's group at the Brompton Hospital used a pulsed gradient SE sequence with phase mapping to determine the velocity and direction of flowing blood following earlier work at the CRL.(77) Donald first arrived at Hammersmith Hospital in his 1962 Bentley Continental S2 four door saloon (the last ever built) with its customised number plates, DBL1, and parked it inside the hospital grounds. To our undisguised amazement, he went back about an hour later and found both the car and its number plates in exactly the same place that he had left them.

Donald's group published studies on the heart (78) before he installed his own machine at the Brompton with help from Gordon Higson.(27) His unit was opened by Margaret Thatcher on 1 March 1985. She said:

"The production of medical images by means of Nuclear Magnetic Resonance was invented in the United States in 1973, but most of the important work on developing it into a practical technique was done at the Universities of Nottingham and Aberdeen and at the Central Research Laboratory of EMI. The first commercially made Magnetic Resonance scanner was introduced at the Hammersmith Hospital in 1981."(79)

We knew there was going to be trouble. Placed within the foyer of the MRC head office at 20 Park Crescent London NW3 there was a statement that MRI had been invented by Peter Mansfield of Nottingham in 1972, and that he had been supported by the MRC. In addition, we found out from the MRC that the EMI effort was of no consequence and should not have been mentioned.

We were next to find out from the MRC that Margaret Thatcher only had a second class mind (she had only obtained a second class honours degree in chemistry at Oxford in 1947), and that Oxford University had been right to refuse her the award of an honorary Doctorate of Laws, a little over a month previously on 29 January 1985. The University had awarded honorary doctorates to each of the previous six Oxford-educated Prime Ministers who had taken office since the end of World War II. It was a disappointment to those of us who had been brought up to respect and admire the Great Institutions of State and Learning within the Queen's realm.

14. The Short Inversion Time Inversion Recovery (STIR) Pulse Sequence and Respiratory Ordered Phase Encoding (ROPE)

Now that we had brain and spine examinations under control, we returned to the body. Frank Smith had remained highly productive and had done competitive studies with Nuclear Medicine, but we were keen to compete with CT.

We adjusted the short inversion time (TI) IR (STIR) sequence to suppress fat signals. It also added contrast for lesions with an increase in ϱm, T_1 and T_2 which is the common pattern seen in disease. As a result, lesions were often shown as very high signal against a muted anatomical background. The fat suppression also reduced motion artefact and the sequence tolerated poor B_0 and B_1 homogeneity as well as eddy current problems. It was easy to implement. The images looked similar to CT with fat low signal, but unlike CT, lesions were highlighted i.e. they appeared white, rather than dark due to lower x-ray attenuation than normal tissues as was the case with CT (Fig. 20).(80) It was another five years before reliable chemical shift based fat suppression techniques became available at higher fields to allow production of this type of appearance.

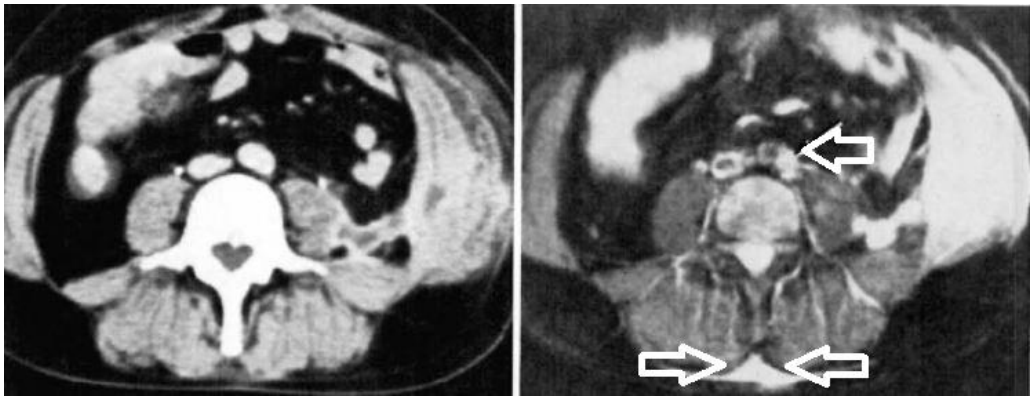


Fig. 20. Psoas abscess. CT (left) and STIR (right) images of the abdomen, 1985. Areas of abnormality (lymph node and fluid) are highlighted on the STIR image (arrows) but are not seen on the CT image.

We coupled the STIR sequence with a T_1-weighted SE or medium TI IR sequence using Respiratory Ordered Phase Encoding (ROPE).(81) This was David Bailes' invention. He re-ordered the phase encoding during a Spin-warp acquisition according to the amplitude of respiration. This process treated the patient's breathing as though he or she had only taken one breath during the examination. It reduced ghost artefacts in the phase encoded direction. The combination of a T_1-weighted sequence with a STIR sequence at the same position in the body was another MSA. It was not only useful in the body, but also in the spine and musculoskeletal system (Fig. 21).

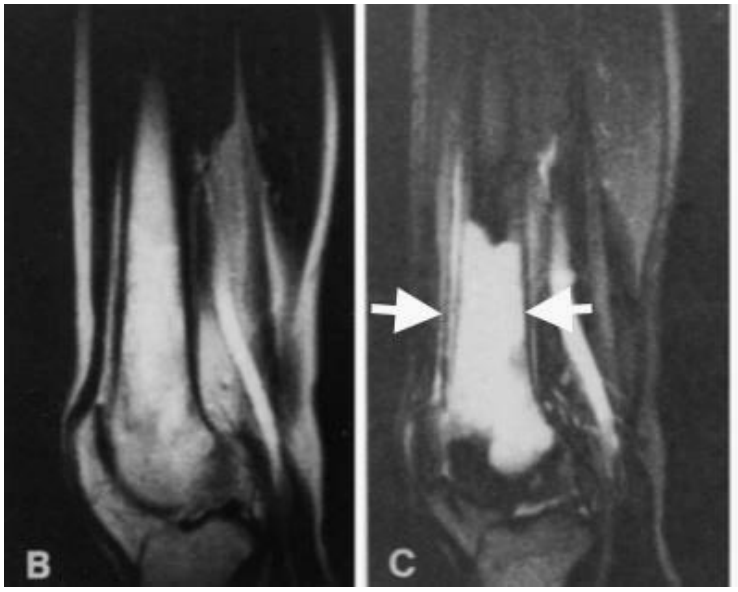


Fig. 21. SE (left, B) and STIR (right, C) sagittal images of lymphoma in the lower end of the femur. The abnormal region is far better seen with the STIR scan (arrows) on the right.

My late night international phone calls, which were usually about machine problems or image interpretation issues, now included enthusiastic calls about STIR images including successes in the head and neck, and the mediastinum which were difficult areas, and ones we had not yet studied with STIR and the MSA.

15. The Fourth SMRM Meeting at the Barbican London, August 19-23, 1985

The London meeting held at the Barbican in 1985 was the fourth SMRM meeting and was held after five years clinical work in MRI and MRS. The local committee chairman was Ian Young, Queen Square had installed an MR machine for the study of MS and a social evening was planned in Queen Square itself. Ten UK imaging groups were represented: Aberdeen (Frank Smith), Edinburgh (Jonathon Best, David Kean), Glasgow (Donald Hadley), Manchester (Ian Isherwood), Nottingham (Peter Mansfield, Brian Worthington), St Barts, London (Judith Webb), Queen Square, London (Ian McDonald, George du Boulay), the Brompton, London (Donald Longmore) and ourselves (Hammersmith Hospital, London).

We had 22 MRI abstracts which was only exceeded by MGH with 24. The new developments which we described included: (i) Contrast agents' applications for meningiomas and gliomas, acoustic neuromas and the spinal cord, (ii) STIR and ROPE. These were both published in July 1985 a month before the meeting. (iii) High resolution neonatal images including periventricular leukomalacia, (iv) flow measurements using slice selection, (v) artefact control in measuring T_1 and T_2, (vi) stereotactic biopsy, (vii) colour display, and (viii) phase cancellation effects between water and fat with the PS sequence.

After the first five years of clinical MRI we had published five of the ten most sited clinical papers in the field with two of the others from UCSF and one each from Case Western Reserve, the Mallinkrodt Institute and the Huntington Institute. The most successful application of MRI was the brain which we had concentrated on, and the signature disease for the technique was imaging of MS which we had first described.

There were now 511 MR scanners installed worldwide, brain and spinal cord MRI were both effective, and body and musculoskeletal imaging had considerably improved. There were also many useful new ideas available for future work. We had hoped that the meeting would showcase the UK work favourably in an international setting, and that this would lead to increased funding for MR across the country.

16. Magnetic Resonance Spectroscopy (MRS)

In 1986 we were invited to the MRC head office to be told their strategic plan for MR. This was to support three groups: (i) MRS at Oxford. (ii) ourselves to do MRS, and (iii) MRI which would be done in Nottingham by Peter Mansfield using EPI. The plan was designed to exploit the success of MRS by spreading it more widely, and not to waste effort on what the MRC regarded as unimportant forms of MRI.

It was a throwback to the thinking from 1980 and early 1981, with the only imaging to be a single sequence approach (SSA) in a unit without an industrial collaboration. There was no understanding of k-space, Spin-warp, pulse sequences, the need for the MSA to achieve different forms of contrast, or the need for contrast agents to make brain and spinal cord MRI competitive with CT. There was little or no evidence that anyone at the MRC had attended the Barbican meeting, or noticed what we had achieved in MRI of the brain and body over the last five years during which time virtually nothing of clinical importance had been achieved with EPI in the UK or elsewhere.

It was not negotiable, and if we did not apply to do MRS the funding would go elsewhere. A condition of doing MRS was not to use the whole body high field (1.6/1.5T) system for imaging. This made little sense because MRI and MRS had been combined in GE systems for three years and imaging techniques were increasingly being used for spectroscopic localisation. However, we received funding on a scale we had never even asked for in our previous imaging applications and were able to triple the number of core staff, and increase the average IQ of the unit by about the same factor. It was an All-Star Group. After tutelage from Brian Ross (Oxford, Trinity) and then David Gadian (Oxford, Merton) and Richard Iles, all the recruited research fellows (David Menon, Carol Peden, Simon Taylor-Robinson, Jimmy Bell) went on to have highly successful careers.

David Bryant implemented 2D and 3D phase encoding and the group pursued 31P, 1H, 19F and 13C studies in the brain, musculoskeletal system and liver with later studies on lipids and their metabolism. The work was fully competitive with other clinical MRS groups and resulted in over 200 papers but, like many achievements in medicine, it was hard won success accomplished over a sustained period, not the near instantaneous biochemical revolution of clinical medicine which the MRC wanted.

17. Further Low Field Development

Since we were not permitted to use our 1.5T system for imaging we had to persist with the old 0.15T system with its tiny computer and obsolete one-off software. Gordon Higson negotiated some additional funding from the MRC for imaging so that we could "finish off" the work he had previously funded. We were again going to be in direct competition with modern 1.5T systems for the next five years with our competitors having state of the art machines, and us trying to squeeze something more out of our old low field prototype.

If we needed any reminder about commercial realities, Technicare, who had the largest installed base of MR systems in the US, was sold to GE. GE discontinued manufacturing Technicare products, provided only limited support for the existing ones and replaced them with GE products whenever possible.

The next high field-low field showdown was scheduled for the SMRM meeting in Montreal on 19-22 August 1986. GE had finally got a 1.5T clinical system operating at the University of Pennsylvania (U Penn) and advertised it as "On track, on time". "The situation is often the opposite of the way it appears in the press" (Immutable Law 20). The radiologists at U Penn published a paper on intracranial haemorrhage using T_1 and T_2-weighted SE sequences. This showed new appearances in haemorrhage and these were related to the MR properties of the iron containing haemoglobin breakdown products that appeared after the initial haemorrhage and evolved with a characteristic time course.(82) It was the most significant advance in the understanding of MR images since the studies with T_1 and T_2 done by us three years previously.

The authors stated unequivocally that two of the imaging patterns seen, namely central and peripheral dark areas, could only be seen at high field. They were attributed to susceptibility effects which increased as the square of the static field strength and were therefore 100 times more evident at 1.5T than at our low field of 0.15T, and so were not going to be seen by us. Even at a field strength of 0.5T there was only one tenth of the effect and the two effects were unlikely to be seen either. They concluded their paper with an aphorism for all time: "Iron is to high field what calcium is to CT". It

was presented as a decisive clinical advantage – later to be called a "Killer App" - which was going to put lower field systems out of business.

We were scheduled to present after Bob Grossman of U Penn in the morning plenary session on the opening day of the conference. He was able to show the diagnostic low signal (black) areas centrally in acute haemorrhage and peripherally in chronic haemorrhage and repeated his scientific arguments proving that the changes could not be seen at low field.

We then followed and were able to show low signal areas centrally and peripherally in haemorrhage in case after case with reckless abandon, apparently quite unaware of his arguments proving that this was impossible (Fig. 22). We had known what was coming, and had used very long TE (up to 240 msec) gradient echo sequences which were far more sensitive to susceptibility effects than the two SE sequences used by Bob Grossman. Using this approach, some of the effects he said could not be seen at low field were actually more obvious at low field than on his high field images. Lower field imaging would survive after all. For a third time, in the high field-low field controversy people I hardly knew greeted me as though I was a long lost friend.

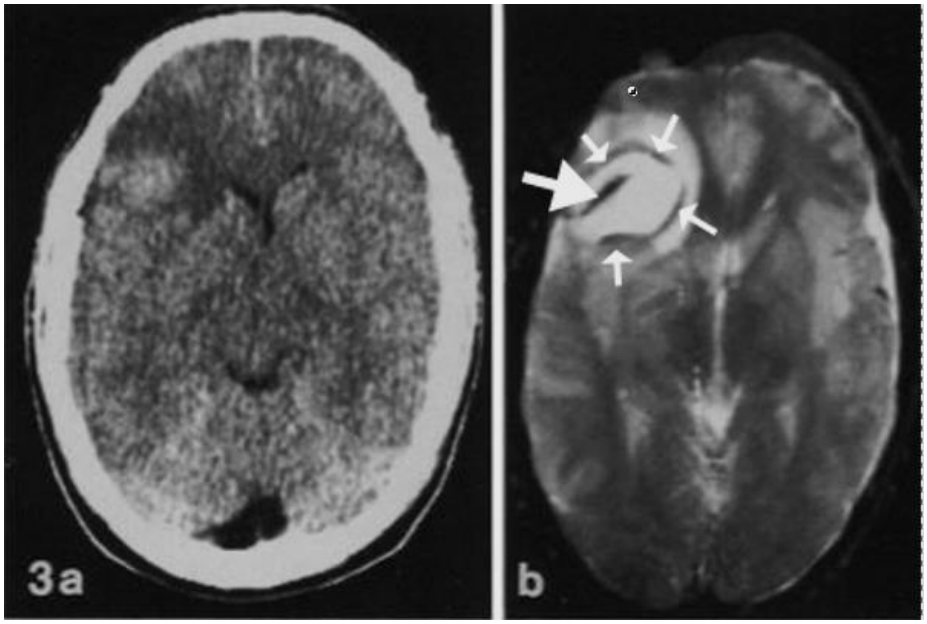


Fig. 22. Upper: CT scan (left) and long TE gradient echo (right) images of a subacute haematoma. The lesion is better seen with the T_2* weighted gradient echo image and has a central low signal (dark) region (large arrow) as well as a peripheral dark rim (small arrows).

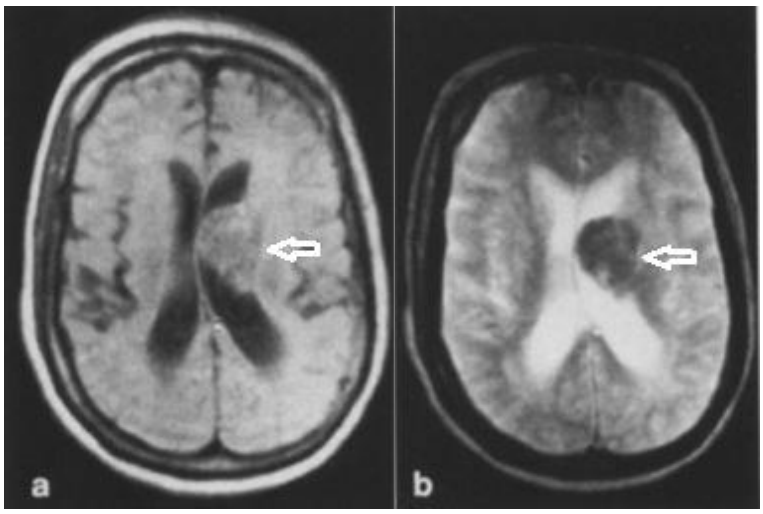


Fig. 22. Lower: SE (left) and long TE gradient echo (right) images of a subacute haematoma. The lesion is intermediate signal on the SE image (arrow) and low signal on the gradient echo image (arrow).

We would continue at low field developing coils, using low bandwidth long data collections to increase SNR, exploiting STIR, and using an insertable gradient set to increase gradient field strength for brain diffusion examinations.(83)

We would be asked frequently whether this was deliberate British government policy to ensure that low cost low field machines would be available for the NHS and the rest of the World. It was Japanese groups and the companies Hitachi and Toshiba which followed up on low field work and produced low cost low field MR systems as a consequence of government imposed low reimbursement for MR examinations. (Asahi had previously lead the way by manufacturing and selling 0.1T versions of the Aberdeen 0.08T system.) Japan would end up with the highest number of MR systems per capita in the world, far exceeding the US and Germany.

18. Susceptibility

We had used phase maps from the pulse gradient SE sequence for flow measurement, but following an abstract written by Paul Margosian in 1984 Ian Young came up with the idea of using phase difference maps from two gradient echo sequences with different TEs (e.g. 33 and 113 msec) to map tissue susceptibility. We studied 22 cases including six hematomas and showed marked changes in susceptibility which frequently exceeded those seen with the magnitude images even at the low field of 0.15T.(84)

It was the first paper on susceptibility mapping as documented by Jeff Duyn (85) and we published another two papers during the next two years before the first paper on the subject from another group appeared.(86,87) Mark Haacke combined the phase and magnitude images, marketed the combination with great success and helped edit a textbook on the subject.(88) Susceptibility effects increase with field strength and are now an established part of the MR examination. Advances in quantitative susceptibility mapping were a major feature of the ISMRM meeting in Hawaii in 2017.

19. Diffusion Weighted Imaging

However, while we were improving our low field system, things elsewhere took a dire turn.

The Royal Society had discovered that the excellence of Margaret Thatcher's undergraduate dissertation describing determination of the structure of Gramicidin S with x-ray crystallography had somehow been overlooked at the time (1947), and had elected her an FRS in 1983.

This had not immediately resulted in a change in her views about how research should be funded - "Marketing effects take place over an extended period of time" (Immutable Law 11) - but when it came to giving her speech to the Royal Society at the Fishmongers' Hall, City of London on 27 September 1988, the hard-headed, fiercely-determined Margaret Thatcher FRS ("the lady is not for turning," "the Iron Lady"), staunch champion of purposeful directed market-driven research, scourge of self-indulgent frivolous curiosity-driven research, backbone of the nation, Churchill and Elizabeth I re-incarnate, publicly recanted. She purred:

"It is astonishing how quickly the benefits of curiosity-driven research sometimes appear",

"… we should be ready to support those teams which demonstrate intellectual flair and leadership driven by intense curiosity and dedication", and

" …. the value of Faraday's work today must be higher than the capitalisation of all the shares on the Stock Exchange".

The Fellows gave her a standing ovation. Thomas Cranmer (Cambridge, Jesus) would have wept.

Jon Agar (Cambridge, Wilkins-Bernal-Medawar Medallist, 2016) said (14):

" …. there was a sharp shift in science policy, one that separated Thatcher's early and late years as Prime Minister. Early on, say 1979 to 1987, there were increasing frustrations with the unresponsiveness of science to markets, and rising anxieties among ministers about maintaining the state of the 'science base' as state funding was cut back. Then there was a crystallization of policy: government funding for near-market research was abruptly curtailed (because private industry should step up) and, to balance this, the science base especially "curiosity-driven" research was heralded."

We had previously done work on diffusion weighted imaging (Fig. 23) and filed a grant application on the topic with the MRC in 1990 to extend and develop it for body work. We were then visited by John Alwen and Tony Peatfield of the MRC who said that under no circumstances could the MRC fund our application. This was a unanimous decision taken at the highest level and could not be challenged. We pointed out that diffusion weighting had worked well in animals as presented at RSNA in 1989 by Michael Moseley and published in 1990 (89,90) and was therefore very likely to work in humans.

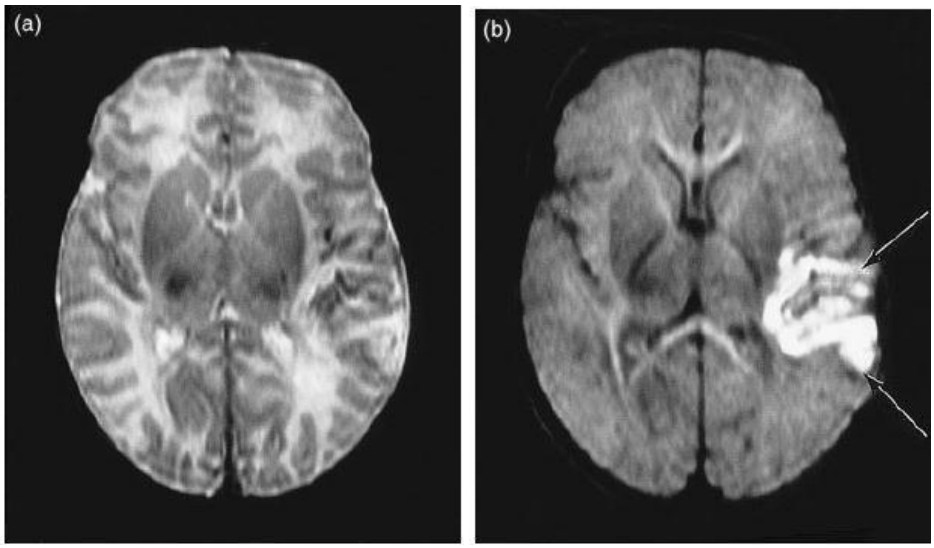


Fig. 23. Neonate with acute infarction (1990). The lesion is barely seen with the SE image (left) but is obvious with the diffusion weighted image (right) (arrows).

This turned out to be the problem, or at least the main one. The MRC could only fund the work if we could guarantee that it would fail. This was because if diffusion weighted imaging was going to work this would make it "near-product" and industry should fund it, not the MRC. (The lesser problem was that if we pursued imaging it might detract effort from the scientifically more important spectroscopy which they were funding.) Iron Young (now FRS, 1989, to be Clifford Paterson Medallist, 1993) politely demurred, and thanked both of them for their very helpful advice.

It was ironic in other ways too. Diffusion weighted imaging was actually a genuine clinical use for EPI, albeit not in pure form, but alloyed with diffusion weighting and STIR to produce a single sequence. When this was combined with T_1-weighted SE imaging as a MSA it would prove to be a very effective way of detecting advanced malignancy in the body. But this would not be pioneered by us. Patients would have to wait another 14 years for it to be implemented and described by Toru Takahara et al from Tokai in 2004.(91)

Donald Longmore proved more adept at dealing with the MRC approach to research than we were. He would write a single author paper saying that EPI in pure form was the best option for the cardiac imaging he needed (92) (for Nobel Prize purposes, although Hans Ringertz might see through it in about 30 seconds), while his physicists concurrently wrote a paper pointing out that EPI was inferior to gradient echo Spin-warp.(93) As a result of this, EPI was not "near-product" and could be supported enthusiastically by the MRC because no company would want to develop it.

20. The Fluid Attenuated Inversion Recovery (FLAIR) Pulse Sequence

In the new order of things Jo Hajnal used an inversion pulse to null CSF signal within the ventricular system and around the brain, and doubled the TE of a SE sequence to give a much more heavily T_2-weighted sequence without confounding effects from high signal CSF. This was the Fluid Attenuated IR (FLAIR) sequence.(94) The work was done on a 1.0T Picker system shared 50/50 with the

uniform branch. In many situations the images dramatically highlighted abnormalities in the brain (Fig. 24).

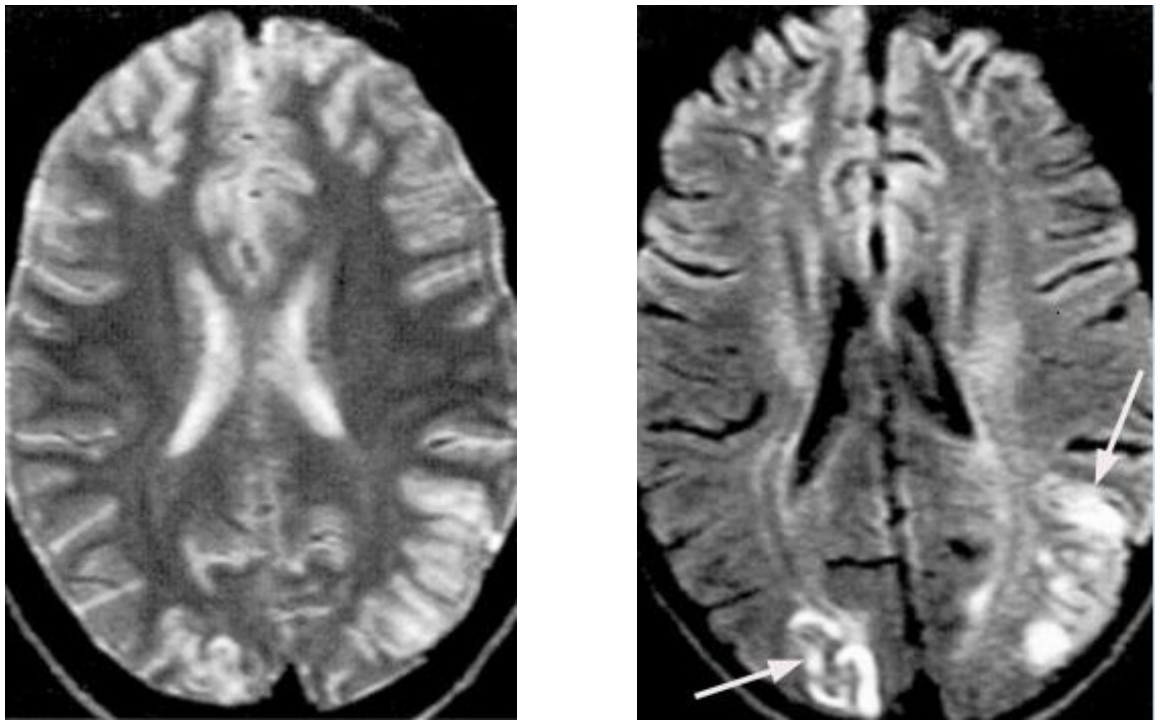


Fig. 24. T_2-weighted SE (left) and FLAIR (right) images in cortical infarction (1992). Areas of abnormality are better seen on FLAIR image (arrows).

Following this: (i) the MRC would not fund it; (ii) the company would not patent it; (iii) three UK journals would not publish it; (iv) the uniform branch refused to let their patients be examined with it; (v) the Queen Square MS group wrote a letter to the Lancet saying it did not work (95) (this was presumably to obtain MRC funding for it on the grounds that there was no prospect of it becoming a commercial product); (vi) Bob Quencer published our paper on it in the US; (vi) the Mayo clinical patented it, and (vii) Bill Bradley in the US replicated our results (Fig. 25). Imperial College later showcased FLAIR in their 2014 Reference Excellence Framework submission as a major success despite blocking the use of it on their patients. The sequence became very widely used. People assume that it was patented by us and that either, or both, Jo Hajnal and I are rich as a consequence.

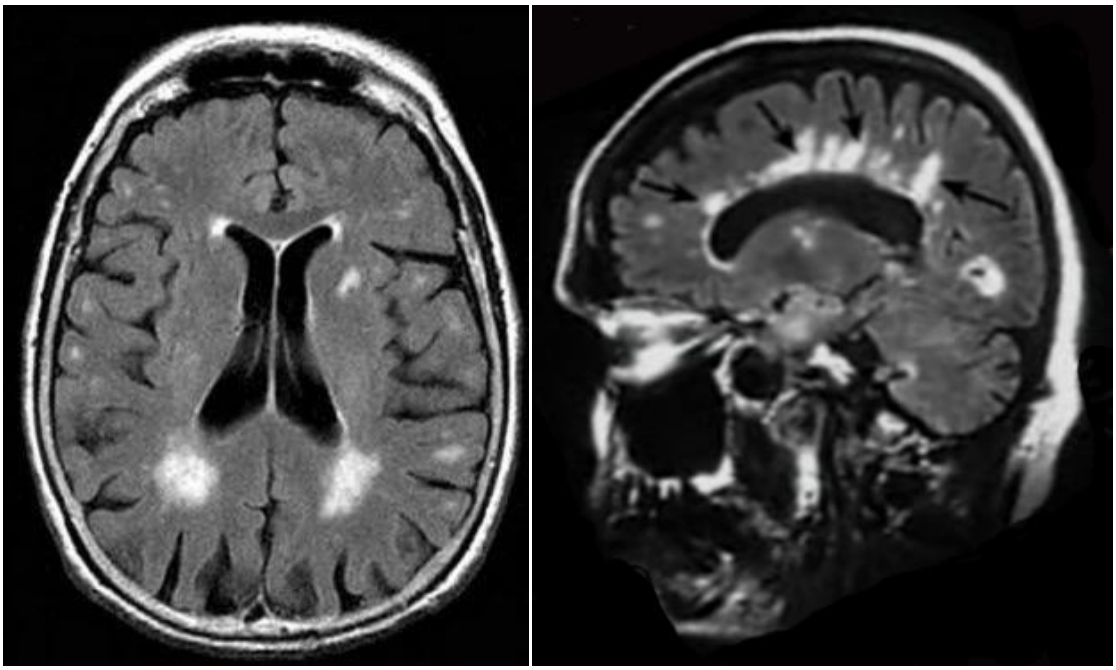


Fig. 25. MS FLAIR images. The plaques are very obvious on the transverse (left) and sagittal (right) (arrows) images.

Henry Marsh, a neurosurgeon who worked at Atkinson Morley's Hospital (the site of installation of the first head CT scanner that James Ambrose had used) and St George's Hospital, wrote two books on his practice of neurosurgery which both became very popular: "Do No Harm" and "Admissions". CT and MRI were essential to his practice, but the only technical term about either technique that he mentioned in the two volumes was "FLAIR". It came up when he was instructing a new trainee who was floundering, on what type of MR images she should look at to reach the correct diagnosis.(96) It was a triumph for the Louis Kreel approach, even if we had succumbed to the "apparent logic of the customer-contractor principle".

21. The Interventional System and Internal Coils

The 0.15T system was finally decommissioned in 1992 and shipped to the Science Museum together with the coils. We received a grant for the interventional work and internal coils from the Wellcome Trust and Picker provided a 0.5T system which became Nandita deSouza's own. She organised image guided laser surgery, and, with David Gilderdale's help, performed examinations with anal, prostate, cervical and vaginal internal coils which provided unique high quality images.

She had an enthusiastic surgical following (Wit Kimiot, colorectal surgeon as well as Pat Soutter and Angus McIndoe, gynaecological surgeons), and wrote a book about it.(97) For 20 years she remained (and continues to remain) the only person in the World able to obtain high resolution images of early stage cancer of the cervix for fertility-sparing surgery.

The MRC fired her for her efforts, preferring to have her system sit idle than for her to use it to advance imaging of the pelvis and women's health. She then put a lot of work into helping the uniform branch set up their own MR scanner for which the new head of the radiology department

(Phil Gishen, uniform branch) was very grateful. She later left for the Institute of Cancer Research (ICR).

22. Registration of Images

Jo Hajnal and Nadeem Saeed also implemented rigid body registration to precisely align repeated 2D and 3D images of the brain so that small changes occurring between the two examinations could be detected on subtraction images.(98) On these images unchanged areas cancelled out, but differences in signal and changes at the boundaries around lesions were highlighted or darkened with T_1-weighted images. On these images when a lesion decreased in size its tissue boundary appeared white, and when it increased in size the border appeared dark.(99) Using this technique differences between two examinations that were difficult for radiologists to interpret using the conventional approach could become very obvious even to people who were not familiar with MRI.

We studied normal changes in the brain in pregnancy directed by Anita Holdcroft, changes in the brain following cardiac surgery directed by David Harris and schizophrenia with Basant Puri. We also studied high grade gliomas and Glioblastoma Multiformes (GBMs) in patients referred by Ed Newlands from Charing Cross Hospital. He had previously had great success in treating hydatidform moles and choriocarcinomas, where he had achieved remarkable patient survival rates (90+%). He now wanted to treat malignant brain tumours with Temozolamide after surgery and/or radiotherapy, and we agreed to follow a series of 120 patients undergoing this treatment until they were cured or died.

We scanned the patients on Monday and Tuesday nights. After the initial treatment most patients would see on the prints of the subtraction images that the tumour had a white border within tissue on T_1-weighted images showing it had decreased in size, and their return journey in an Oak Tree Cab from the Hammersmith Hospital forecourt back to Charing Cross Hospital was usually an optimistic one with high expectations. The front of the hospital had spotlights directed upwards to highlight its architecture. This was to compete with the adjacent gatehouse of Wormwood Scrubs Prison whose more famous architecture had been featured in innumerable British movies and TV series - "In the long run, every market becomes a two-horse race" (Immutable Law 15). The soaring lighting made the front of the hospital look like a dramatic film set, but failed to provide light at ground level to help with loading patients into cabs.

However, later on when the tumour recurred (as most of them did) its tissue border would be outlined in black on T1-weighted images or it could show a mixed pattern with some parts of the tumour regressing but other parts progressing (Fig. 26).

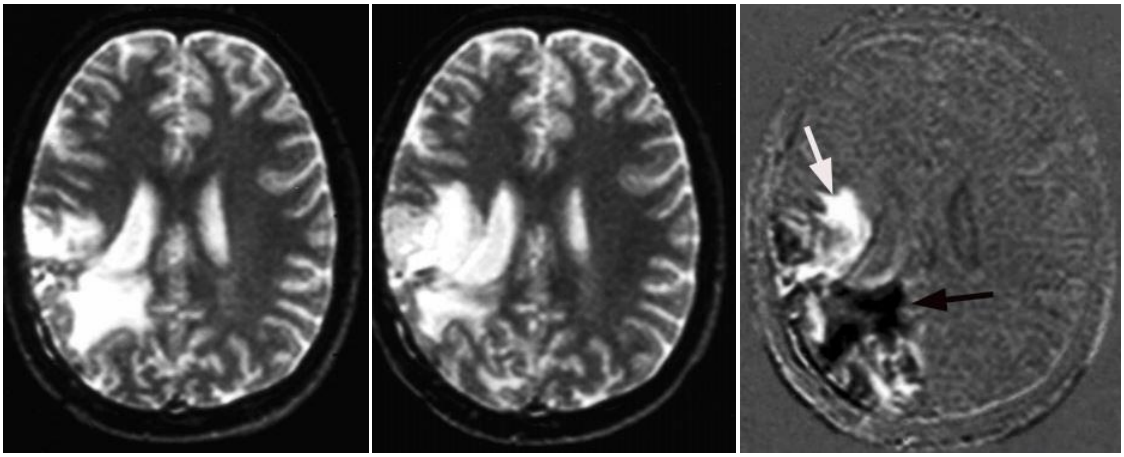


Fig. 26. Registered subtracted SE T_2-weighted images of a cerebral tumour before treatment (left), after treatment (centre) and with registered subtraction 'after treatment minus before treatment' images (right). Parts of the tumour have progressed and appear white on the subtraction image (e.g. white arrow), and parts have regressed and appear dark (e.g. black arrow). The changes are much more obvious on the registered subtraction image than on the original images.

There would be tears, fears and last farewells as the prints came through on the processor in the dark room and, late at night, I would wheel patients out to the Hospital forecourt and, in the dark, gently lift their often limp or partially paralysed bodies into the cramped back seat of an Oak Tree Cab for a last sorrowful trip back to Charing Cross Hospital (Fig. 27).

Fig. 27. Hammersmith Hospital (1996). The forecourt from where patients were taken back to Charing Cross Hospital is behind the OUT sign and in front of the entrance to the Hospital.

Temozolamide improved patients' quality of life but did not improve their survival.(100) Ed Newlands took early retirement at age 64 to fulfill his life-long desire to travel, but died about one month afterwards from a coronary.

23. The Neonatal System

Ian Young and Alasdair Hall organised the construction of a dedicated 1.0T neonatal MR system and installed it in the Neonatal Intensive Care Unit (NICU) on the Fourth floor of D Block in 1995. It was the first such machine in the World.

The machine made it possible to examine very premature and very sick infants. Previously this was not possible because the infants were too sick to be taken outside the NICU. Neonates as young as 25 weeks of gestational age (GA) were examined (Fig. 28). The germinal matrix could be seen as well as the relatively unfolded cerebral cortex. Repeat examinations (up to eight before 40 weeks GA) could be performed and intracranial infection was diagnosable with Gd-DTPA.

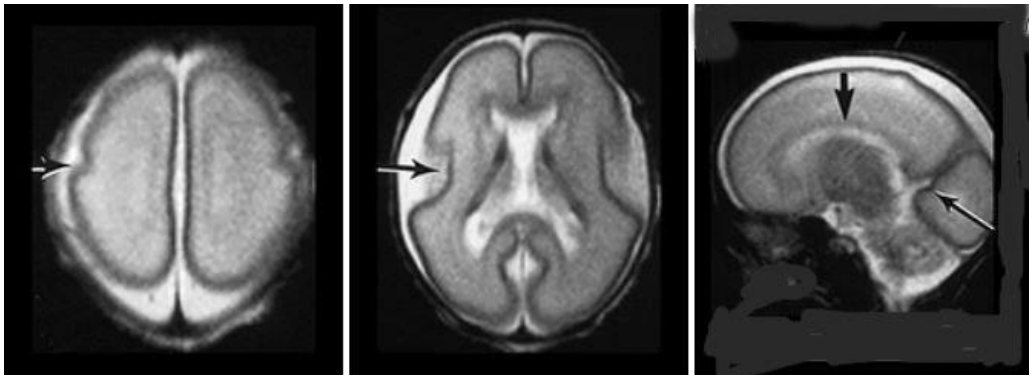


Fig. 28. Neonatal brain at 25 weeks gestational age, T_2 weighted SE images. The brain shows only a few fissures (black and white arrows) and the corpus callosum is dark (dark arrow).

The installation was chosen as the site to celebrate the 50th anniversary of the beginning of the NHS on 5 July 1948. Although the Department of Health had contributed nothing towards it (Gordon Higson had gone by this time), it was officially opened by Frank Dobson Secretary of State for Health under the new Prime Minister, Tony Blair (Oxford, St John's).

I took the opportunity to complain to Frank about the shortage of NHS staff and, at his invitation to document this, followed up my complaint with examples of unreported films, unscheduled examinations etc which had lead to adverse clinical events, and supported this with annotated MRI prints in Louis Kreel style. It proved futile and brought on me long lasting opprobrium from both the uniform and plainclothes branches of the radiology department for bringing the hospital into disrepute.

The neonatal unit provided an excellent view of Wormwood Scrubs Prison next door. Originally the prison had been paired with a work-house, the first being for criminals and the second for bankrupts. The work-house was converted into a military hospital during World War I and later became Hammersmith Hospital. The prison achieved its heyday in WWII when most of the prisoners were evacuated and much of the building was occupied by MI5 which had been shifted there after its offices in central London had been bombed. The prison was also bombed. When the staff attempted to extinguish the resulting fires it was found that the fire hoses were full of holes. While this resulted in a picturesque fountain-like effect, very little water reached the site of the fires and important documents were lost. As a consequence, on Churchill's orders some of the staff including Anthony Blunt (Cambridge, Trinity, to be Sir, 1956) were evacuated to Blenheim Palace where Anthony conducted guided tours of the artworks in the Palace, including very informative commentaries that were much appreciated by the staff.(101)

However, of those MI5 staff remaining at the prison, Victor Rothschild, Third Baron Rothschild Bt, GBE, GM, FRS (Cambridge, Trinity) English aristocrat extraordinaire, was probably the best known. He had been a member of the Apostles' debating society at Cambridge University and while there had driven one of the only three Bugatti type 57SC Atlantics that were ever built. He had also scored 36 runs for Northamptonshire in 1929 against Harold Larwood and Bill Voce of Nottinghamshire when he was 18 years old after the county had been precariously placed at five wickets down for 39.

During the war he was awarded a George Medal for defusing explosives hidden in cases of Spanish onions in a ship's hold. He had carried this out using jeweller's pliers and screwdrivers supplied by Cartier. He later obtained a DSc from Cambridge and an FRS for his work on fertilisation in sea urchins.

He was, of course, the author of the Rothschild report which successfully advocated the commissioning of applied research by government departments rather than the Research Councils. He later became the chairman of Edward Heath's "Think Tank" and was subsequently an adviser to both Labour and Conservative governments on security matters.

However, things became awkward for him when in 1979 Anthony Blunt was revealed as the fifth man in the Cambridge spy ring (after Kim Philby, Guy Burgess, Donald MacLean and John Cairncross), and there was enough suspicion that Victor might have been the sixth (or even the tenth) man for Margaret Thatcher to issue a terse statement in 1986 saying, "We have no evidence that he was ever a secret agent".

Malcolm Muggeridge (Cambridge, Selwyn) was to say of Victor: "Somewhere between White's Club and the Ark of the Covenant, between the Old and the New Testament, between the Kremlin and the House of Lords, he had lost his way. This socialist millionaire, this Rabbinical sceptic, this epicurean ascetic, this Wise Man, had followed the wrong star and found his way into the wrong manger – one complete with chef, central heating and a lift."(102)

This was, of course, not much help to us. We had achieved our initial success as a result of market-driven research funded by the Department of Health and this was now completely out of fashion with Margaret Thatcher having recanted, Victor Rothschild now discredited, and Gordon Higson gone from the DHSS.

It got worse. GEC, who had been supporting us, collapsed and sold off Picker to Philips who then stopped support for the Neonatal system. Arnold Weinstock, Baron Weinstock of Bowden, had built up GEC over a lifetime to become one of UK's leading firms but his son Simon who had been the heir apparent died of cancer at the age of 44 years. Arnold handed over management of his company to George Simpson, Baron Simpson of Dunkeld, who rapidly spent Arnold's cash mountain on US mergers and acquisitions, most of which failed, and was then caught out by the bursting of the Tech bubble in 2001. The GEC share price dropped from about £12 to four pence. Arnold, who had been worth about £480M, became worth £2M. To try and obtain some equity, the parent company GEC sold Picker to Philips for £800M in 2001. Philips discontinued all the Picker products and laid off large numbers of staff, many of whom had their pension funds invested in now virtually worthless GEC stock.

24. Ultrashort Echo Time (UTE) Pulse Sequences

By this stage I was excluded from using MR systems at Hammersmith because my work "lacked merit" – it was better to keep the MR machines idle than let me use them. I therefore worked with Peter Gatehouse at the Brompton Hospital (courtesy Donald Longmore, Dudley Pennell and David Firmin) as well as with Matt Robson (Cambridge, Emmanuel and Oxford) at the John Radcliffe Hospital Oxford (courtesy Stefan Neubauer [Oxford, Christ Church]), both of whom had implemented ultrashort TE (UTE) pulse sequences with TEs 100-1000 times shorter than

conventional sequences. As a result, they could detect signals from MR "invisible" tissues such as cortical bone, tendon, ligaments, meniscus, periosteum and the deep layers of articular cartilage. These tissues had always appeared dark with all other sequences and the lack of signal from them meant that their MR properties could not be measured. The technique eliminated the phase encoding step used with Spin-warp and used the old radial (r-theta) reconstruction that we had begun with, but which now performed much better because of the improved static field homogeneity now available on modern magnets.

I recruited patients from Charing Cross Hospital and transported them to the Brompton with the help of Oak Tree Cabs. By performing subtractions and/or inversion and nulling of long T_2 components it was possible to produce images of cortical bone showing it white and the highest signal tissue on the image (Fig. 29). The appearance was iconic for a new era in musculoskeletal MR imaging as cortical bone had always been black previously and now looked white as it did on plain x-rays and with CT (Louis Kreel principles). We did the same thing for other tissues, such as the red and white zones of the meniscus and entheses. We detected evidence of iron in invertebral discs in thalassaemia, and saw increased perfusion in the periosteum after fractures etc.(103,104)

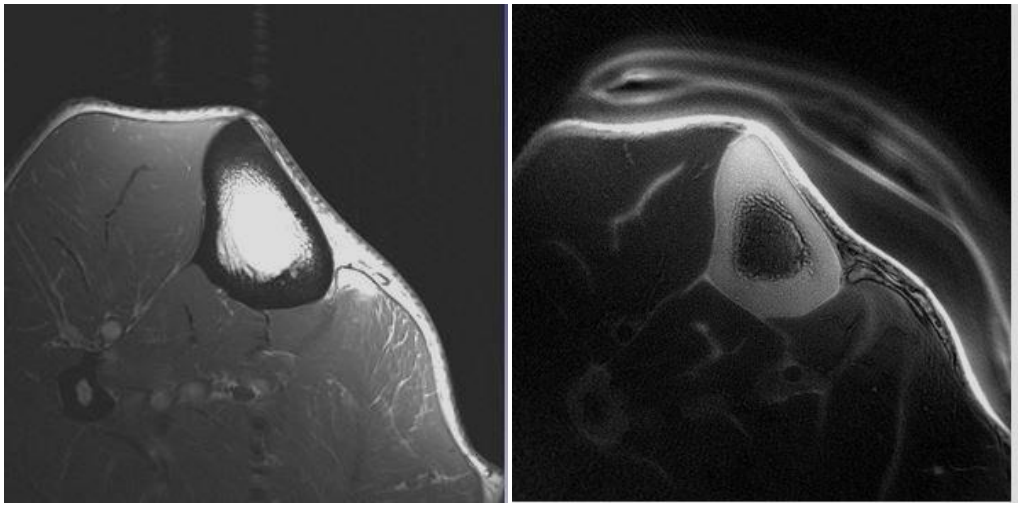


Fig. 29. SE (left) and UTE (right) transverse images of the tibia, 2003. The cortex of bone has a high signal and appears light with the UTE sequence.

To work with Matt I would drive out to Oxford along the M40 to arrive about 3 pm and work through for 10-12 hours finishing between 1 and 3 am the next day. The MR machine was sited next to the now abandoned Sir George Radda FRS MRS laboratory. I would make tentative exploratory visits of it late at night in the dark hoping not to be confronted by ghostly or other forms of Sir Hans Krebs, Anatole Abragam or the Bleaneys.

When we had finished scanning, I would go up four floors to the darkened and deserted Hospital cafeteria to the two snack dispensers from which I would extract chips or chocolate to achieve a sugar high to keep me awake during my drive back to London along the M40. This I did alone, in an old second-hand 1200cc Renault Clio with weak headlights, poor brakes, and ineffectual windscreen

wipers. The journey was often made in driving rain through parts of the M40 which had little or no lighting, and had to be done at the prevailing speed of much larger trucks whose drivers might not notice me and run over me, or force me off the road in a shower of spray from their tyres.

On permanent guard duty near the snack dispensers, to try and ensure that no counterfeit coins were used, or that there were no attempted break-ins, was a bronze bust of Field Marshall Harold Alexander, First Earl Alexander of Tunis, KG, GCB, OM, GCMG, CSI, DSO, MC, CD, PC, PCc. As Supreme Commander Allied Forces in the Mediterranean Theatre, he had accepted the surrender of the German Army in Italy on 29 April 1945. After being Governor General of Canada from 1946 to 1952, he had served as Minister of Defence in Churchill's post-war government from 1952 to 1954. He also played in what some regard as the greatest cricket match ever played, namely Eton vs Harrow at Lords on 8-9th July 1910, "Fowler's match". He was last man in for Harrow but was caught at slip at the end of their second innings with his team ten runs short of their target. Fowler took 8/23 for Eton in this innings. Eight of the 22 players who took the field during this match died during the First World War. Harold had not attended Oxford as a student but was appointed Honorary Colonel of the Oxford University Contingent of the University Officer Training Corps in 1951.

To ease any distress his current position might have been causing him, I would first stroke his brow, and then plead for his intercession (urgent) for any sins I had committed against Oxford that evening, or at any previous time during my life, before setting off on my journey back to London.

By this stage the uniform branch at Hammersmith Hospital was coming apart. At any given time there were about 12,000 unreported films, each of them a potential clinical and medico-legal problem. It was covered up, but the tipping point came when 14 women with breast cancer diagnosed by mammography at other hospitals appeared on ITV, each with the same story, namely that they had had an earlier mammogram at Hammersmith or Charing Cross Hospital, and when these had been requisitioned by staff at their current hospital, the films had shown evidence of cancers that had not been reported.

Scapegoats were needed and these happened to include Peter Dawson (uniform branch) who had repeatedly reported the problem but was suspended, and Walter Curati (uniform branch) a conscientious, hard working radiologist who was also trying to hold the place together. By this time three of the four senior consultants doing MRI had gone (Nandita, Peter and Walter), and I was the last one left, and next in line with a short survival time very likely. I therefore applied for a job at the University of California, San Diego (UCSD) in Bill Bradley's department of radiology.

We next heard from the MRC that the British nominations for the Nobel prize in Physiology or Medicine in 2003 were going to be Sir George Radda FRS (Buchanan Medallist, 1987), Chief Executive of the MRC, and Sir Peter Mansfield FRS (Mullard Medallist, 1990).

25. University of California, San Diego (UCSD)

I joined the radiology department in UCSD in July 2003. Bill Bradley had received a mandate to improve the rating of the department in terms of NIH funding, from the mid 40s to within the top 10, and he set about doing this with enthusiasm and energy. He achieved number eight rating after eight years. He actively recruited in MR, MEG, image processing, molecular imaging and PET and

brought in GE. I began again with two and a half people, linked up with the musculoskeletal (MSK) section (a major strength of the department), and also pursued liver and brain disease.

The announcement of the award of the Nobel prize to Paul Lauterbur and Peter Mansfield for MRI came in October 2003 and there was some comment about Raymond Damadian's whole page advertisement in the New York Times soon afterwards, but the UCSD department was a service orientated one, and there was little interest in this at that time.

UTE was the main new idea in MSK for the next 10 years and we extended applications and improved acquisitions, and presented about 15-20 abstracts per year at each ISMRM, mainly written by Jiang Du and Christine Chung with their teams (Figs. 30, 31). It built on real UCSD clinical strengths as a consequence of Donald Resnick's MSK work. We later edited a book on the clinical use of UTE and related sequences.(105) There was no comparable work in the UK.

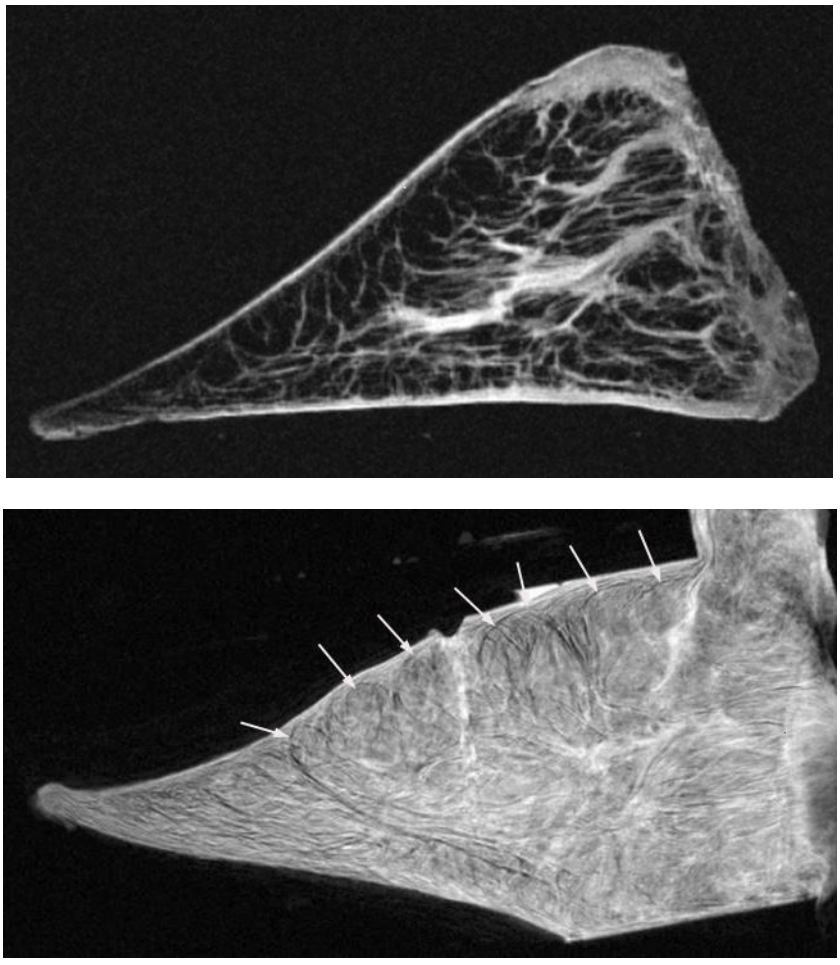


Fig. 30. Coronal views of the meniscus of the knee with SE (upper) and UTE (lower) sequences. Radial fibres are highlighted (upper) and dark arcute fibres are seen with UTE (lower) (arrows).

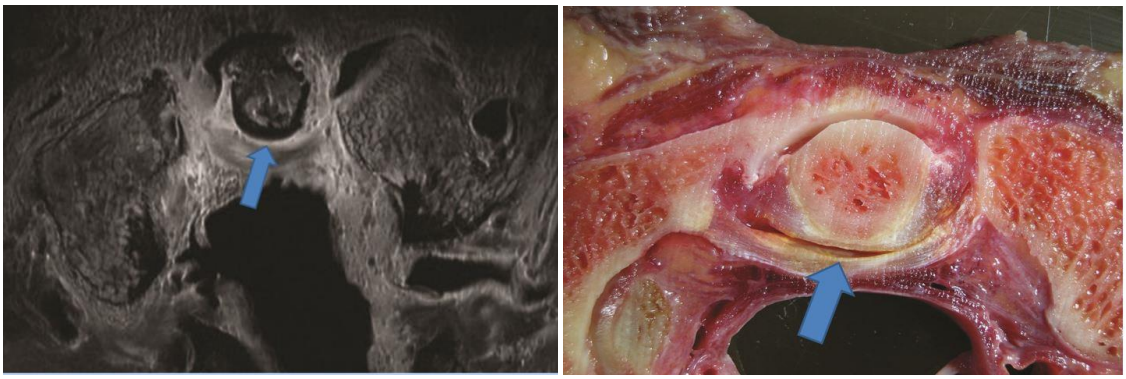


Fig. 31. Transverse Ligament of the Atlas. Enthesis fibrocartilage is seen in the ligament on the UTE image (left) (arrow) and confirmed in the tissue sample (right) (arrow).

Our son Mark worked with Gavin Hamilton and Claude Sirlin to refine and validate liver fat quantitation in order to make it an everyday diagnostic tool. We worked with Bob Mattrey and Roger Tsien ForMemRS (Cambridge, Churchill, Nobel Prize Chemistry 2008). Unfortunately he suffered a cerebral haemorrhage while doing pull-ups as part of his exercise regime. This left him with a right hemiplegia and anomic aphasia. He subsequently designed a tricycle to allow him to become more mobile, but died in an accident when riding this in 2016 at the age of 64 years.

We studied collagen and fibrosis in the liver (Figs. 32, 33), and did extensive MR microscopy of human tissues at 11.7T in conjunction with Nick Szeverenyi.

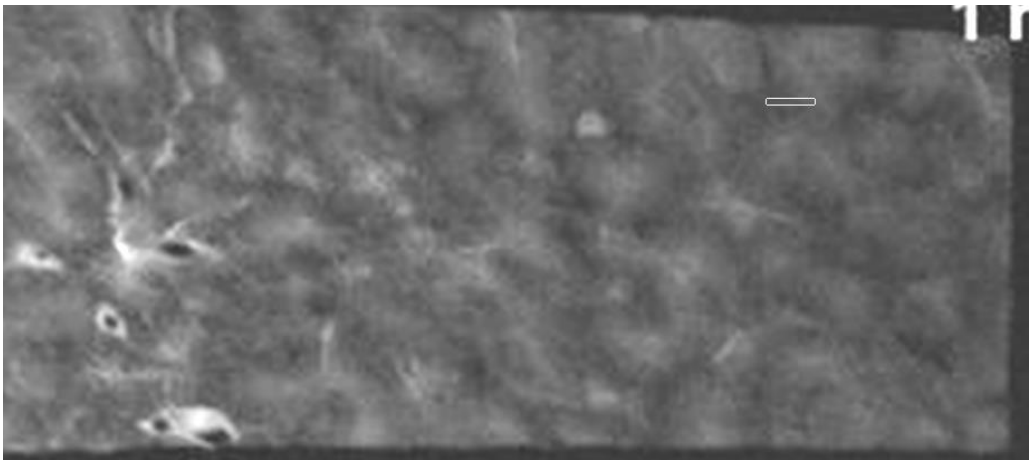


Fig. 32. Normal liver showing lobular architecture.

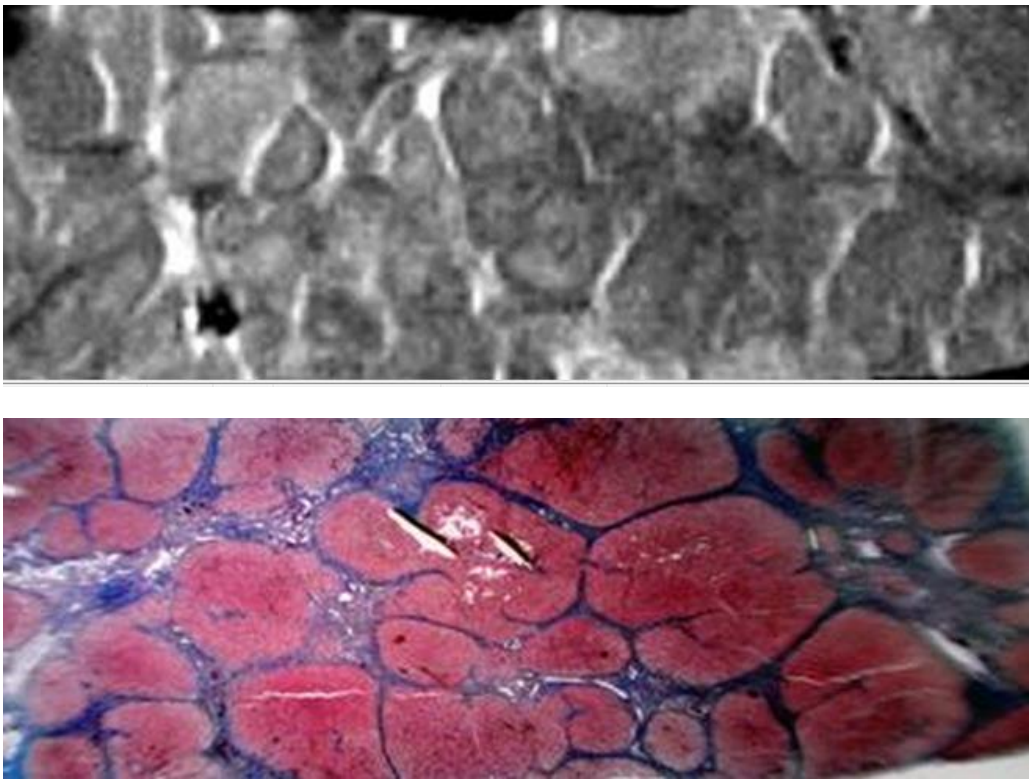


Fig. 33. In cirrhosis the nodules are seen with their vertical fibrotic collagenous margins highlighted using diffusion weighting (upper). Histology shows the centre of the the nodules as red and their fibrotic collagenous margins as blue (lower).

We were able to study tissues such as peripheral nerve at 10,000-40,000 times the clinical spatial resolution and produced new findings which could be applied clinically (Figs. 34, 35).

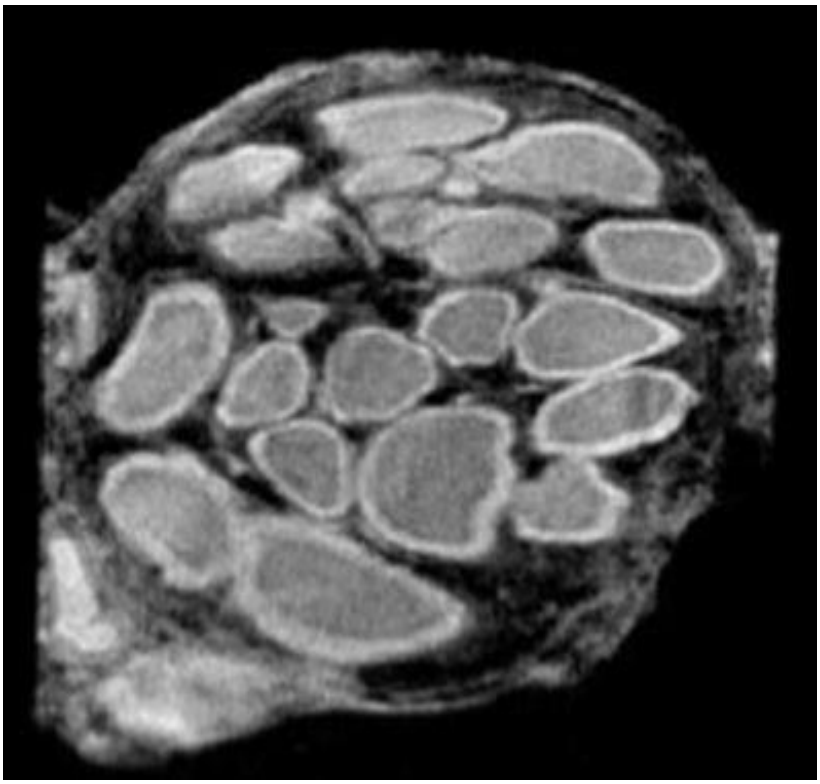


Fig. 34. The median nerve shows fascicules with the perineurium around the fascicules highlighted.

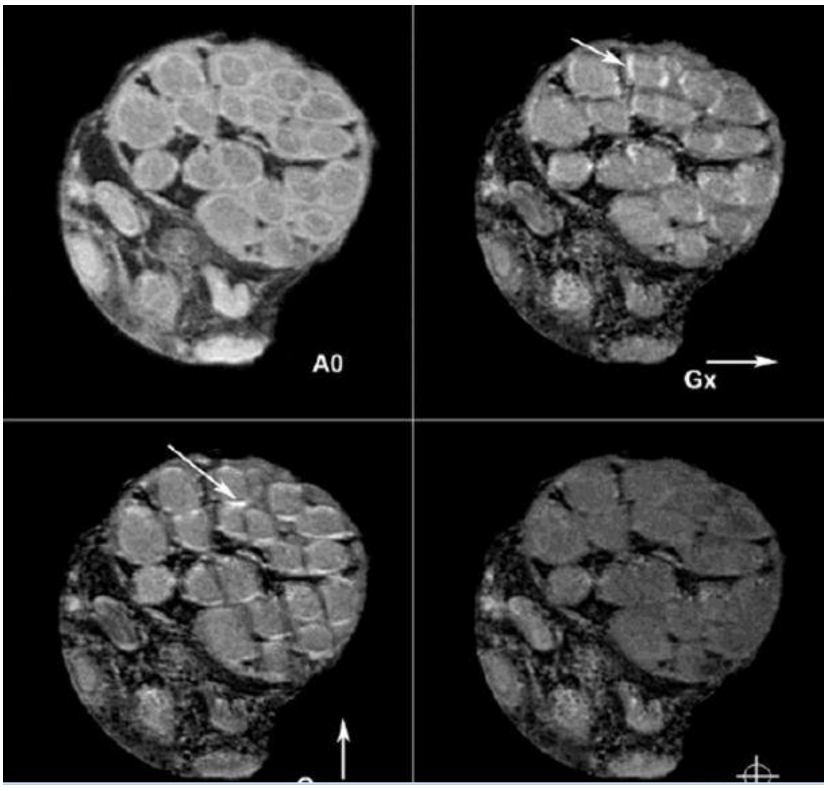


Fig. 35. With diffusion weighting vertical (right upper) and horizontal (lower left) parts of the perineurium are highlighted (arrows) as the direction of the diffusion gradient is changed from horizontal to vertical.

We followed up on an idea of Godfrey Hounsfield's described in his Nobel prize lecture (106) relating image signal intensity to MR tissue properties (Fig. 36).

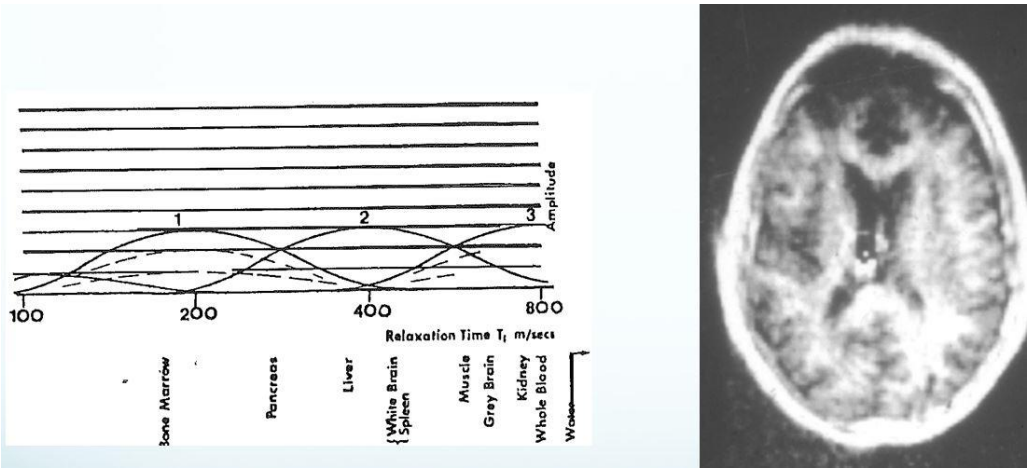


Fig. 36. Fig. 19 (b) from Sir Godfrey Hounsfield's Nobel Prize lecture (8 Dec, 1979) showing his plots of signal vs log T_1 (left) to explain the contrast seen in the IR image of Ian Young's brain obtained with the Walker 0.1T system (right). The image shows high contrast between gray and white matter and Godfrey shows several functions which might relate the signal seen on the image to the log of tissue T_1 values.

Using the Bloch equations we could plot signal against tissue property (or the log of the tissue property) with the first derivative representing the tissue property weighting (Fig. 37).

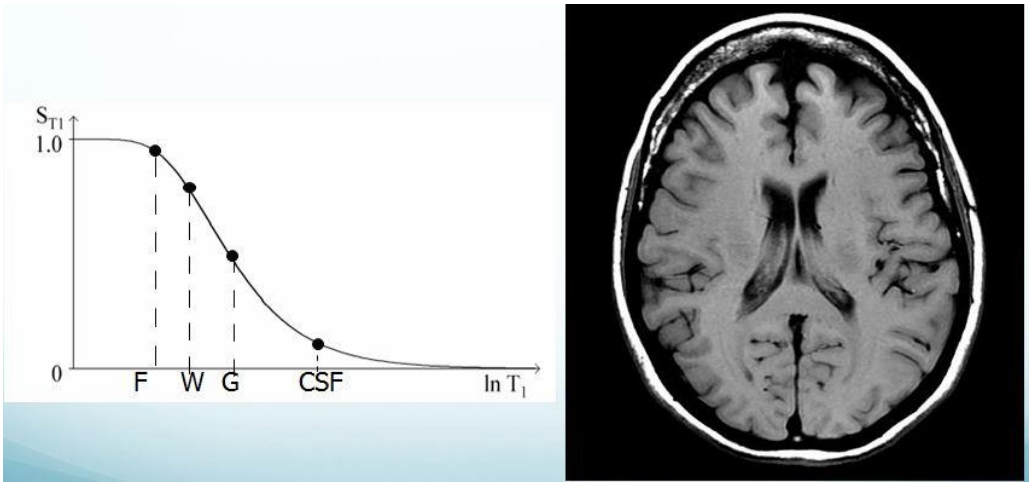


Fig. 37. SE sequence. Plot of signal vs $\ln T_1$ for fat (F), white matter (W), grey matter (G) and CSF from the Bloch equations (left) with their signal levels corresponding to what is seen on the image (right).

This provided a much better understanding of the signal, contrast and weighting of images than the conventional approach, and led to new IR sequences such as STAIR (Subtracted Tissue Attenuated IR) (Fig. 38).

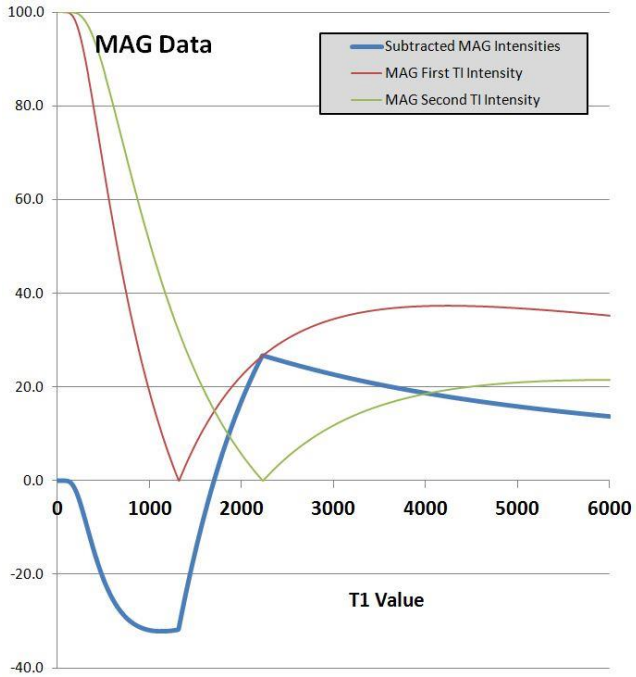


Fig. 38. STAIR (Subtracted Tissue Attenuated IR) sequence. Plot of signal vs T_1 for two IR images with different TIs and subtraction of the longer TI image from the shorter one. On the subtracted curve (blue) there is a rapid increase in signal when the T_1 is increased in the range corresponding to the two null points of the two IR sequences. In this range there is very high sensitivity to changes or differences in tissue T_1.

We could also use DESIRE (Double Echo Sliding IRE) sequence in UTE form to provide a series of radial k-space IR images at different TIs for processing and quantitation (Fig. 39).

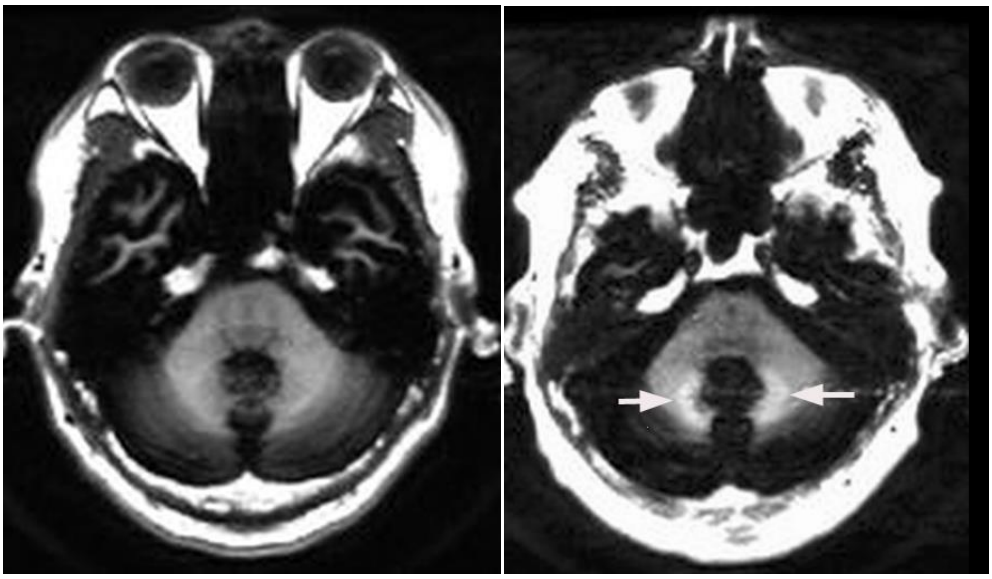


Fig. 39. DESIRE images of the normal dentate nuclei (gray matter) which are low signal (left) and of abnormal high signal in the nuclei (right) due to Gd-DTPA deposition (arrows).

The STAIR sequence showed increases in T_1 in white and gray matter as predicted from Fig. 38 in MS particularly well (Fig. 40). It was one of the group of Multiplied, Added and/or Subtracted (MASIR) pulse sequences.

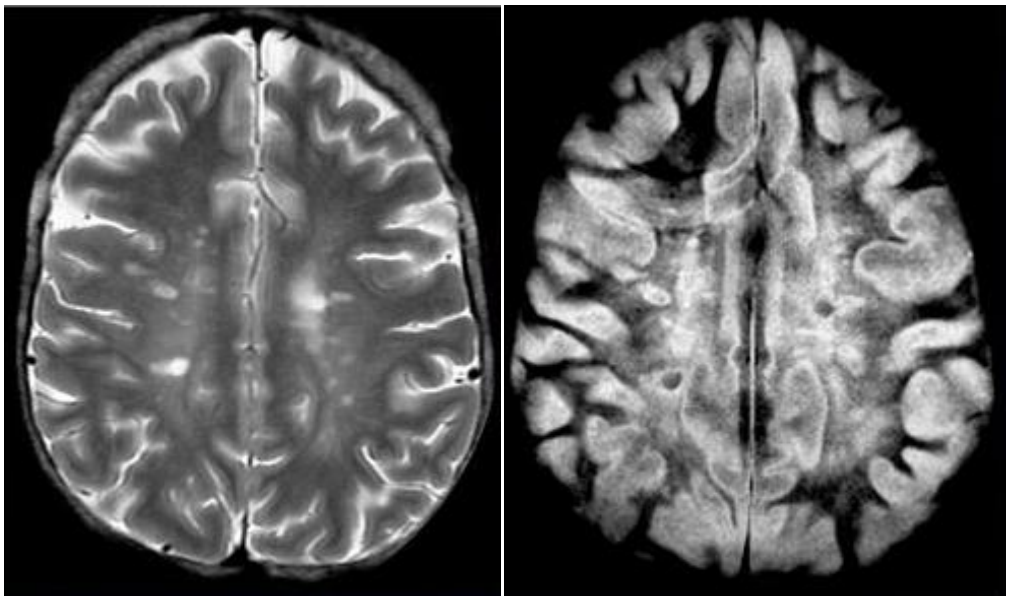


Fig. 40. MS with T2 weighted SE (left) and corresponding STAIR (right) images. Much more obvious change is seen in the central white matter with the STAIR sequence.

After defying the odds since his first heart attack at the age of 38, Bill Bradley died on 20 Nov 2017 aged 69. More than any other radiologist in the US he had helped to make MR a clinical reality. Roz

Dietrich his wife said that there were many many tributes, but there was a remarkable similarity about them – almost everyone said that Bill was their best friend.

26. Epilogue

Of those most involved:

(i) After Louis Kreel left Northwick Park, he worked and taught actively at Queen Mary Hospital for the East End until it closed and was incorporated into Newham District Hospital. He then worked in Hong Kong teaching a new generation of Chinese radiologists. He wrote a second edition of "Outlines" with Anna Thornton.(107) Later he returned to Europe and went to live in Bataille (N of Monflanquin, N of Villeneuve-sur-Lot) in the South of France to paint.(108) Jenny Ellert also became an artist.

An ex-radiographer of his, Stephen Henman organised a commemoration of his work in 2006 (Fig. 41). Louis had edited with Ann Paris the tenth edition of "Clark's Positioning in Radiography" (109) and actively taught Radiography. The event was attended by Janet Husband (to be Dame, 2007) an ex-trainee of his and then President of the RCR. Adrian Thomas talked about the importance of Louis' books and papers in the history of radiology (e.g. Figs. 5 and 6). Adrian Dixon, Professor of radiology (Cambridge, Kings, Peterhouse to be Master, 2008-2016) wondered why Louis's work at NPH had not received more support.

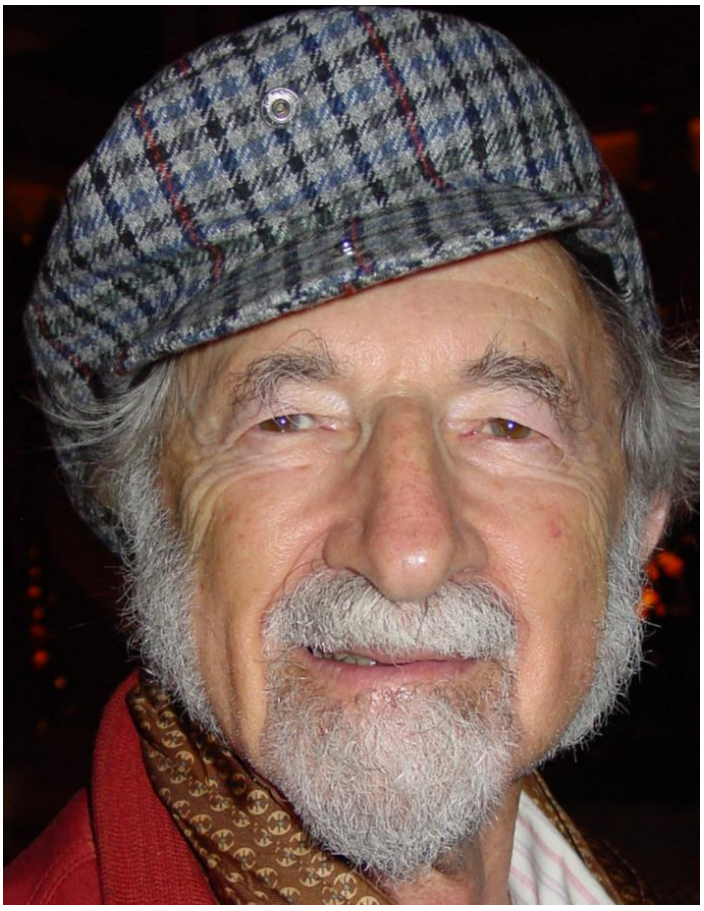


Fig. 41. Louis Kreel in 2006.

(ii) Gordon Higson left the DHSS in 1988 following 19½ years service after his unsuccessful application to head the Supplies Technology Division of the NHS Procurement Directorate which was a newly reconstituted successor to the Scientific and Technical Services Branch. He established his own company which specialised in the national and international regulation of the safety of medical devices. He became an international authority on the subject including the harmonisation of safety requirements between regulatory authorities. He died from a stroke on 2 August 2001. His book "Medical Device Safety: the Regulation of Medical Devices for Public Health and Safety" (110) was published posthumously in 2002.

(iii) Frank Doyle eventually was able to walk unaided but remained severely aphasic. He attended the 1983 SMRM meeting in San Francisco without assistance, but never went to another radiological meeting. His brother Jim and his sister-in-law Jean helped him greatly.

(iv) Frank Smith continued working at Aberdeen Royal Infirmary.(111) He was subject to a name and shame exercise initiated by the Hospital which was eventually terminated with the help of Clive Bartram. He expanded into sports medicine, remained a strong supporter of Raymond Damadian and continued to publish prolifically.

(v) Brian Worthington received a Picker 0.15T resistive system in 1984 courtesy of Gordon Higson but three years had been lost. He remained active in clinical research and helped Peter Mansfield with EPI studies after Peter got a whole body 0.5T system in 1985. In 1986, as a cost-cutting exercise, I shared a room with Brian in a cheap hotel in Montreal during the SMRM meeting that year. Early one morning in the dark I heard rapid and laboured breathing from his adjacent bed and was in a dilemma whether to call 111/999 first, or start CPR on him immediately and then call the emergency services after I had stabilised him. But it then occurred to me that the hotel emergency staff might misunderstand the situation when they arrived ("Yeah, yeah, we've heard that CPR story a hundred times"). On hurrying to his bed and inspecting him closely, I was relieved to find that he was just doing his early morning exercises. It seemed that he might have understood one of Sir Peter's (i.e. Medawar's not Mansfield's) more profound aphorisms better than we had.

Brian was elected FRS in 1998 but had become marginalised within his radiology department and took early retirement at the age of 60 to pursue his longstanding interest in Icelandic language and culture. He suffered a distressing final illness with cancer of both the pancreas and the prostate, and died in 2007.

(vi) Peter Dawson received a large settlement from Imperial College after his suspension which had not followed the statutory procedure. He headed the department of radiology at UCL until his retirement.

(vii) After he left Hammersmith Hospital, Walter Curati became a well liked and respected Clinical Director of the radiology department of Ealing Hospital until his retirement in March 2010. In this role he continued his crusade to reduce the waiting times for unreported x-rays at that hospital. As a Professor (personal chair) at the University of Geneva, he continued to teach and examine radiation biology and protection until Summer 2008.

(viii). Nandita deSouza became Professor of Translational Medicine at the ICR. She continued to provide unique diagnostic examinations. She did a great deal of work using diffusion weighted imaging in cancer involving the abdomen and pelvis. She chaired European Committees on diagnostic imaging and strongly supported women's health issues.

(ix) Dulcie Rodrigues, who was appointed secretary in 1987, remained having served the unit and the MRC with remarkable dedication and panache for over 30 years.

(x) Margaret Thatcher FRS was created a Baroness in 1992. Her coat of arms was designed by Sir Colin Cole KCVO, KCB, FHS (Cambridge, Pembroke, Oxford, Brasenose) the Queen's Garter Principal King of Arms of the College of Arms. He was also known as "Garter" and "King Cole".

In obituaries published in the Daily Telegraph (145) and the Independent (146) the obituarists said:

"Sir Colin was substantial of frame, florid of visage and rough of tongue".

"He liked to escape from the office to spend an afternoon with friends in El Vino's in Fleet Street."

"His strong streak of shrewdness and worldly wisdom was rarely deployed to the benefit of the College."

"Something of a ladies' man, he nevertheless enjoyed a long and successful marriage, his wife Valerie being admirably tolerant of his many outside commitments."

"He was hampered by a lack of rapport with his sovereign. Cole would perhaps have been better suited to the early Hanovarians many of whose tastes he shared."

"At the wedding of the Prince of Wales in 1981 Cole's inability to find the relevant file of precedents drawn up in the reign of Queen Victoria, led to the Officers of Arms not being invited to the wedding."

"When a patent for a Knight of the Garter was belatedly presented to the Queen to sign, it came back with a a note: 'Her Majesty prefers to sign these while the recipient is still alive'."

For Baroness Thatcher Sir Colin designed a lozenge circumscribed by the Garter and the Ribbon of the Order of Merit with dexter supporter a Fleet Admiral of the Royal Navy/Captain Birdseye commemorating the Falklands War in 1982/the Baroness's origins as the daughter of a grocer from Grantham/her recantation of purpose-directed research in the Fishmongers' Hall, London in 1988, as well as sinister, Sir Isaac Newton PRS commemorating her career in science and her election as an FRS in 1983 (Fig. 42).

Fig. 42. Baroness Thatcher's Coat of Arms designed by Sir Colin Cole KCVO KCB FHS. The dexter supporter is an Admiral of the Fleet/Captain Birdseye, and the sinister supporter is Sir Isaac Newton PRS.

Controversies:

1) Magnet type

Resistive magnets which had been used by most physicists before 1980 declined in popularity because of field and stability limitations. The use of cryogenic magnets expanded rapidly. Permanent magnet usage increased slowly.

2) Field strength

Over time 1.5T became a benchmark clinical field strength. 3T expanded and became more generally accepted. Nearly a hundred 7T magnets have been installed and there are a very few (≤5) operating at 9.4T and 10.5T. Toshiba (now Canon) and Hitachi have specialised in lower field permanent magnets with field strengths up to 1.2T. Easote produces small 0.12T systems for dedicated MSK use.

3) MRI vs CT

MRI forged ahead, but CT came back with spiral and multi-detector row systems which produced 3D images of the chest and abdomen in a few seconds. Lower radiation dose, single photon and multispectral imaging CT techniques are being developed.

4) MRI vs MRS

Clinical MRS became accepted as a useful addition to MRI – the equivalent of another pulse sequence providing more specific supplementary information at lower spatial resolution.

Research in spectroscopy continues to be an active field.

5) Single sequence approach (SSA) vs multisequence approach (MSA).

Although the SSA was used initially, MSA in various forms became almost universal. SSA was then seen largely as an MRC construct to promote EPI.

6) The Nobel Prize in Physiology or Medicine in MRI, 2003

This generated more controversy than usual although there were parallels with 1979 and the case of Bill Oldendorf. The loudest protest came from Raymond Damadian (34) with Hans Ringertz later defending the Assembly's decision.(112)

(i) It was incontrovertible that Paul Lauterbur had produced the first widely recognized MR image in 1973.(113) Detailed scrutiny of lab note books, papers, theses and reports going back over 50 years had shown nothing remotely comparable prior to this time.

(ii) The other two principal prize contenders Peter Mansfield and Raymond Damadian followed the First of the 22 Immutable Laws of Marketing, namely: "It is more important to be first than to be better". Both were able to prove that they had invented imaging in 1972 a year before Lauterbur. This was an extreme application of the First Law because, in both cases, the price of being first was to have no image at all. Peter did it with a paper on diffraction in solids published in 1973,(114) seven months after Lauterbur's paper, and Raymond did it with a patent filed in 1972.(115) The end result in both cases was not entirely convincing particularly in comparison to the precisely timed and dated iconic images that had substantiated Röentgen's discovery of x-rays in 1895 and Hounsfield's invention of CT demonstrated in a patient in 1971.

Both of the contenders then invoked the Second Immutable Law, namely that: "If you cannot be first in one category, invent another one that you can be first in". Peter pursued the best pulse sequence category using EPI, but the problem was that Spin-warp was far more clinically effective and far more widely used.

Raymond pursued the first body image category for both normal volunteers and patients,(116) but the problem with that was that there were also claims for the first in vivo image, first mouse, first finger, first wrist, first head, first clinically useful and other categories, and it was not clear which of these firsts was the most important.

Peter then tried another round of the Second Law using gradients for slice selection but David Hoult had spoilt this by pointing out the need for rephasing, and slice selection was not used with 3D imaging (117,118). Also, others had used gradients with the NMR experiment from the early days.(119,120)

For Raymond the next application of the Second Law was showing an increase in relaxation times in disease, but Eric Odeblad had done a lot work on normal and abnormal relaxation times including gingival tissue,(121,122) so Raymond's claim had to be confined to cancer.(123)

It was all a bit inconclusive. While there was no question about who had produced the first recognised image, there was also no question that British groups had contributed a great deal to the success of MRI in the 1970s and early 1980s.(79) The problem was an embarrassment of riches.

It was easy to make a list of ten British (or British based) physicists or engineers who had made major contributions to MRI: John Mallard, Jim Hutchison and Bill Edelstein from Aberdeen; Raymond Andrew, Peter Mansfield, Waldo Hinshaw, Bill Moore and Paul Bottomley from Nottingham; as well as Ian Young from EMI, and Martin Wood from Oxford Instruments. And after this, there were another dozen or more people where they had come from, all of whom had made important contributions, namely: Meg Foster, David Lurie, Tom Redpath, Glyn Johnson, Peter Sharp and Linda Eastwood from Aberdeen; Andrew Maudsley, Allen Garroway, Peter Allen, Roger Ordidge, Ian Pykett, Peter Morris, Bob Turner, Rob Hawkes and Neil Holland from Nottingham; and David Hoult from Oxford. Choosing from amongst all of these was going to be very difficult.

Peter Mansfield (124) had strong institutional support from the MRC and the Royal Society. In accordance with company policy, Ian Young (125) had not published or presented at meetings in the 1970s and so had not shaped the field in its formative years. Also, completely contrary to the First Immutable Law, in pursuit of a "decisive clinical advantage", he seemed to believe that it was more important to be better than to be first.

John Mallard (126) (Wellcome Medallist 1984, Mullard Medallist 1990) was a strong contender, but the most important work in Aberdeen (Spin-warp) was done by Jim Hutchison (Wellcome Medallist 1984, Mullard Medallist 1990) and Bill Edelstein,(127) and they hunted as a pair. To give it to them both, as well as Peter Mansfield, would take the total number to four and the upper limit was three. Not for the first time in Nobel Prize history, the arithmetic did not work out.

Raymond Damadian had damaged his case by changing from focussed NMR to Spin-warp in 1980. He had to do this because he had his own company and needed to be competitive in order to sell machines. Peter Mansfield could stay with EPI alone, funded by MRC, even if it did not work well clinically because he was not having to compete commercially against all other sequences and all other vendors. All may be revealed in 2053.

After the announcement of the Nobel Prize accounts of MR imaging by Kudravchev at the NIH in 1959 (128) and Vladislav Ivanov in St Petersburg in 1960 (129) emerged with Kudravchev's images having been observed by living witnesses.

The bandwaggons have started to roll again, and since clinical MRI has had its turn, I'm backing Sir George Radda FRS for MRS, as well as Seiji Ogawa and Karl Friston FRS (ex-Hammersmith MRC Cyclotron Unit) for fMRI. As with MRI there were many others who had made major contributions such as David Gadian, John Griffiths, Joe Ackerman, Paul Matthews, Peter Styles, Roger Ordidge, Kevin Brindle and Paul Bottomley in MRS, and Peter Jezzard, Andrew Blamire, Bob Turner and Derek Jones in fMRI. If PET has to come first then the nominees would be Michael Phelps (UCLA) for PET, as well as Ronald Nutt and David Townsend (ex-Hammersmith MRC Cylcotron Unit) for

PET-CT. In both scenarios the MRC would be able to draw attention to the high quality of work performed by its scientists in units which it had shut down.

It may take some time and, as the MRC had gone to some lengths to point out in the past, the Nobel Assembly is not infallible. Egas Moniz was nominated 19 times before he was finally awarded the prize for frontal leucotomy in 1949. His 12 nominations for arteriography were all unsuccessful.(112)

7) Contrast Agents

Although the general complication rate of Gadolinium Based Contrast Agents (GBCAs) was lower than that of iodinated agents used in CT, a specific syndrome of Nephogenic Systemic Fibrosis (NSF) developed in patients who had renal failure and did not quickly eliminate GBCAs. In a series of 408 biopsy proven cases reviewed in 2011,(130) out of 248 patients with follow-up data: 55 improved, 63 were stable and death occurred in 71. In three of these cases death was attributed to NSF. Restrictions on the use of GBCAs in patients with renal failure were introduced and new cases are no longer reported.

In 2015 it was observed that Gd-DTPA accumulated in the dentate nuclei and globus pallidus of the brain in patients.(131-133) This was much more obvious with linear than with macrocyclic GBCAs with changes becoming apparent after about five standard doses with linear agents. To date the only associated symptom reported has been a loss of verbal fluency, but caution has been advocated and linear agents have been banned in Europe except for some specific liver agents.

By the time this was reported I had received about 130 doses of linear GBCAs during some 1200 MRI examinations over a 30 year period. This was about 50% higher than the next closest person reported in the literature. That person had received 86 doses and shown evidence of additional Gd deposition in the cerebral cortex which had not been seen previously,(134) but the situation was complicated by his disease (Neurofibromatosis Type 2) and its treatment (multiple surgeries and stereotactic radiation). In my case high signal could be seen in the dentate nuclei using a DESIRE sequence (Fig. 39). Forthcoming complications might be seen as divine retribution for sins committed against Schering and Roland Felix. I did not entirely wish to serve as the canary in the coal mine for others who had received high doses of Gd-DTPA, or be the ultimate Gad Head. However, there were responsibilities associated with possibly, or probably, having the World's highest level of Gd in the brain. There was the closely argued case presented to me that my brain could be of considerably more value to medicine after death than it had ever been during life by providing a timely opportunity to correlate tissue Gd levels with histological changes throughout a supposedly normal brain, should I be properly disposed.

8) Global Health

Two-thirds to three-quarters of the World's population have no access whatever to medical imaging. To address this:

(i) The World Health Organization has promoted the World Health-Imaging System (WHIS) to supply basic radiological facilities, but the cost of about $3 per conventional radiological film is a significant barrier and investigation of digital options is being pursued.

(ii) Relatively inexpensive ultrasound has been developed both independently and in association with iPhones.

(iii) Much cheaper CT and MR imaging systems are likely to require radical inventiveness and present major challenges such as using solar power (135).

Organisations:

1) Thorn-EMI demerged in 1996 into EMI group plc (entertainment) and Thorn plc (electronics and rentals). EMI plc was bought by Terra Firma in 2007, then Citigroup in 2012. The CRL (135) was closed in 2007 but was resurrected in a different form in 2012 as a technology incubator.

2) Picker/GEC

GEC underwent near collapse. The Picker name disappeared after the company was bought by Philips. Many of the staff joined other companies in Cleveland and elsewhere in the US. Chris Randell who had worked with GEC earlier set up his own company (PulseTeq).

3) Oxford Instruments

Oxford Magnetic Technology was partially, and then totally sold to Siemens Healthcare and continued as a major manufacturer of magnets as described by Audrey Wood.(29) Later other firms including Magnex and Tesla followed the Woods' lead and helped establish "Supercon Valley" around Oxford.

4) GE dropped from market leader to become a distant third in MR behind Siemens and Philips. Its shares which were worth $47 dropped to $8 when the global recession began in 2008. The value recovered to about $22 but has decreased over the last year (2017) by 40%, the dividend is being cut and parts of the company are being sold as a major restructuring exercise (2018). "Success often leads to arrogance, and arrogance to failure" – Immaculate Law 18. FONAR marketed upright niche machines but faded out, and sold only two machines in 2016.

5) The MRC Clinical Research Centre (CRC)

The MRC announced the closure of the CRC (its largest clinical facility) in 1985. It was not clear whether the Director (Sir Christopher Booth) was the problem, or not. He was generally obnoxious and poorly informed in our experience, but this was not uncommon within the MRC and he could have easily been replaced by someone similar or different. It was suspected that the main reason for closure was a failure of the clinical staff to understand the hypothetico-inductive process in science and other associated concepts as propounded by Sir Peter Medawar. Sir Peter suffered further strokes and died in 1987. What remained at NPH on the MRC scientific side was transferred to Hammersmith Hospital as part of the MRC Clinical Sciences Centre (CSC), recently re-named the London institute of Medical Sciences (LMS) reflecting a shift away from clinical work. Other CRC staff such as Eve Johnstone and David Owens moved elsewhere and pursued successful careers.(136)

6) Hammersmith Hospital

The MRC closed down virtually all of its MR section. In some ways the most inexplicable thing amongst many was the loss of David Edwards (Oxford, St Peters) who gained double first class honours in English and History, had done excellent clinical work and research in neonatology, and had been head of the Department of Paediatrics, Obstetrics and Gynaecology. He later set up a neonatal MR unit at King's College, London and made it the World leader in this area.

The long established MRC Cyclotron Unit (since 1950) with about 150 employees was also closed down after very successful development of PET imaging.

The MRC later pulled out of a collaboration with Glaxo Smith Kline who established a Clinical Imaging Centre beginning in 2004. The centre was closed down about after about three year's operation. Part of the residue was operated by Imanova which was taken over by Invicro which in turn was taken over by Konica Minolta.

Sir Christopher Booth, whose most famous quote was: "Taking a doctors' pay demand to Margaret Thatcher was not like taking a red rag to a bull, it was like taking a red rag to an old cow", had his wit and wisdom commemorated at Hammersmith Hospital where a ward was named after him.

The site of the NMR Unit at the Hospital became part of the MRC's Mansfield Centre for Innovation. The rebranding was a classic application of the Fourth Immutable Law i.e. "Marketing is about perceptions not products". Ian Young and his team had spent 20 years working at the site developing clinical MRI while Peter Mansfield had never set foot inside the building, let alone done any work there. Peter was notable for persisting with his EPI pulse sequence while Ian Young and others in the MR field actively innovated to develop the sequences necessary to make MRI a clinical success. Also, Ian's team had never been funded by the MRC; their support had come entirely from industry and the Department of Health. The Fourth Law was elaborated on further by Al Ries and Jack Trout in their follow-up book to the "22 Immutable Laws" entitled "Positioning",(137) although it was not positioning as taught by Louis Kreel to generations of radiographers.

The Centre was adjacent to the site of the old work-house stone-breaking shed which had been used by the blood transfusion service. It was said that their initial validation study had been funded by the MRC, but once their work had become near-product, MRC support was stopped.

Gypsies had been part of the Hammersmith scene for many years and they usually occupied the Scrubs at the back of the hospital. The adults had helped us with our research when it was difficult to recruit normal controls by volunteering not only themselves, but their children as well. They were generous in other ways too. When we sought their professional opinions on what the future was likely to hold for us they said that it looked very bad. They also said this was so obvious that it did not require their expertise to foretell it, and therefore it would be unethical to charge for their services - and waived their fees.

The gypsies were usually evicted by a large police contingent through Artillery Lane which ran between the hospital and the prison. Some of the onetime employees of the MRC felt an affinity with them, and afterwards would remember them in the words and music of another Nobel Laureate:

"The jacks and the queens have forsaked the courtyard

Fifty two gypsies now file past the guards

In the space where the deuce and the ace once ran wild."

- assuming that the deuce was T_2 and the ace was T_1 and that Bob Dylan was referring to the MSA in the last line. (Bob Dylan, Nobel Prize Literature 2016, Farewell Angelina, 1965)

It also brought to mind another of Sir Peter's (i.e. Medawar's) quotes:

"The case I shall find evidence for is that when literature arrives, it expels science,"

but, in this instance, Sir Peter was quite wrong, for of the two Nobel Prize winners it was the science laureate who expelled the literature one.

Dulcie Rodrigues, who had been in the unit since 1987 and was the last remaining member of the original group, sent off the bronze bust of Frank Doyle (sculpted by John Laws), which had stood in the unit for many years to the RCR for safe-keeping.

7) The MRC

On a wider front the MRC had the distinction of closing down successful imaging units in each of CT, US, Nuclear Medicine and NMR in London where the modern era of medical imaging had begun. It was the opposite of the future for medical imaging that Louis Kreel had predicted in 1977.

The government infrastructure funding directed by the MRC in 2015 had been focused on a few expensive very high field (7T) MR and MR-PET systems in research units rather than in parallel addressing the needs of the NHS as an expression of Sir Peter Medawar's concept of the unity of science.(8)

8) The Department of Health.

The DHSS, which had widely supported MRI development in the UK (2,27), ended up with:

(i) the number of MR systems per capita installed in the UK (6.1 per million) placing the country 30th out of 31 (ahead of Hungary) in Europe, with less than one fifth of the number of systems that Germany and Italy had.(138,139)

(ii) A per capita number of radiologists 28th out of 31 in Europe, with an estimated shortfall of 1048 consultant radiologists (judged by expenditure in outsourcing) compared with the national total of about 2500 consultants.(140)

Nicola Strickland (Oxford, St Hilda's, uniform branch, Hammersmith Hospital) now President of the RCR, and speaking for the nation, said that the national total of unreported CT and MRI scans had risen to 230,000 and that there was no end in sight for the UK's radiologist staffing crisis.(141) Much of her presidency has been spent addressing this issue.

(iii) The quality of MR examination was also low with a long list of more advanced examinations which staff wanted to do but did not have time or equipment to perform. Hospitals were generally only providing the more basic MR examinations.(138)

These problems might have been addressed with a research programme organised in parallel with that supported by the MRC which had included:

(i) The production of lower field MR systems with 1.5/3.0T performance, but costing half as much as an extension of earlier lower field development. This was unlikely to be done by major manufacturers who had a vested interest in making sure that their more expensive high field products always out-performed their lower field ones.

(ii) On the uniform branch side, further development and ongoing support for AI to make it integrated, efficient, effective, accessible and validated in a wide variety of applications and a genuine help in dealing with the problems created by the shortfall of radiologists, radiographers and other medical imaging staff.

On the plainclothes branch side, a whole range of new applications including integration of clinical MRI, microscopic MRI and digital pathology to improve the effective clinical performance of the technique.

(iii) Funding of research groups embedded in radiology, cardiology, oncology, neurology and other departments specifically targeted on developing and disseminating more advanced MR techniques in the way Gina Brown of the ICR had developed MRI for rectal cancer (142) and Nandita deSouza had developed diffusion weighted imaging of the body.(143) In the absence of targeted initiatives, the UK was likely to end up waiting for other countries to perform the development of more advanced clinical MR techniques and then hoping that those already working to capacity in the NHS would somehow find the time and funding to implement and exploit them for the benefit of patients.

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29. Chronology

1975	EMI NMR group established
1978	23 November EMI head image New Scientist
1981	4 January Cryogenic magnet transferred to Hammersmith
1981	25 March three patients examined
1981	11 July Lancet paper (18)
1981	1-3 October Winston-Salem Meeting (32)
1981	14 November MS paper Lancet (26)
1981	November Posterior fossa and MSA (40)
1982	July SE paper (41)
1982	August 140 cases (47)
1982	September Paediatric brain (60)
1982	28 November-3 December GE 1.5T images
1983	March Posterior fossa (53)
1983	30 July Lancet GE letter (56)
1983	September Posterior fossa tumours (54)
1984	3 March Gd-DTPA paper (74)
1985	July IR paper (80)
1985	July ROPE paper (81)
1985	19-23 August Barbican meeting SMRM Fourth Annual Meeting
1986	19-22 August Montreal meeting SMRM Fifth Annual Meeting
1987	January Susceptibility paper (84)
1990	1.0T system (installed)
1992	November FLAIR paper (94)
1993	0.5T Interventional system (installed)

1995	March Registration paper (98)
1995	Neonatal system (installed)
2003	UTE papers (103,104)
2003-2018	UCSD

30. Gallery

See website.