The Three Worlds of MRI

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Abstract: The development of MRI from its beginnings in 1972 provides many lessons in the mutual benefits obtained when experts in three quite different disciplines learn to communicate with each other. Important technical breakthroughs have occurred every few years. I will describe eight of these, largely based on my own experience, and show how the differing perspectives of basic scientists, industrial engineers and medical professionals such as radiologists have combined fruitfully to enable a transformation in how we humans understand our bodies and brains, in sickness and in health.

1 INTRODUCTION

The development of MRI from its beginnings in 1972 provides many lessons in the mutual benefits obtained when experts in three quite different disciplines learn to communicate with each other. The disciplines concerned are of course physics, in particular the physics of nuclear magnetic resonance and of electro-magnetism; engineering, including radiofrequency and audio-frequency electrical engineering, together with cryoengineering; and radiology.

Each of these disciplines can be regarded as a social and economic arena with its own particular structures of authority, culture, validation and economics. Entrepreneurial innovation can exist in each of these arenas, but because of the essentially scientific nature of MRI, the most penetrating innovation has tended to come from physicists in university laboratories, who generally have the most freedom to explore crazy ideas. Large engineering firms such as General Electric, Siemens and Philips have strict administrative hierarchies which limit unsupervised enquiry by junior staff. However, this is not to discount the usefulness of what have been called ‘skunkworks’, groups of engineers who operate under the radar with the tacit encouragement of their immediate management, pursuing potentially useful ideas which may be far from the priorities of their senior management. In a similar way, while radiology departments are normally under the autocratic authority of the senior radiologist, and junior staff may have very little time available for exploring and validating new techniques, there are outstanding exceptions where entire laboratories based in radiology departments are totally focussed on innovation.

I will not discuss the initial inventions and discoveries on the part of Richard Ernst, Paul Lauterbur and Peter Mansfield that led to MRI as a clinical modality, based entirely within the realm of physics. Since 1980, important technical breakthroughs have occurred every few years. I have picked eight of these as illustrations of the type of interaction between the three disciplines that results in significant changes of practice, largely based on my own experience.

These are as follows:

1) Observation of coronary arteries in adult human heart, in Nottingham in 1986.
2) Dramatic improvements in gradient coil technology, from 1986 to 1990, at Nottingham and elsewhere.
3) Development by Pykett and Rzedzian of a purpose-built whole-body MRI scanner capable of snapshot echo-planar imaging, at Advanced NMR Systems in Massachusetts in 1987
4) Introduction of diffusion-weighted EPI by Turner and Le Bihan as a clinical modality in radiology at NIH, between 1989 and 1992. Turner R, Le Bihan D, Maier J, Vavrek R, Hedges LK, Pekar J. Echo-planar imaging of intravoxel incoherent motion. Radiology. 1990 Nov;177(2):407-14. doi: 10.1148/radiology.177.2.2217777. PMID: 2217777.
5) Implementation of EPI on a clinical Siemens scanner by Schmitt at Erlangen in 1991-2

Turner, R.
The Three Worlds of MRI.
DOI: 10.5220/0012639900003657
Paper published under CC license (CC BY-NC-ND 4.0)
In *Proceedings of the 17th International Joint Conference on Biomedical Engineering Systems and Technologies (BIOSTEC 2024) - Volume 2*, pages 9-15
ISBN: 978-989-758-688-0; ISSN: 2184-4305
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6) Discovery of BOLD contrast fMRI between 1990 and 1992, at Bell Labs, Minneapolis, Boston and NIH
7) Establishment of routine functional MRI scanning for studies of cognition at Functional Imaging Laboratory, Queen's Square, London in 1995
8) Development of NextGen 7T MRI scanner, Berkeley, by Feinberg and colleagues, 2022.

1) Observation of Coronary Arteries Using MPI In Living Human Heart, 1986.

The demonstration of coronary vessels in 1986 (Stehling 1986) was ground-breaking, showing that magnetic resonance imaging could be performed sufficiently rapidly to obtain snapshots of the human heart with sufficient spatial resolution to reveal proximal portions of coronary vessels. By then over 400 MRI scanners had already been installed in hospitals worldwide, many of them with 1.5 T superconducting magnets, but the imaging sequences which used hundreds of radiofrequency pulses spaced at least 100 milliseconds apart, were too slow to capture the rapidly moving coronary vessels. It was the work of Peter Mansfield and his team of physicists, working in the Physics Department of Nottingham University with an MRI scanner at only 0.1T magnetic field, that showed that echo-planar imaging (EPI), with which an entire 2-D image can be acquired in 30 milliseconds, could freeze the cardiac motion and thus enable viewing of structures clearly identifiable as coronary veins and arteries. This breakthrough was driven by the physicists and engineers of the Nottingham Physics Department, and facilitated by a radiologist, Brian Worthington, at the Queen's Medical Centre in Nottingham. No engineers from the growing MRI manufacturing industry were involved. The electronic hardware was largely home-built, and the MRI sequences and reconstruction code were written by members of Peter Mansfield's team (including the author).

2) Improvements In Gradient Coil Technology, 1986-88

The key to much more efficient MRI sequences, such as EPI, was the development of coils delivering strong magnetic field gradients that were accurately linear and providing fast rise times with few eddy currents. Existing gradient coils in 1985 were primitive in their performance in every one of these respects, and few researchers were making any attempts to improve them. I could see a choice of two basic design improvements: either make the coils much smaller than the magnet bore radius, or shield their fields to prevent their interaction with other conducting surfaces that would impair their performance. In Peter Mansfield's group we explored both possibilities. Even before I joined this group in 1984, his students had devised and built several types of gradient coil, but it was during 1985 that I derived the formal mathematics of cylindrical coil design, the 'target field method' which included the simple shielding equation, allowing the fabrication of coil assemblies--primary and shield--with very low fringe fields and fast rise times (Turner 1993). Barry Chapman (a brilliant post-doc) and I built such coils by hand at first, using patterns printed out from the computer and pasted on to strong GRP tubes, onto which we glued the wire with a glue gun. Later Peter Mansfield persuaded Oxford Magnets (at that time the world's major supplier of MRI hardware) to manufacture a double-screened coil set, to my design, thus establishing the concept of multi-layer gradient coils that has proven to have critical importance in state-of-the-art gradient coils that are currently being built (see below).

During the same period, completely independently, Peter Roemer and Bill Edelstein, engineers working in GE's MRI research lab in Schenectady, had been developing 'fingerprint' design gradient coils which were a major step forward from previous designs. A few months after my derivation, as it turned out, they had themselves discovered the shielding equation. GE went on to incorporate these design principles in manufactured gradient coils, firstly for a preclinical scanner intended for small animal scanning, and then for their 1.5 T Signa clinical MRI scanners. After some arguing about patent priorities, GE conceded and large royalty payments duly arrived at Nottingham University. GE and the other major MRI manufacturers redesigned and rebuilt their scanners over the next few years. The result was a dramatic improvement in gradient coil performance.

For this major development in MRI both teams consisted of physicists, one in a university research lab and the other in an industrial laboratory, in the years before most large multinational companies were closing down their research labs. Such industrial labs would often maintain the ethos of university labs—opportunities for independent research, rewards for innovation, minimal management intervention, etc., but by the 1990s became viewed as unprofitable by senior management. Radiologists at the time were completely unaware that MRI performance could be greatly improved by better engineering physics; they were mostly simply

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delighted by the diagnostic quality of the images provided by the first round of installations.

Completing the MRI hardware transformation was another major improvement in gradient driver technology, led by Siemens, whose engineers (notably Franz Schmitt) designed extremely powerful gradient current amplifiers with water cooling to enable a much higher duty-cycle.

3) Development by Pykett and Rzedzian of a Purpose-Built Whole-Body MRI Scanner Capable of Snapshot Echo-Planar Imaging, at Advanced NMR Systems in Massachusetts in 1987

Another variation on the theme of a breakthrough at the combined hands of scientists, engineers and radiologists came about between 1986 and 1990. Two of Peter Mansfield's former PhD students, the physicists Ian Pykett and Richard Rzedzian, left the UK and set up a venture-capital funded development company, Advanced NMR Systems, Inc (ANMR). This was located in Woburn, Massachusetts, and it was greatly aided by the financial and logistic support of the Radiology Department of Massachusetts General Hospital (MGH), then headed by Thomas J Brady, a man of great vision who could already see the enormous potential of an imaging technique that took only a few tens of milliseconds to acquire an entire image. Remarkably, the company attracted significant investment capital, and they were able to recruit highly competent additional physicists and engineers. By 1987 they had constructed a 2.0T whole-body EPI scanner capable of producing cardiac images of diagnostic quality (Rzedzian 1987; Cohen 2012). The scanner was striking in its novelty, using new concepts in gradient driver and coil technology to generate powerful resonant oscillating gradients, and novel data sampling and analysis strategies. ANMR was soon employed by GE to retrofit a GE Signa 1.5 T scanner installed at the MGH NMR research laboratory in Charlestown, Boston with the special hardware and software required for EPI. This GE/ANMR hybrid scanner was used to obtain the first non-invasive images of human brain function in 1991.

The MGH Radiology Department played a crucial role in the success of this development, giving it institutional backing and international credibility, as well as providing seed funding and backing for NIH grant funding proposals. However, according to Mark Cohen, one of ANMR's recruited physicists, it was the engineering perfectionism of the physicist Rzedzian which drove the project to its ground-breaking fulfilment.

4) Introduction of Diffusion-Weighted EPI by Turner and Le Bihan as a Clinical Modality in Radiology at NIH, between 1989 and 1992

That nuclear magnetic resonance could be used to study the self-diffusion of liquids was recognised by the physicists Stejskal and Tanner in 1965. Using magnetic field gradients applied after spin excitation but before data acquisition enables the tracking of molecular-level Brownian motion, but also sensitizes the signal to bulk movement of the sample. It was not until the implementation of MRI in the 1980s that the idea of spatially mapping the diffusion constant of water in tissue was conceived as a potentially clinical biomarker. This was largely the work of Denis LeBihan, a French MD/PhD radiologist, then working at the Ecole Polytechnique, Palaiseau, France. In 1987 he was recruited to the Diagnostic Radiology Department at the Clinical Center of the National Institutes of Health, Maryland, which is where I met him when I moved there in early 1988.

The diffusion-weighted images LeBihan had been obtaining with the current standard slow technique of spin-warp imaging often suffered from artifact due to involuntary head or body movements, which could completely rule out any diagnostic value. I had already proposed the use of EPI for imaging diffusion at a summer school in Italy in 1986, realizing that its ability to acquire images as a snapshot would avoid these artifacts. At NIH I was busy implementing EPI on all the scanners available. This worked best on a 2.0T GE animal scanner fitted with an actively-shielded gradient coil that had recently been developed by the team at Schenectady mentioned earlier. LeBihan and I were able to produce excellent maps of diffusion in cat brain. The hope I then shared with LeBihan was that brain MR images with diffusion weighting would not only reveal basic water diffusion parameters, but would also provide a means for mapping rates of cortical blood flow and thus brain activity.

It turned out that the scanner's limited sensitivity ruled out this latter possibility, because flowing blood contributes only about 2% of the MRI signal. However, the by-product of this enterprise was the method of diffusion-weighted EPI that has now become standard across the world for clinical diffusion imaging. In 1989, in order to image the human head, I implemented this method on a GE Signa clinical MRI scanner. I designed a local, single-axis head-only gradient coil which I arranged to be constructed by NIH engineers in the Biomedical Engineering and Instrumentation Program. When driven by a conventional Techron power audio amplifier, this coil could generate very strong linear gradients along the z-axis, which could be rapidly switched, sufficient to enable EPI and to provide excellent diffusion-weighting of the signal. The coil was light enough to be portable and could easily be installed in the GE Signa 1.5T scanner housed in the NIH NMR Imaging Center. To adapt the gradient power supply to its new load, only a small control board of electronic components needed to be fitted.

Two GE engineers, Bob Vavrek and Joe Maier, based at GE's MRI factory at Waukesha, Wisconsin, had already been attempting to implement EPI on a GE Signa scanner, and had written some of the sequence software, with the tacit connivance of their line manager. This was a classic instance of a 'skunkworks', far from the official job description of the employees concerned. However, they had had no experience of the practical details required to produce good images, and no access to the gradient coil hardware needed to give sufficiently powerful rapidly switchable gradients. I was introduced to Maier and Vavrek by an MRI scientist called James McFall, who had previously worked for GE. In several visits to Waukesha, I passed on to them my detailed experience from my time with Peter Mansfield in Nottingham and further work at NIH, and we worked together to perfect the imaging sequence code (Turner 1990). Once I had it working at NIH, I took my coil to their lab in Waukesha.

It is an interesting reflection that despite the rapid success of this unofficial project in implementing EPI, GE's senior MRI management decided that the company would instead focus its efforts on obtaining the EPI technology developed by ANMR, which was held by its management as a zealously guarded secret. GE progressively bought a larger and larger share of ANMR and undertook the responsibility of marketing the GE/ANMR hybrid scanner, hoping that eventually ANMR would reveal everything. Meanwhile GE's gradient technology continued to improve, and by 1994 their sequence development engineers were able to implement EPI in a more conventional way on their standard Signa 1.5T scanner. This implementation had serious limitations, however.

Meanwhile, diffusion-weighted EPI (DWI) was being adopted in several other labs around the USA. Michael Moseley, working at the University of California at San Francisco, found that rat brain ischemia showed up strikingly in such images. This led to DWI's rapid clinical uptake worldwide as a means of stroke diagnosis and evaluation. Moseley also found, working with celery stalks and then with rat brain, that DWI could be used to detect very clearly the alignment of fibres in tissues, such as in the white matter of the brain. This discovery has primed an immense field of enquiry directed at exploring the human brain's connectome, the pattern of connections across the brain that underpins cognition and thought.

So it was that the combined efforts of physicists, radiologists and engineers broke open entirely new areas of diagnostic medicine and the scientific understanding of how the brain's circuitry is connected. Without the recognized status of Le Bihan in the field of radiology, evidenced by his invitation as a speaker at the 1989 annual meeting of the Radiological Society of North America, it is entirely possible that measurement of water diffusion would not have caught on as a clinical methodology in that conservative and sometimes complacent discipline. And without that clinical uptake it is hard to see how DWI could have come to play such a major role in neuroscience.

5) Implementation of EPI on a Clinical Siemens Scanner by Schmitt at Erlangen in 1987-92

In the early 1980s, engineers at the major multinational companies investing in MRI technology took little note of echo-planar imaging, because the spatial resolution was obviously poorer than desirable and the hardware demands were much greater than the first commercial scanners could provide. However, within one Siemens development laboratory in Erlangen, Germany, the engineer Franz Schmitt and his colleagues realized that this much faster method might have some potential, and they began to implement it in 1987. A group of six engineers led by Franz Schmitt was brought together within the Siemens Medizintechnik basic R&D group, and they considered all aspects of the challenge, from gradient coil development to imaging sequence coding. Encouraged by the early ANMR results shown by Rzedzian and Pykett in 1987, they were able to produce their first images later that year, using a home-built single-axis head gradient coil fabricated in another Siemens workshop (Cohen 2012). Interaction with Peter Mansfield's lab at Nottingham was soon established. Initially the main target was fast cardiac imaging, as it was in Nottingham, but one of Mansfield's PhD students, an MD named Michael Stehling, joined Schmitt's team from 1990 and 1992 and encouraged the use of EPI for neurological investigations.

The striking results of this independent foray into making EPI work on a commercial MRI scanner were a thoroughly well-engineered robust implementation with performance superior to that of the GE counterpart in several respects, and an enduring collaboration with me, which later bore rich fruit.

6) Discovery of BOLD contrast fMRI between 1990 and 1992, at Bell Labs, Minneapolis, Boston and NIH

It was Linus Pauling who recognized in 1936 that deoxygenated blood has a higher magnetic susceptibility than oxygenated blood. However, it was not until 1990 that it became clear that this difference would affect MRI brain image intensity, as shown by Seiji Ogawa and his team of biophysicists working with rats at AT&T Bell Laboratories in Murray Hill, New Jersey. The key to this discovery was the use of an imaging sequence that did not use spin echoes, which largely remove the effect of the magnetic field inhomogeneities caused by the presence of deoxyhaemoglobin. When Ogawa changed the animal's breathing gas the MRI contrast changed. He used the relatively slow multi-pulse technique known as FLASH (Fast Low-Angle Shot) to obtain images clearly showing the cortical veins. He dubbed the phenomenon BOLD, standing for Blood Oxygenation Level Dependent imaging. Having heard Ogawa present his results at the annual meeting of the Society for Magnetic Resonance in Medicine (SMRM) in 1990, I realized that a time course of single-shot EPI images would provide much better temporal resolution of any changes in blood oxygenation, and I quickly performed a series of experiments with cats on the 2T animal scanner at NIH mentioned earlier. The normal breathing gas was changed to pure nitrogen for 60 seconds while a brain EPI image was obtained every 3 seconds. The results were dramatic. The image of the cat brain grey matter darkened by over 20%, and recovered and over-shot as soon as the normal breathing gas was restored. When I showed these results to an MGH researcher, Ken Kwong, at a meeting in Washington in April 1991, and suggested that we could try such an experiment in humans with a breath-hold, he became very interested. He told me that he would try the experiment, using the hybrid GE/ANMR scanner and giving the volunteer subjects periods of visual stimulation. By May 1991 he had the first positive results. In August the MGH Radiology Department head, Tom Brady, presented the preliminary results at that year's SMRM meeting, which caused a sensation. For the first time in history, the activity of the human brain in response to a sensory stimulus could be mapped entirely noninvasively.

The history of this discovery has been described in many publications. At NIH I worked rapidly to obtain the hardware needed to try out this effect at the higher field strength of 4T, using a scanner that had been donated to NIH by GE as surplus to their needs. By February 1992 I was getting good results, with the help of my postdoc Peter Jezzard. Soon I was bombarded by requests from researchers at the National Institute for Mental Health (NIMH) who wanted my help to explore several fundamental questions of localized brain function (Turner 2012).

In this discovery of BOLD contrast and its initial application to imaging of human brain, only physicists were involved. This development took place without the need for advice or assistance from MRI industry engineers or radiologists.

7) Establishment of Routine Functional MRI Scanning for Studies of Cognition at Functional Imaging Laboratory, Queen's Square, London in 1995

Only three years after its discovery, abstracts describing research using BOLD contrast to observe functional activity in human brain started to appear at the annual meeting of the Society for Neuroscience, in 1993. I was a co-author of four of them. At that time, most of the research which explored functional localization and integration in the human brain was performed using positron emission tomography and electroencephalography (EEG). The first of these was invasive, using a radioactive tracer (oxygen-15 water) injected into the bloodstream, and had a poor resolution of about 5 mm. Furthermore, the radiation dose was such that volunteer subjects were permitted to participate only once in their respective lifetimes. EEG is entirely non-invasive, and provides excellent temporal resolution, but the electric fields due to neural activity that can be detected on the scalp have experienced significant attenuation as they pass through the brain tissue and skull, and their sources are difficult to localize without making speculative assumptions.

BOLD fMRI thus comprised a scientific revolution. Human subjects could be scanned again and again, and activity in their brains could be observed with a spatial resolution of one or two millimetres, throughout the entire brain volume. The main limitation arose from the fact that the BOLD functional signal depicted changes in blood oxygenation that were a downstream consequence of neuronal electrical activity, an indirect measure, a much slower counterpart with a time scale of seconds compared with the millisecond timescale of neuronal firing.

My introduction of the techniques of EPI, and thus DWI and BOLD functional MRI, to the world-class brain researchers at NIH and NIMH resulted in several new research programmes and plenty of publications. It also led to the offer of a professorship at the Institute of Neurology in London, to become a co-founder of the first purpose-built laboratory in the world to study human cognition using brain mapping techniques, funded generously by the Wellcome Trust.

This laboratory, known as the Functional Imaging Laboratory (FIL), included a PET scanner and small cyclotron for generating oxygen-15, originally conceived as the mainstay of the planned brain research. The decision had already been made to install a Siemens MRI scanner, based on the advice of an excellent MRI scientist already working in London, David Gadian. But at that time it was still uncertain how useful functional MRI might become, and it was my challenge to establish techniques that were robust and user-friendly. Most of the research team recruited by my lab director colleagues Richard Frackowiak, Ray Dolan, Karl Friston, Chris Frith and Cathy Price were psychologists, psychiatrists and neurologists by training. They had little or no experience of the technology of MRI.

I returned to the UK in late 1993 in order to assist the preparations for the new lab and to establish fMRI data analysis strategies with Karl Friston, the computational neuroscientist. The FIL opened its doors in 1995, with a 2.0T MRI scanner and closed cycle helium liquefier. By 1998 a stream of high-quality research papers was flowing from this laboratory, and by 2000 it was recognized internationally to be the most influential research institution in the growing field of imaging neuroscience. One of the keys to this success was the excellent support which I experienced from Siemens engineers based in Erlangen, Germany. Before the scanner was installed in 1995, I spent several weeks in Erlangen getting to know the development environment and the specific engineers who might be helpful to the FIL's research needs. Of particular importance were Franz Schmitt, a physicist and engineer, and Edgar Mueller, an applications manager, who became personal friends and ensured that our scanner always had the best hardware available. With this excellent partnership support, I and my small team of physicists at the FIL were able to introduce standards of data format, quality, processing availability, and reliability which enabled the lab's cognitive science researchers to explore a wide range of profound questions regarding perception, cognitive control, emotion, memory and consciousness (Turner 1998). Our success prompted a growing number of imaging neuroscience labs around the world to invest in Siemens scanners, thus amply rewarding the company for their special attention to our research needs.

8) Development of NextGen 7T MRI Scanner, Berkeley, by David Feinberg and Colleagues, 2022

For my final example of fruitful interactions between physics, engineering and radiology, I have chosen the recent remarkable combination of skills and expertise leading to the NextGen 7.0T MRI scanner now installed at the University of California at Berkeley.

From its inception in 1995, for the next 20 years, imaging neuroscience using fMRI made only incremental improvements in spatial resolution and quantitative accuracy, largely because the preferred analysis strategies Sused spatial smoothing of the images in the process of aligning and averaging results from sufficiently large cohorts of experimental subjects. Thus more detailed exploration of the patterns of brain activity associated with specific tasks was neither feasible nor desired. It was not until 2010, when Joseph Polimeni and his colleagues at MGH showed that fMRI at 7.0T could begin to resolve brain functional activity at the level of cortical layers (Polimeni 2010), that interest grew in the possibility that fMRI could distinguish between top-down and bottom-up signalling by means of their relative position within the cortical thickness, and thereby add greatly to the causally realistic modelling of brain function. Progress was greatly helped by the use of 7T MRI scanners, introduced by Siemens, GE and Philips in the early 2000s, which provide a much greater signal-to-noise ratio than the usual clinical scanners at 1.5T and 3.0T. In 2011 at the Max-Planck Institute for Human Cognitive and Brain Science, Leipzig, again at 7.0T field strength, Trampel and colleagues (Turner 2016) were able to demonstrate a difference between layers of motor cortex involved in motor ideation compared with actual finger movement.

By 2018 it was clear to a Berkeley physicist and radiologist, David Feinberg, one of the pioneering developers of MRI in the 1980's, that the performance of available 7T MRI scanners had not yet been optimized, and that major improvements in sensitivity could be made by radical redesign of two of the hardware components. These were the gradient coils and the radiofrequency coils. He was successful in obtaining a grant to develop such a novel system of $14M from the National Science Foundation and NIH, and work could begin. The gradient coil development group at Siemens, led by Peter Dietz, enthusiastically took up the challenge of designing and building a far more powerful head-only gradient coil, and Bernhard Gruber, working at the RF coil development lab of the Athinoula A. Martinos Center for Biomedical Imaging, in the Department of

Radiology, Massachusetts General Hospital undertook the building of multi-element RF coils with unprecedented performance. The results of this remarkable collaboration are described in a very recent paper in the journal Nature Methods (Feinberg 2023). A massive improvement in spatial resolution has become available on a scanner which is still relatively easy to operate and has excellent properties in regard to human imaging.

2 SUMMARY AND CONCLUSIONS

I have described a series of breakthrough technological and biophysical developments taking place over a period of 37 years. Each of these has been fundamental to the next one, and to the current state of the art in imaging neuroscience.

A set of take-home messages can be inferred from these examples, as follows:

a) In fields like MRI, the inventiveness of physicists is vital but also greatly needs the amplification factor of radiological interest to make any change to standard equipment and practise. Physicists need to learn to think and speak like radiologists.
b) MRI scientists are strongly encouraged to develop personal links based on shared research interest and mutual respect with engineers in the companies that provide their equipment.
c) Wise management is required when the skills and objectives of all three worlds, physics, radiology and engineering, need to be combined. Interests and rewards need to be carefully balanced.
d) Large companies often benefit by quietly encouraging the independent enterprise of their more ambitious engineers.
e) The limiting factor for scientific discovery should never be the inadequacy of the equipment, but only the creative imagination of the innovator.

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