TODAY'S NEUROSCIENCE, TOMORROW'S HISTORY

A Video Archive Project

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Interview transcript

Nottingham University – imaging research with Peter Mansfield

I went to Nottingham because it was a good university with a good physics department and a lovely campus, and it also had some reputation for having good sports facilities, which I was interested in at the time. So yes, and I had a very good time there.

When I came to my third year, they had this open day, and all the research groups were opening their labs, and of course I went round to see Mansfield's lab and was absolutely fascinated by this crude map of a finger. It was the crudest thing you could imagine, I mean, but just the concept of using physics to get an image from biological tissue was so interesting that … and I couldn't believe that nobody else was interested in doing a PhD with this chap. So I just took it with both hands, and Peter said, 'I'll take you, as long as you get a first.' First class honours, and so that's what I did.

I started in 1977 and the PhD was going to be about high-speed imaging and also T1 mapping at the time, but the high-speed imaging part I found by far the more interesting and obviously, it was using the echo-planar imaging (EPI) sequence that Peter had come up with a year or two earlier. I think it was extremely exciting. I think we all – all my colleagues recognised that they were in on the ground story of a very big event, and I think were … I always remember that we had tea and we had coffee and often lunch together, and we were continually talking about the field, about the … almost inventing sometimes new terminology to understand it, and it was very intense. I always remember, Peter didn't take - Peter Mansfield this is - didn't take many holidays, but when he did you'd always get a phone call in the middle of the week of 'What's going on this week? What are you doing?' So he couldn't keep away from it himself. It was a lovely time.

The Royal Society meeting was really one of the first ones, which generated a huge amount of excitement. And actually, the big story there, I felt, was the work coming out of the Hammersmith group. Because Ian Young - Professor Ian Young - was there, and they generated these marvellous brain images, which they showed at the Royal Society. In the meantime, Bill Moore started producing his excellent images and the subject took off.

Creating the world's first Magnetic Resonance Imaging (MRI) movie, 1982

I mean, EPI produces images in a twentieth of a second - really a snapshot - but those images are very poor in quality and very low resolution, and compared with images that have taken five minutes to generate, they didn't look very good at all. So, one wondered even, if they were produced so quickly, what they would be useful for. The obvious thing was looking at the heart, and so that was where EPI started, as a technique for perhaps looking at the heart, the moving heart.

So I got my PhD in 1981 and then within a few months was asked to give a talk in Winston Salem in America – my first visit to America, and it was an invited talk as well, and they paid for it, even more amazing. But what really excited me was, you know, I had some good data. I had the first real-time images on a rabbit's heart and that was the title of my talk, so I was a little bit amazed that the previous lecturer to me had said that MRI (magnetic resonance imaging) could never generate movie images of the beating heart. And, of course, when I actually got up within minutes and showed the first images, that really amazed everybody, and at the end of the talk, I was besieged on the podium with people congratulating me and slapping me on the back, so it was one of the high, high points of my career, I must say.

What we had done is, in a period of you know a few seconds, we'd actually produced a series of images, which clearly showed the rabbit's heart beating. You know, when other people were taking five minutes to generate an image, it was clearly a step forward.

The process of patenting started in, I would say, 1979, when I was actually a new PhD student because I came into the group and I looked at this method – echo planar, as Peter had described it – and I said, 'I really don't think this method's going to work.' Well, previously - the previous year or two - Ian Pykett had actually generated an image using the technique. So, not surprisingly, Peter Mansfield was rather not inclined to believe that his method didn't work when he had the evidence of this image, but the key point was the image they got was the image of a perfectly symmetric object placed in the centre of the field of view. And my problem with the technique was that it uses an oscillating gradient, and in

periods of negative gradient, you would expect the image to be the mirror image of what it should be. Of course, when the object is perfectly symmetrical, the mirror image is still correct and so that was why the image worked, because the object was symmetrical. And I … the subject of the patent was fixing that problem by generating additional data in a second pass, and you splice together these two sets of data and you did it in a very rapid way. The first set of data was obtained with a 45-degree pulse and then, immediately, the second part of the data was acquired with a 90-degree pulse, and so they had an equal signal intensity and you could put them together to generate an image. So, that was really the modification to make the technique work, and after I convinced Peter that that indeed was the problem with the technique, we had to patent it because, you know, the previous method was not operational.

The MRI Scanner – how it works

In hospitals and clinics today the MRI scanner is common. Thirty years ago it was merely a gleam in the inventor's brain. The patient is slid into the middle of the main magnet, which is just like a giant doughnut. The magnetic field goes right through the centre of it. In the magnet tube there are also radio frequency (RF) coils that deliver the 90-degree pulse to excite the signal and to receive the signal coming back from the body. Usually, outside of the RF coils are the three magnetic grading coils. They impose spatial information along the X, Y and Z-axes. The main magnet itself is a superconducting magnet cooled to about –270 degrees centigrade with liquid helium. It is surrounded by a magnetic shield, which confines the magnetic field so that you can place it in a reasonably sized room without having the magnetic field escaping into the corridors outside and maybe causing danger. Behind the massive and sophisticated scanner, there are fundamental scientific principles to be revealed. Long before imaging, Nobel prizes were won for discoveries about nuclear magnetic resonance.

Nuclear Magnetic Resonance – how it works

It all starts with the spinning hydrogen nucleus. Biological tissues contain water - and hydrogen, of course, is part of that. Because the hydrogen nucleus has a positive charge - being a proton - when it spins it generates a magnetic field, so it has a magnetic dipole moment: a north and south pole. Now, in the scanner, the basic magnetic field – we call it B zero – runs along the Z-axis, the same direction the patient is lying. Consequently, the spins on the tissues' protons are now at a frequency that is precessing like a gyroscope, directly related to the strength of the magnetic field B zero.

I think it's worth showing what precession really looks like using the example of a top. What you're seeing is that the process of precession means that there's a fixed angle that the top maintains with the earth's gravitational field, and the motion is one of precession when it goes round at this fixed angle spinning at its resonant frequency. In the case of magnetic resonance, what's precessing is the magnetic field of the hydrogen in the presence of an externally applied magnetic field - in this case we call it B-zero. The magnetic fields of many of these nuclei - and there are trillions in the body - add together to perform a macroscopic magnetisation which we call Vector M and that is aligned with the field direction. Aligned, in other words, with B-zero.

To excite the signal from these protons, we use the RF coil in the scanner to send in a pulse. Remember that until this happens, M and B-zero are aligned in the same Z-axis in which the patient is lying, but the RF pulse generates a weak oscillating magnetic field - call it B1 - which can only tip M out of alignment if it oscillates at the same frequency as the protons. We call this resonance. In this case, it tips it 90 degrees into the XY plane. Once in the XY plane, the macroscopic magnetisation, M, rotates around the B-zero direction, so it starts rotating in this plane, and this rotation causes an oscillating magnetic field, which is picked up in the receiver coil, which is typically a loop of wire that surrounds the object. After the excitation of the 90-degree pulse, the protons begin to relax and so to realign with the B-zero field in the Z-axis. They manage this relaxation by exchanging their spin energy with the surroundings, what we call the lattice. The exponential curve, shown in this graph, is known as T1 relaxation - a measurement of the time it takes for the protons to get less and less excited and return to equilibrium. At the same time, there's another completely independent process of proton relaxation happening. Instead of giving up their excess energy to the lattice, the protons also relax by exchanging magnetic energy with each other. This exponential decay we measure in the XY plane. The exponential decay rate is characterised by the T2 relaxation time, which is typically of the order of tens of milliseconds, and this also varies between tissues.

So there we have it! T1 and T2 - measurements that can mark the difference between biological tissues, but how do we progress to imaging, magnetic resonance imaging? Now we can explore the process of acquiring an image.

Magnetic Resonance Imaging – how it works: Fourier transform and use of contrast

Crucial to the production of an MR image are the magnetic field gradients from these coils. They generate a magnetic field that varies linearly in space, like this. So over here we have a lower field than over here, and we've already seen that the frequency of the signal is directly

dependant on field strength. Therefore, material over here in a weaker field has a lower frequency of resonance than material over here in a higher magnetic field, and so, using this frequency we can see where the signal has come from.

The signal that we measure is then taken and digitised and we apply a Fourier transform. Now what the Fourier transform does, it does a frequency analysis of this signal, so after the Fourier transform, we have a plot of signal intensity versus frequency, and because frequency is, via the field gradient, the same as spatial position, we now have a profile of the object.

Now, we use contrast in MR images to improve the delineation of different tissue types, and contrast based on the T1 of different tissues, is created by repeating the image of the sequence before the nuclei in tissue with a long relaxation time have had time to fully relax. So in this experiment over here, which is performed with a short repetition time, the cerebro-spinal fluid - referred to as CSF - has not had time to relax between experiments up to its full value, and therefore appears dark in the image because you're only capturing a small amount of its magnetisation each time. Whereas, if you had a long relaxation time, CSF, which has a very long T1 value, has had much more time to recover, and therefore, in the image appears much more bright, and almost the same signal intensity as white and grey matter in this example. So, if you don't use this contrast behaviour, or use it in the wrong way, you won't see where the grey matter is - as simple as that.

Now, how about T2 contrast? Remember, T2 is the relaxation time for protons exchanging their extra magnetic energy, not with the lattice surroundings, but with each other. T2 contrast is introduced by delaying the signal acquisition, following the 90-degree pulse by a time, which we call the echo time TE, to allow T2 relaxation to occur. So we simply apply our pulse, wait a certain amount of time for T2 relaxation, and then we capture our image, and as you can see on the example here, if we wait 50 milliseconds, you can see, via these curves, which show the signal intensity, decaying is a function of time.You can see that at 50 milliseconds, white matter, grey matter and in fact CSF, all appear to be about the same signal intensity. However, if we wait until 100 milliseconds after the 90 degree pulse to acquire the signal, CSF, having a very long T2 relaxation time, clearly appears much more brightly, than grey and white matter.

T2 contrast is by far the most common form of contrast that is used in diagnosis, and I'm showing … showing you here an example of stroke infarctions in the basal ganglia, which are clearly depicted by the T2 weighted imaging. You can clearly see these regions of high signal

intensity because the tissue there has a high T2 value, and we pick that out using T2 weighting.

Magnetic Resonance Imaging – how it works: gradient echoes and K space

Finally, gradient echoes. These are created when we introduce a negative magnetic gradient followed by a positive gradient to displace the signal at a later time and produce an echo. The blocks shown in this diagram represent the application of magnetic field gradients. During the negative block, a negative gradient is applied, which decreases with location along an axis through the object being scanned. This is followed by a positive gradient during the positive block, which produces a field that increases with location along the object axis.

What echo planar does, is it's a recipe, if you like, for covering the whole of K space in a single trajectory, which it does by using an oscillating gradient, which is taking you in this direction, in addition to a constant gradient that progressively takes you through the image in the orthogonal direction, so that at the end of the sequence, you've covered the whole of K space and you've got a complete image, which has taken tens of milliseconds.

In order to really understand how MRI imaging works, you really have to know how K space works. K space is a method of understanding the MR experiment because in order to produce an image, you have to sample all your points in K space at the correct point in time, and gradients are what take you from one point to the other, so a little bit of gradient for a little bit of time, will move you in a direction in K space between points, in the direction in which you are applying that gradient. So, if you apply two gradients, that will move you at 45 degrees, which is a combination of X and Y - and that's what K space is. K space is the recipe that you've got to map out the whole of this two-dimensional K matrix in order to get sufficient signals in order to reconstruct an image.

My contribution to this was to understand that not only do you have to cover K space, but you actually have to cover it in a certain order, and the original echo planar sequence was incorrect in the order in which it covered K space. My contribution was to reverse the order of alternate echoes so that you could generate an undistorted image no matter what the object is.

Into industry - Magnetic Resonance Spectroscopy (1982-86) applied to body metabolism

There's a personal reason why I left Nottingham. My wife became pregnant and I decided I should get a proper job. My daughter, in fact, is 25-years-old today. But there was another

reason, and that is that echo planar is a wonderful technique but it was still producing quite low-resolution images, and I was concerned that that might be the sum, you know, where it had finished, and I really saw the opportunity to contribute to the localisation of spectroscopy, which was all happening in Oxford University and at a small company in Oxfordshire. And so I decided to go to Abingdon and use my imaging principles in order to improve NMR spectroscopy of metabolising the body.

Previously, Professor Radda and others had been using the coil itself to localise the signal, essentially. The coil – they'd used surface coils - they'd put surface coils over the tissue that they were interested in, and they did precious little else really to try to localise the signal. There was a technique called Topical Magnetic Resonance, which is profiling the magnetic field - trying to localise the signal a bit more accurately - but I always had the feeling that magnetic field gradients could be used much more effectively to define the area that you're interested in, and in fact, to move it around the body without having to move any of the coils or anything. So, I really saw there were some imaging principles that were going to have a major impact, and in fact, ISIS was one of the techniques that was good for phosphorous spectroscopy, for looking at phosphorous metabolites in the body - phosphoro-creatine, ATP, inorganic phosphate. And the other technique that I developed was later called PRESS, by General Electric, but it's basically … I published the technique first … and that's very good for proton spectroscopy, looking at hydrogen in metabolites such as lactate, choline, and creatine.

What was nice about ISIS is that you imposed your spatial information. You selected a cube by using pre-pulses. These are pulses that are applied before the 90-degree pulse, and you invert set planes. At the intersection of these inverted planes, you then formed a volume - a cubic like volume - that you could interrogate with a 90-degree pulse, and that's why you could read the signal out immediately after the 90 degree pulse and there's no T2 weighting. So, nuclei with a short T2, such as phosphorous, are particularly suited to localisation via the ISIS technique.

I did collaborate with a number of the people in the Oxford group, although they were less keen on my localisation techniques since they'd developed a few of their own, but nevertheless, there was no doubt that we worked together on many occasions.

Magnetic Resonance Spectroscopy (1982-86) – revealing tissue biochemistry

I think MRI is very good at telling you when the tissue structure has broken down. That's what they are - they're structural images. I think, before tissue breaks down the biochemistry

goes wrong so the interest in studying tissue and its biochemistry is it will tell you that something's wrong before the tissue actually disintegrates. And so, it's an earlier process in the death of tissue and, therefore, holds a lot of promise at understanding the progression of diseases, maybe diseases that take a long time to develop. You know, biochemistry is key to understanding those earlier changes.

So there was lots and lots of interest early on in *in vivo* spectroscopy. I think, what's happened over the recent years, is that spectroscopy has not lived up to the promise of those early years, and imaging has just got better and better, and so now we've had a change of emphasis back from spectroscopy to imaging. So all those citations were because there were a lot of people interested it at the time.

Nottingham - the Birdcage Coil

I returned to Nottingham – I think it was in 1986 – because I had the opportunity to become an academic and I liked the idea of that, to be honest. The academic lifestyle appealed to me, and of course, I was going back armed with all this information that I got in industry: I was much more useful to Peter Mansfield that I had been when I had left because now I could make things like the Birdcage Coil. Peter hadn't got a Birdcage Coil in Nottingham and I could take that knowledge back that I'd learned in Abingdon, and the first year or two we were making those coils and really making echo planar much more powerful in terms of its resolution and its performance than it had been before. So, I think Nottingham benefited a lot. Again, I could see that I had very relevant knowledge that Peter needed in the group at the time.

Well, as it turns out, I've got a Birdcage here, and it was actually invented by an American scientist working at General Electric, and it's a really clever design. I mean … I think, after this gentleman, Cecil Hayes, invented it, I really think MR imaging began to take off. It was so important. This particular Birdcage Coil is used for head imaging. So, people would be in the scanner with their head in the middle of the coil here; their shoulders resting against here, and the Birdcage would - they'd have ear defenders obviously, because of the sound – and this actually picks up the signals from the human head very uniformly, very evenly inside. It's a very uniform coil and it's also a very sensitive coil. Its invention enabled high field MRI to be done for the first time at about 1.5 Tesla and upwards.

Scanning for birth defects

When I came back to Nottingham in 1986, it was clear that after we'd improved the image quality, that we now suddenly had a range of applications that we had to go through and get

publications to show where echo planar could have its biggest clinical impact. Most of that work was so large that we formed a team of people involving Bob Turner, Barry Chapman, Michael Stehling, and we really rattled though, in a period of a couple of years, loads of applications of EPI, mainly to do with looking at changes to the human body. For example, we did a lot of work in pregnancy because the baby's moving and EPI can freeze the motion. We went through the heart, and we looked for all the applications where EPI could freeze the motion and enable us to produce good MR images. So, it was an extremely fertile time, but it was really the applications of EPI rather than actually making it work in the first place.

I think with the fetus *in utero*, we were scanning to look for birth defects prior to birth so that they could have an operating table ready to treat the infant when they were born, and there were several conditions that we'd diagnosed prior to birth that would have helped them treat the baby. Professor Coopland was probably the first clinical collaborator that Peter had when he'd first developed the sequence, and I think over the years, they had quite a good … very close relationship of working together.

Tagging the blood

We were still looking at all the applications of echo planar in moving tissue, and obviously one, you can consider blood as a moving tissue. And so we immediately saw the application of EPI with doing a preparation pulse to tag the blood - to make its appearance depend on the velocity of the blood, and so we produced a paper in 1991 describing this technique, which you can actually selectively label blood travelling in a specific direction with a relative range of speeds. So, I think this technique actually generated a patent that was very successful and is now commonly used in many other related methods.

Inventions and patents

In my particular experience of patents, my first patent was the echo planar imagining methodology with Mansfield, that turned it into a technique that worked, and we patented it very early on, round about 1980, and a patent only lasts for about 18 years in the first instance. Unfortunately, the major applications of echo planar imaging probably occurred after the patent ran out, in 1998, so I didn't see the returns that perhaps the … I deserved. But it was such a joy doing the work that it doesn't matter.

Barry Chapman was one of the key people that contributed to the idea of actively shielded gradients, and it was simultaneously invented by scientists at General Electric. In actual fact, when it came to the court cases that tested the validity of the patents, it was the Nottingham group that won, and they are recognised, at least financially, as receiving … as the inventors

of shielded gradients. Of course, what you get from a patent also depends on how many people you share it with, and also, you don't necessarily share it in equal proportions either. So, when you make a patent, I think you have to decide who came up with what proportion of the idea as well. So, some people that maybe could have contribution got more money than others.

Detroit - applying MRI to visualise brain ischemia

In 1989 I made the decision to go to Detroit. There were a couple of reasons - one was the advancement of my career. Obviously, Professor Mansfield even then was a top scientist and you tend to get underneath his umbrella a little bit, and I felt that my career needed to be seen in its own light, as it were. And so one of the reasons for going to Detroit was to develop my own career. The second reason was, again, I was interested in stroke. I thought that MRI could have some major applications in stroke, and stroke is a condition which effects black people, and so, not surprisingly, the Americans made their National Stroke Centre at the time, Detroit, and so that was where there was plenty of access to these type of patients. I have to say also, I thought it was a … would be, a life changing experience for myself and my family - I had three children at that time, and we had a wonderful time.

They were the second centre to get a 3 Tesla magnet at the time - second one in the world. So, part of the attraction also was to get my hands on the latest, top range of high field magnets, and so the first thing I had to do was actually get the thing working. So we started. At the time, diffusion was one of the areas that we wanted to exploit.

Diffusion is the random motion of water molecules in anything like a liquid, a glass of water. In the brain the diffusion of water molecules takes the water in and out of cells, and therefore, it is actually sensitive to the structure of the tissue itself. Now, the diffusion coefficient changes within minutes of brain tissue running out of oxygen, and this mechanism is thought to reflect the swelling of cells. Water goes into cells; inside the cell it's in a lower diffusion environment and therefore the diffusion coefficient, when the cells swell - and there's more of the water inside the cell than outside - that causes a reduction in the diffusion coefficient, which we can measure in an MR image. The way that we measure it is simply by putting enormous magnetic field gradients into the imaging experiment, and those magnetic field gradients sensitise the position of water in two points; and if the water has moved between those two points in time in this very large gradient, the signal is changed and you can actually measure the diffusion coefficient. So, it's a very important parameter because it changes very quickly, and literally you could almost hold your breath and see the changes in the brain. It's very, therefore, very useful for looking as ischemia such as a stroke.

Solving the problems of diffusion weighted imaging with navigator echo

The problem though, with diffusion weighted imaging, is that you've made your image very sensitive to this very small motion of water, and we're talking about water that's moving five or ten microns. The problem is that the human head cannot be fixed rigidly enough to stop motion confusing this measurement so we have motion of the whole head, and what we're really interested in is the random motion of the diffusion of water inside the brain. And so one of the ways in which we can freeze that motion is to use echo planar imaging. Just do the image very quickly and we can freeze the motion, and the images come out undistorted. However, if you've got to take several minutes to obtain an image, which is required to get high-resolution diffusion weighted imaging, you're going to have to deal with the problem of motion of the head. And so what I did was develop this way of measuring the head position in part of the imaging experiment and subtracting any motion on a shot-to-shot basis to correct for the motion of the head, so that the measurement that you actually, finally take, truly reflects the random motion of water in the brain. And the extra signal that I used was called a navigator echo.

Disappointments and successes

I think one of the disappointments of my working in Detroit was that we didn't have early enough access to stroke patients. We had plenty of stroke patients, but of course, the imperative is to get them in the hospital and treat them first. You don't … if part of the treatment does not involve the MR machine, they would much rather be in the ward treating the symptoms of stroke rather than actually having … aiding us doing our research down in our machine. So I … there were … really wasn't enough stroke patients that we could get into the machine in the early phases of the stroke in order to definitively say that diffusion weighted imaging was great at detecting the tissue that's going to die because it's run out of oxygen. So, that was one of the great disappointments, and because it was a national stroke centre, they had four or five other clinical trials that were going on, and people tend to grasp at straws. If there's the possibility that something, some experimental drug, would actually help them, they're going to go into that trial rather than just be scanned, so that was the real problem with humans. As far as the rat work, there are many things that … rats you can generate very reproducible strokes in, and it's an ideal way … there's the middle cerebral artery occlusion model in rats was developed, and in the right hands, will produce a very well defined region of stroke damage in a rat. And it's a very reproducible way of testing new therapies, and so we were interested in trying out new therapies in rats preclinical use, in other words, prior to use in humans at a stage or two before, to see if those treatments would shrink the amount of stroke that we see in this very reproducible model.

It was understanding the process of stroke damage over a period, not of just the first day, but a period of weeks. We were interested in other long-term changes to the brain biochemistry, and so the phosphorous was a way of measuring the high-energy phosphates and looking for a pattern of injury in the longer term. I think everybody that's involved in the area tried to combine the techniques so that you get, you're really looking for what several measures will tell you rather than just one measure. You're hoping that the tissue will have a certain signature by using a combination of these methods that will tell you that it's the path of the penumbral zone, for example, in stroke. So, it's really doing more, getting richer information and I think its still going to be of interest to us for a long time to come.

University College London – a new lab at Queen Square for Europe's highest field magnet, 1994

In 1994 I came back from America to join University College London as the Joel Professor of Physics Applied to Medicine. The group I joined was … had been established for at least ten years prior to that and had been responsible for obtaining the first phosphorous spectrum of a human brain. And the … in fact, a couple of the scientists were made Fellows of the Royal Society on the basis of that - Dave Delpy and Os Reynolds - and so it was … had a really good reputation even before I came. And my input was on the imaging side, because they were famous for doing spectroscopy and I was really bringing in more of an imaging technology to them. Once I got back, I decided that I'd like to get into high field imaging and applied to the Wellcome Trust. And the Wellcome Trust said, 'Yes, but the environments that we'd like you to do that research in is more the neuroscience environment.' So, they asked me to establish a new lab in Queen Square and funded the purchase of a 4.7T system, which was the highest field magnet in Europe at the time.

Well, the high field gives you a larger signal strength and you can use that signal strength to get either more accurate measurements or a higher spatial resolution. The other advantage that it gives you is that you can perform spectroscopy. The separation between the peaks in spectroscopy increases as the field strength increases, which enables you to more accurately measure the metabolites, and I discovered that at least half the groups in Queen Square were actually more interested in the MR spectroscopy side of the brain, rather than the structural imaging. So, I wanted a machine that would do both rather well, and 4.7T was the magnitude of magnet that … it could be placed in the environment of the centre of London. Higher fields obviously require more and more iron. We've already got about 250 tonnes of iron in our magnetic shield. 7T would have required maybe 500 tonnes of iron, and so the cost goes up and up. So, basically, I wanted it for those two purposes, and I chose a

scientific instrument manufacturer because the standard imaging companies (the Siemens, Phillips, GE's of the world) just weren't offering anything more than 3 Tesla at the time. So, I had to go with one of the scientific magnet manufacturers and one of the scientific instrument manufacturers for the spectrometer. I went to Surrey Medical Instruments at the time, who later were taken over by Picker International, who were subsequently taken over actually by Phillips. So that's the history. At the time, I *had* to choose them.

High field magnets and the magnetic susceptibility of tissue

Yes, of course, there *are* problems associated at all field strengths with MR images, and one of those problems is caused by the magnetic susceptibility of the tissue itself. Essentially, tissue is very water-like and has a magnetic susceptibility, I think, of minus ten parts per million, whereas the surrounding air has a susceptibility of zero. So, when these two types of material come together, you create a magnetic field gradient between the two, particularly in the frontal lobes and around the ears, and that distorts the images, particularly echo planar images, which are obtained with a very low bandwidth per point. The distortion is dramatic around the frontal lobes. The solutions are hard to come by. One could introduce magnetic material around the head to try to reduce those gradients, and people have been trying that, particularly the Oxford group. You could put things in people's mouths to try to do the same thing around the brain stem, but none of the solutions are perfect. They may improve the situation but we're still working on further solutions.

The problems, however, with high field magnets, are much more to do with the properties of the tissue itself and the high frequencies that you are using in order to produce the image. So when we get to 4T and particularly 7T, the dielectric properties of the tissue mean that we have what is called a field focussing effect. The field is … it's a bit like an optical lens, which focuses light. The head, being a spherical object, when you apply radio frequency field to it, you can get destructive and constructive interference caused by the waves arriving at different times in different parts of the head, which causes severe differences in the signal intensity throughout the image. So they are very non-uniform images. But, I felt that 4.7T offered the … perhaps the optimum field strength for a number of purposes. I was pretty sure that we could develop MR imaging techniques to overcome the field focussing effect of ,,, that's the problem with high field magnets. That effect has still not been overcome at 7T, but we have overcome it at 4.7T, and so that, in some way, vindicates my decision. It's the field strength where I could solve the problem, and even to this day, Nottingham, with their 7T magnet, are still working on the problem. Minnesota have worked on it for five years and not solved the problem. All these people are buying 7T systems, but there's a problem they haven't solved. I think there's going to be twenty, thirty 7T systems very soon around the

world, but they *all* have to face the field focussing effect as their main source of not producing uniform MR images.

Well, what I was really trying to do was to convince the world that the optimum field strength for looking at the human brain was indeed 4.7T. So, all the methodology on imaging was designed to produce the highest resolution, the best quality images we could, within a five-minute scan, and all the methodology in spectroscopy was to overcome the problems of high field and produce the sharpest, most localised spectra that we could, of the highest quality. It was then my hope that we could actually sell these techniques to all the neuroscientists round Queens Square and start really showing the world that 4.7T was a great choice as an MR system. However, it took three or four years to develop those techniques and the machine was really quite unreliable in a way because it was made by a scientific instrument maker. It wasn't built for reliability like a commercial machine is, and so we found it very difficult to actually translate that work into clinical studies because the machine just kept breaking on a too regular basis.

Imaging the brains of birth asphyxiated babies

We have a group here - the paediatric group in University College Hospital – has a long tradition of looking at birth asphyxiated babies. I've been involved with that work for many years, and we decided to give it a go, and we took all the necessary safety precautions and we were very successful, successfully imaged each of the babies – I think there were about eight or nine in total – and we got good results on all of them. So it is possible, but we did have to go to an awful lot of work to make sure that the machine was working on each of those days.

On the good days, they were delighted with the quality of the data we've got. I think they hadn't seen before images of the infant brain quite of this quality, and I think they still are great quality, as indeed, all our images are fantastic quality. It's just that to take the next step, I think we needed to persuade a commercial manufacturer to give us a console that was reliable, so that we could then start proper clinical studies, and I was unable to do that because they are all focussed on 7T at the moment.

A new MRI machine and 32-channel head coil

The actual death of the 4.7 system: there was really two factors. Firstly, we didn't get continued funding from the Wellcome Trust, but we did get guidance that they wanted us to do more clinical based research; but also, at the same time, the magnet quenched. It quenched over Christmas, it lost all its helium, and it would have cost something like £50,000

to bring it back up to field, and we simply didn't have that money to spend for that purpose. So, we decided to call it a day there and spend all our efforts to try and get a new 3T system, which we've done.

The 3 Tesla machine, we accepted in August, so it's a relatively new machine. It's top of the line. We're waiting for a 32-channel head coil, which will improve the performance dramatically. The multiple channel receiver coil is a very exciting development. Essentially, what it means is that the coil is broken down into a number of elements. We're looking forward to getting a 32-channel coil, and that will have 32 separate receiver channels and the signal can be measured from each of those. The first improvement it gives you is more signal to noise ratio, because the closer you can get your receiver coil to the brain, the larger the signal that you can measure, and you can put these all around the brain very closely and get a huge signal. So, the improvement is about a factor of three on the outside of the brain, going down to about a factor of one and a half in the centre of the brain, in terms of signal to noise ratio. But, also you have the information that these coils are more localised and see local parts of the brain, so that means that you can actually do away with some of the encoding steps that you need to produce an image, which means you can shorten the imaging experiment; and shortening the imaging experiment reduces the distortions, particularly the susceptibility to distortions that we see at the frontal part of the brain. So, I think the parallel imaging, in combination with these new coils, could have some terrific benefits for functional MRI, not least of which removing some of these horrible susceptibility dropouts and reducing the distortion in the brain through reducing the length of the imaging experiment.

Cooling the brains of birth asphyxiated babies, and other projects

An example of the type of thing that we do as MRI scientists is the neonatal work. We determined that there was pattern of damage there that is interesting … that the babies that suffer birth asphyxia appear to … appear to be quite normal after ten hours and then over the next couple of days, their brain actually deteriorates, and so that gives you a window of opportunity for a therapy. And the therapy that was chosen was hypothermia, to cool down their brains for that two-day period, to stop that damage occurring. As an MRI scientist, we, we've had the … had to answer several questions. What was the correct temperature? For how long do you cool the brain and how do you measure the temperature inside the brain? So, we've actually, in the Bloomsbury group here, with Ern Cady, developed a temperature mapping technique, which enables us to actually know what the deep temperature of the brain is, and it was determined from piglet studies, actually, using MR, that the optimum temperature for cooling the centre of the brain is 35 degrees centigrade, but the cortex

survived better at 33 degrees centigrade. So, it was necessary to create a temperature gradient for optimum cooling of the head. However, we were fortunate in that we found a cooling cap that did just that - generated a temperature gradient in the baby's brain which approximately matched that profile, and that is now being applied in babies with … I think they've already done a couple of hundred in UCL, and hopefully it's helped all those children be a bit better.

The 3.0 Tesla machine will be shared, if you like, between the Wellcome Trust Centre for Neuroimaging – they are going to do … be doing functional MRI for half the week. We then have one physics day where we continue to develop the methodology - both the functional MRI and for spectroscopy and imaging elsewhere in the Square. And then the remaining two days in the week will be used by other neuroscientists around the Square, particularly a big project we're just starting. It's a multi-centre trial on Huntington's disease, and we are also starting spectroscopy studies on multiple sclerosis. So, these are just the forerunners of how I think the machine will be used over the coming years.

Reflections on a career - Lauterbur and Mansfield's Nobel Prize

Well, the one thing I remember about my early days at Nottingham, when I was a PhD student, and I hadn't been there all that long - maybe a year or two - but I'd always believed that Peter (Mansfield) would win the Nobel Prize. I was pretty sure about it because I looked at the work that he'd done and I was so excited about the work he'd done in the past, and the work that we were doing then, that I really felt he deserved it. So, I was somewhat disappointed that it didn't happen. Then, of course, it did happen recently and I was absolutely delighted for him. It did take a long time. I think there was some very confusing crosscurrents of who did what, but I believe in the end they … it was much deserved by the people that got it - Lauterbur and Mansfield.

I think all our PhD students in my department are encouraged to take courses in physiology and anatomy. In fact, more than encouraged, they are required to do that as part of the PhD. But, generally speaking, I mean, when we see people win Nobel Prizes for this type of physics, I think that is one of the great things to encourage people to actually go into that area, because the importance of these scientists are now being recognised with some major awards.

Not quite scientists

The balance is learning enough about the neuroscience that you understand what the researcher's trying to do, trying to achieve but you really can't be expected to become an

expert in each of several areas, so you've got to also keep to doing what you're good at doing, which is the MR science, and marry the two together. So, it is a balancing act where you certainly do have to know what the details of the latest theories are in Huntington's disease or on stroke. What do people want to do? Because you have to help the researchers do it. I think, it's also much … it's also often a very personal relationship that you have with the other investigators and that obviously helps when you can form that trust. It really is a matter of trusting each other that you both get rewarded for doing the work.

Physicists have often looked at us as being 'not quite scientists', being medical physicists, and I think that is from a generation or two ago when we were looked at as people that looked after the safety in hospitals. And when new, big machines, expensive machines, started appearing in hospitals, designed by physicists – the first CT scanners, the first MRI scanners – I think that was a real jolt to physicists because, you know, it was seen that we really were applied physicists at the cutting edge of doing something for mankind.

Highlights of my career

My personal highlights over the last twenty-five years are clearly the times I was involved in the echo planar, the initial theory of it, and then subsequently, a few years later, the application; and also the same with spectroscopy - localised spectroscopy. Developing the methodology and then trying to apply it. I've also done a lot of work in animal models, which I've convinced myself, have made important contributions in certain areas. So, those are my highlights.

The previous lecturer to me had said that MRI could never generate movie images of the beating heart, and of course, when I actually got up within minutes and showed the first images that really amazed everybody. And at the end of the talk, I was besieged on the podium with people congratulating me and slapping me on the back.

It was that Bowman Gray conference that really made me want to do that again and again, and I've been striving all along to try to get the same sort of feeling of success at doing these techniques, and you know, I've come close several times, but that's what keeps you going. You really want to do the next thing.