TODAY'S NEUROSCIENCE, TOMORROW'S HISTORY

A Video Archive Project

Professor Terry Jones

Interviewed by Richard Thomas

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Interview transcript

The MRC Cyclotron Unit and the world's first hospital-based cyclotron

Whereas today there are genuine medical physics courses you can go onto after you do your Honours degree, which equip you to do … to cover biological principles etc., in the early sixties that wasn't the case. I was fortunate enough to find an MSc course in Birmingham on radiation biology. So, I was coming out of University of Birmingham in 1964 with a Master of Science degree and also an Honours degree in physics, and I wanted to go and live in London. That was the ambition. So, putting two together, I wrote to three or four of the large London teaching hospitals, Medical Physics department, 'Have you got a job for me?' And …Barts, Middlesex and Hammersmith … and I didn't know anything about these places other than looking up their prospectus in the library and saying, 'Oh, that looks good.' And I wrote … one guy I wrote to at the Hammersmith Hospital was a guy called Professor Jack Fowler, and he was a professor in Medical Physics … was a name I found, and he didn't have a job but he passed my letter on. It was a very general enquiry, 'Do you have an opening in Medical Physics' type of thing, and I'd got a health physics background as well – radiation protection sort of background – and he passed it on to the Medical Research Council Cyclotron Unit, which was just across the campus. And lo and behold, they had a vacancy for a Health Physicist because the lady there was taking maternity leave and she wasn't going to come back, and there was an opening. So, I appeared just by chance, this opening for this job in 1964, at the MRC Cyclotron Unit, and it was the first hospital-based cyclotron in the world. In 1948, the MRC decided they would need to have a cyclotron in a hospital, because this was just after the war and radioactivity was beginning to be used for peaceful uses, and also beams … radiation beams from the cyclotron - in particular, a neutron beam - was being used for radiotherapy. And they realised they didn't have … and there was a very brave act of a bunch of scientists at the time who made the case at the MRC for a cyclotron in a

hospital, to research the effects of radiation on tissue, to develop short-lived radioactivity for clinical research uses, and to develop a beam for radiotherapy. Very innovative, and they had … it had to be home built so they employed a bunch of engineers who worked on Wormwood Scrubs – an old ex-prisoner of war prison camp, putting together this home-built cyclotron.

If you are going to make radioactive oxygen-15, which we'll discuss later … has been useful for clinical research purposes, the beam is extracted from the cyclotron. It then leaves the beam line through a very thin foil into the atmosphere and then into a box, which contains nitrogen gas - stable nitrogen, small amounts. And then when the beam - of two deuterons in this case - hits the nitrogen, it transmits them. It makes them radioactive, it changes them into oxygen-15, effectively. The path enters the nucleus of the nitrogen and the result of that is oxygen-15, so it's a constant supply of oxygen-15. So, if I'm doing a study in adjacent laboratories at the Hammersmith, the cyclotron is constantly bombarding nitrogen gas and it's then piped continuously to the lab in question. Because, in this case, oxygen-15 had a radioactive half-life of only 2.1 minutes so you make 100 units of oxygen; after two minutes, you've only got fifty left. So, you have to have it really on tap, and this was the justification for the cyclotron actually being in the hospital to make isotopes, which rapidly decay and couldn't be transported from Harwell or other nuclear centres.

First gamma camera images of the brain's metabolism and blood flow

In 1967-68, one began to explore medical research uses of isotopes from the cyclotron. Now, the core concept is that to administer radioactivity and be able to pick up where the radioactivity is in the body by virtue of the fact that it's emitting gamma rays, which are coming out of the body, and you can then detect them with a radiation detector. Now, eventually we'll talk about cameras and how we imaged that in three-dimensions, but in that time - that mid to late sixties - all we had were individual detectors which just gave you a signal if it was radioactive, like a Geiger counter equivalent.

We didn't have a positron camera, so all we had was the nuclear medicine department equipped with its gamma cameras, but that was seven hundred feet away from the Cyclotron Unit. Now, so within the Cyclotron Unit then we didn't have imaging equipment, so I was very fortunate enough that my colleagues at Hammersmith asked some of the world experts in producing short-lived isotopes in … they wrote the definite papers - John Clark, Peter Buckingham – and they said, 'Okay, we'll pipe this from the Cyclotron Unit through the sewer to Medical Physics Nuclear Medicine Department.' So, we would have eight walkie-talkies and Heath Robinson ways of making sure they could deliver the radioactivity in a constant

manner seven hundred feet away, at a distance from the cyclotron. And that allowed us then, in the UK, to begin to image the brain's metabolism and blood flow. It was with a gamma camera and it wasn't so good as the Boston camera, but nevertheless it gave us a chance to see what we will see in different diseases, and allowed us through connections with Queen Square - which we can talk about later if you wish - but it allowed us to look at patients with tumours, with stroke, dementia, Parkinson's disease, lupus, qualitatively, but begin to make an impact. The clinical researchers saying, 'Hello, this is interesting.

Michel Ter-Pogossian and the positron camera

Following the Hammersmith experience, two other centres in America established medical hospital-based cyclotrons - one at the MGH hospital in Boston, Massachusetts; and the other at the Mallinckrodt Institute of the University of Washington in St Louis. And the critical mass of people in this area in the world was extremely small, and there was one particular character by the name of Michel Ter-Pogossian who was established in St Louis, and he spent a great deal of time working with oxygen-15, even with an experimental research cyclotron. And he visited the Hammersmith, and he'd been a big stimulant for the earlier work at Hammersmith in terms of medical applications, and I'd been stimulated by the work in that laboratory, and I'd been stimulated by the work at the MGH where they were developing a new camera called a positron camera, which would give us better images of the distribution of these radioisotopes than the gamma camera which we were using. So I then thought, 'Well, the best thing is try and do a sabbatical, and actually share my ideas with these people in St Louis, and also to gain insight into this new camera technology.'

Positron Emission Tomography (PET), 1972 - measuring brain metabolism

But, I was going to St Louis and Boston with a mission as well … as well as to get a critical mass and share like minds, and to test the camera I had a mission of how to measure the metabolism of the human brain. And the concept I had developed conceptually was, if you could continuously breathe radioactive oxygen, that will allow us to give us an image of the brain where the brain is metabolising oxygen. That to me seemed very important because we all know how important oxygen metabolism is to the brain – fundamental - and if we could see where the brain was consuming oxygen that surely must be a useful clinical research tool. So, my mission was to go to St Louis, where they had done brain metabolism work, but invasively by injecting radioactively into the carotid artery, to share with them my ideas of how to do this non-invasively.

The concept of the steady state is that the cyclotron is constantly making radioactive oxygen - molecular oxygen - and you're giving it … we take oxygen through a facemask as if you're

breathing normal oxygen rather then injecting it. And if you constantly breathe it, because of the two-minute half-life, it will reach eventual equilibrium after three or four half-lives - eight or nine minutes. You'll get a steady state in the tissues. What comes in, goes out; arriving, metabolism, and decay. So, it's frozen, and basically, what you're then looking at in your imaging is whether the brain is converting oxygen into water - is metabolising the oxygen to water. So, you're looking at water and metabolism - it's the exhaust product of oxygen consumption - but you measure it in the steady state, which means even though you've got cameras, which may be inefficient, you can build up the image over a period of minutes to give you good topographic distribution. And that was the attraction: (a) it was non-invasive, and was a natural route, so that was a starting point.

Positron Emission Tomography (PET) – how it works and the first image of regional brain metabolism

I'd only been there a matter of a few months, and Ter-Poggossian and Mike Phelps had gone to the large radiology conference in Chicago, which is an annual event, and they came back and they were full of a new concept they'd seen from UK - EMI - down some small alleyway in the conference, by a guy called Hounsfield. They'd seen tomography, and they were so excited about it; they could see this was the way forward. It was going away from planar images where everything is superimposed, to depth information, and they really were sparked up on it. And while I was there, for the remaining months, they were mainly focusing on X-ray tomography, which they were trying to see if they do it any better or differently from Hounsfield, but my colleague who shared the same office with me, Hoffman … I'd been working on a planar device for detectors, but subsequently - and maybe we'll talk about it later - he'd used the detectors he'd got, and began then to construct then the first … one of the first tomographic PET scanners.

The second part of the sabbatical was to go to the MGH in Boston, and there a guy called Gordon Brownell, and Charlie Burnham, had been working on constructing a positron camera. We were looking for higher special resolution, ideally tomography. Now, these isotopes we've talked about, like oxygen-15, emit positrons - so positron emitters - and that means when they undergo radioactive decay, they emit a positron, which is a positively charged electron-like particle. In matter, the positron doesn't get very far because it's soon attracted by electrons, being oppositely charged. They both – as a result of the attraction – they annihilate, these two, electron and positron. As a consequence of the annihilation, two gamma rays emerge at 180 degrees to each other, so if I take a breath of radioactive oxygen, coming out of my head are pairs of gamma rays at 180 degrees to each other, over 360 degrees. And the positron camera makes use of that in that it doesn't have detectors just

on one side of the body, it has detectors on two sides of the body, and when one detector fires, and the other one fires simultaneously, they know, in between here a positron was captured by an electron. They know specifically, so that allowed you to certainly to pinpoint the position more accurately.

As a result of breathing the radioactive oxygen and taking the images in Boston, when I had begun to post the data in the middle of the night, I saw the distribution of radioactivity in my brain, and I believe that's the first image ever recorded of the regional metabolism of the human brain. We looked at a whole series of blood flow as well as … to have the image, and it was so exciting to be able to see that … that actually you did have as a result of predicting, in fact, you would be able to see this from the animal work. You would have a specific image which would look something like human brain metabolism, and to see that was quite, quite something.

A PET camera for the Hammersmith Hospital

Now, a lot had happened in the three or four years, I suppose, since I'd been there, in that the St Louis group had, in fact, developed a new area of positron emission tomography cameras. They'd taken some of the concepts which Brownell had developed from doing tomography, which when I was there was being done but it wasn't quite perfected, that's for sure. And they had then realised the basic principles of how you would construct a PET camera, which means that you have to put them in a ring, or a polygon arrangement, and make sure that the detectors are well shielded from stray radiation from other parts of the body. They'd looked at the latest basic principles, I think, perhaps more rigorously than had been looked at previously, and from that they'd begun to produce quite convincing and better … better resolution and more quantitative images in three-dimensions. And the people I knew quite well, as I recall, Phelps and Hoffman, had left St Louis and they were now in Los Angeles and were working with a commercial company called Ortech to make a commercial version of the prototypes they had developed in St Louis. And as Feruccio Fazio and I went around America, we would take breaths of radioactive oxygen to image ourselves. We were the human phantoms, basically, and comparing different cameras as we went round the States, and it was clear that the St Louis approach was producing the goods as far as much cleaner images, much more quantitative images. And I was lucky enough, in Los Angeles, to have in-depth discussion with my former colleagues to really get under the skin of why this technology was better.

The commercial device which had been fostered in collaboration with Mike Phelps and Ed Hoffman was called ECAT – Emission Computerised Axial Tomograph - and there was a

Mark 1 and then there was a Mark 2, which had certain refinements. And we'd plumped to buy the Mark 2. At the point when we were going to take … the case for that was submitted in '77, '78, and it was approved then, and it would not be delivered until the Spring of '79. At that point, we would be the fifth or sixth recipient of this technology. Already was Los Angeles and LIH, and I think, Ule in Germany, and one had gone to Orsay, which was a PET Centre in Orsay, in the south, which is about thirty kilometres south of the centre of Paris.

I think there were eight of us went over from Hammersmith in December 1978, which would be about five or six months before we took delivery of our own camera, and that was quite an important visit for lots of reasons. Not least, because there was a neurologist there called Jean-Claude Baron. Now, Jean-Claude was actually doing steady state oxygen breathing at Orsay. He had been at the MGH after my time, and he'd seen the technique I'd developed there and they were beginning to use it, and he'd obviously been quite attracted to being able to look at oxygen metabolism and blood flow, particularly in cerebrovascular disease.

Hammersmith forges ahead in functional imaging studies

The exciting thing about the PET cameras was it was taking us from images which prior, as I say, were planar images and qualitative images, to tomographic images, but they were also quantitative. By that I mean, you could measure the concentration of radioactivity in tissue. It was as if I could take a bit of my brain out and then put it into a laboratory well counter. I was doing the same thing. I was making, how many megabecques or microcuries of radioactivity per ml of tissue, and that was a tremendous leap because it allowed us to do all sorts of measurements. One like, I've injected so much radioactivity, how much ends up in my brain, in my cortex? As a measurement, that's fundamental, like a drug, but also, I could take blood samples and measure them in a lab standard and compare *their* concentration to the tissue concentration in the same units. And that's very exciting because then you can begin to look at relative concentrations against tissue concentrations over time, or in steady state, and then begin to work out equations of rate of exchange between the two, which gave you quantification of the exchange between the blood and the tissue. Right, now, when I did the steady state technique, I wrote the equations for that and I pointed out if we could measure the concentration in the artery and the tissue at the same time, you could solve these equations for blood flow and oxygen consumption. The statement was made. So that was that - the '76 paper. The Boston people then reworked the theory and came up with the same conclusion, so that was fine, and I think they then went ahead and began to quantitate. What they did is murky to me, but Jean-Claude Baron certainly was focusing on the fact that he knew that if he could take an arterial blood sample and measure in the well counter, and do the correction for the brain, he could begin to solve the equations as well. I just think that at

the Hammersmith, we knew that. I think we just forged ahead much more rapidly than anybody else did. We did a larger series of normals before they did, and I think we introduced other techniques where you need initial corrections because in a steady state you have radioactivity in the blood and you have to do another procedure (carbon monoxide) to correct for that. I don't think we were particularly more … smarter than them. We just put a body of data together quickly and published it first.

Building a team – Keith Peters recruits Richard Frackowiack and others

At that time, we'd had a great deal of support from the hospital, the Royal Postgraduate Medical School, and in particular, the Professor of Medicine, Sir Keith Peters, who went on to become RegIus Professor in Cambridge and then *Sir* Keith. And what was necessary was, with a PET scanner - and to bring on more presence in clinical neuroscience - was that we needed good neurological doctors working with us. And Keith Peters told Richard Frackowiak, who was then a neurology registrar at the Hammersmith, 'Go and work at the Cyclotron Unit.' You know, he'd given an umbrella of blessing, if you like, and support, and Richard was then assigned, if you like, to come and bring on the neurological work with us. And that was a very important step because to have someone who was a neurologist. Not only was he committed to doing it quantitatively with the blood sampling, and what have you, but also, it was important that neurologists were talking to neurologists about the results, rather than physicists like myself, and that opened up the links with Queen Square, as I said earlier. It allowed other young enterprising neurologists like Richard Wise, and David Brooks, and Jeremy Gibbs and Sigrid Herold, others from overseas, to come in with confidence, knowing that this was a way they could spend research time - know that it was mainstream - supported of the Hammersmith hospital, and it was blessed by Queen Square. They could go into Queen Square and get their final training. Very important. Allowed us to get a really good critical mass of young people - very articulate - who could take out an original series of studies, as I've described, and communicate that to the international community in a way which perhaps … which is quite unique to these people, these bright young people and their training.

First paper on visual (colour) activation, 1989

I think it was around about 1988, maybe '87, we were approached by a medical student from Oxford called Andrew Dean, who, as I recall, had done a PhD in visual activation, and he approached us about doing brain activation studies, which had already been pioneered with PET at St Louis by Fox and Raichle. And he felt that people like … not only did he feel this was an important area to explore and which we felt we could do, but he also pointed out that, 'I'm sure Professor Semir Zeki would be very interested in this area because he is…' So we

did some pilot studies of activation by administering radioactive water, which we did by breathing oxygen-15 labelled carbon dioxide, which is the same thing as administering water. So, we began to explore that technique. And then Richard made contact with Semir and also Chris Kennard, who was then at the London Hospital, who was also quite active in the visual area, and together they put together a paradigm and protocol of visual activation and colour activation in particular, and that eventually led to a *Nature* paper - the first *Nature* paper.

Statistical Parametric Mapping (SPM) – Karl Friston's 'great leap forward'

A programme of work was being prepared in schizophrenia by Dr Peter Liddle who had obtained a Wellcome Trust grant to study oxygen metabolism and blood flow in the brains of schizophrenics, and he had defined three categories: negative and positive categories, and some other, and he was hypothesising different patterns of metabolic profile in the brains of these patients in the steady state. And he was successful in that grant application, and that came with it funding for a research fellow, and we had two applicants for that position, one of which was a man by the name of Karl Friston, who appeared in the summer in a long brown camel hair coat, which is rather interesting. But clearly Peter knew of him and whereas, he was quite an intellectual force and was very keen, although he didn't come away in a sort of heavy sense at the interview. Karl then systematically and very quickly went about collecting this data, which wasn't trivial because there were thirty schizophrenics. He had to sleep overnight in St Bernard's Hospital to really collect them all and they had to be specially sort of, you know, worked up into these separate categories. He then had the problem of analysing the data, and sort of … how can you systematically categorise these people and look and observe, and search for differences in their neurofunctional anatomy. And at that time, the St Louis group were doing something on statistical mapping of a sort, and I had a paper to referee from *The Journal of CPF Metabolism,* which I didn't fully understand, but I showed it to Karl and said, 'What do you think? This is interesting activity.' And that may have sparked something in him, I don't know, or maybe he'd already been thinking, because he'd got, as I believe, a quantum mechanics background. He originally did physical sciences, and he'd obviously been thinking along those lines. But shortly afterwards he came up with this concept of statistical parametric imaging - mapping. Now this was quite dramatic. I can't overestimate how much it was, because it was a shock to us at the Hammersmith because we were then, at that point - myself, Vince Cunningham, Agen and Mertzemer - were very quantitative, which means measuring blood flow in mls per gram per minute, in great detail. That's quantitation. And here was this guy Friston, sort of running roughshod over all this, and saying, 'Oh, I'll take five of those, and five of those, and look for statistical differences between the topography.' And it was quite a shock because in a way it's as much quantitative as what we were doing, because he was looking at where were the quantitative

statistical differences, where were they quantitatively in Cartesian space? So, it was a quantitative statement he was doing, but it wasn't mls per gram per minute. And I think Karl, and the way - he's quite flamboyant in his speech - and of course, he's eloquent, and there were a number of bray … internal braying meetings which thrashed it all out, and you can imagine the sort of, I wouldn't say culture clash, but I thought it was necessary … it had been necessary to go through that for Karl so that he had his teeth cut, as it were, on the prejudiced world of how we should be analysing data. And I think it strengthened his resolve to go ahead of … I think other people accepted what he was doing, but what he was doing was saying, 'I'm looking for statistical differences. I want to be sure where they are and I'm not just looking at that region of interest where it may happen but I'm looking at the whole brain and seeing the statistical variation of brain. I'm using that whole data set to define what's the chitter in the data, and when I see something over and above that chitter, I know its significant because I'm comparing it to a huge body of data.' It's taken the data as a whole, rather up until then we'd just look at one region and see if it was working, and that was a power. And the power then because you were using the whole data, you could pick up quite subtle differences.

And it suddenly occurred to me that if the statistical differences are not in the raw data before you process the blood flow, they'll never be in the data after processing. Those statistical changes have got to be in the fundamental data you record, and then there was a bit of a stussle amongst … again the culture … people saying, 'You've got to be quantitative,' but no, just use SPM on the raw data. You don't need blood sampling. Just say, 'The radioactivity in the brain, has it changed regionally?' If the rare, raw data upon which you calculate blood flow, if that's not changing statistically in the region, therefore, you haven't got a signal. And that meant you could then begin to do activation work without taking blood samples. You could then do it much easier, much simpler and it blossomed the field. You could do things much easier, ethics were less of a problem. Well, quite honestly, we were making hay then. We had published five *Nature* papers on this stuff, and you need that sort of … to pay the bills basically [laughs] … you need that sort of profile to pay the bills, so you can bring on other things underneath like the more longer term. So, we were doing 120 scans a week. That's about - I don't know how many patients that was - but about twelve patients or something. We were doing a lot of studies.. We had brought on a camera more or less specifically for that, the retractable sceptre camera. We were able to do studies way into the evening, make very efficient use of the facilities. Quite simple studies, I mean, injecting with water, no arterial blood samples. Very challenging in terms of data handling. The unit was doing 3-D reconstructions, really challenging, so we were pushing the system hard, and we were making hay scientifically.

Development of functional Magnetic Resonance Imaging (fMRI)

It would have been either the end of 1990 or beginning of 1991 when there was a *Nature* paper from the MGH group using contrast MRI Gadolinium, and it was an image on the front paper of *Science* where they were showing visual activation using a contrast injecting, serial injection or contrast media, using MRI. That was presented at the Miami, June '91 conference, by Jacques Bellaveau and I was lucky enough to chat with Jacques informally after that about his very impressive work. And he said, 'Yes,' he said, 'But there's something perhaps even more interesting coming up soon which doesn't need to have injections into people.' And then in the autumn of '91, he presented at a small meeting in Milan what he meant, which was the ability to use the BOLD technique to look at activation because of change of levels of oxygen when you activate focally in the brain, changing paramagnetic signal, and he was beginning to pick up activations using MR. It was quite a striking observation. One could see the sort … because they were able … the signals were small but because they were MRI they could do lots of repeat measurements in the way that we had been doing with SPM … SPM type of techniques in PET, and they were then reinforcing the signal and out of that which grew then the use of fMRI for functional neuroanatomy.

There were plans to create, from '92 onwards, '93, a new centre at Queen Square, and although MR was certainly to feature there in the first instance, it was by no means going to be the only technique. PET was still going to be used, so there was some … it wasn't clear as to if and when fMRI would completely take over PET, even in '93.

I understood it that Semir Zeki who obviously enjoyed the work that was ongoing - the visual work at Hammersmith - was quite influential with the Wellcome Trust. I think he paved the way for the Wellcome Trust thinking about setting up a unit for brain activation at Queen Square, and Semir, of course, introduced Richard Frackowiak. And Stan Peart, particularly, was the guy - who was the Wellcome Trust Trustee - who I think really endorsed bringing on that stuff more than anybody else, I understand, and it was quite an investment because it meant that it was to set up a fully self-sufficient brain activation laboratory at Queen Square, within University College, where one knows is very strong in neurophysiology, and adjacent to the National Hospital, National Institute for Nervous Diseases, which I felt was quite an appropriate move. It *was* going to mean that we were aware of that move two or three years before it actually happened, and I think we dealt with that very maturely. We capitalised on the presence of Richard Frackowiak's group - Chris Frith and Ray Dolan, and Karl Friston, John Ashburner. We made hay in the meantime, but I, for one, was quite encouraging of it because it was a natural spin-off, if you like, or transplantation of that bit of expertise into a good fertile environment, and I think that's proven the case since.

PET – the detection of brain chemical activity

The PET technique itself, its real power … it's got unrivalled sensitivity for detecting very small levels of chemical activity in the brain, in tissue. It's the most sensitive and the most specific method for imaging molecular interactions in tissue. Radioactive water is only one level of interaction, and we're talking about things which are 10^9 times more sensitive than MR for detecting molecule work so that was an area that clearly, one had the confidence that is, to develop in the future, and go into chemistry.

My understanding of a ligand is it's a molecule which is specific for a binding site in tissue, as opposed to a biochemical, if you like, which becomes a precursor or a biochemical pathway, which itself may become changed or incorporated into other molecules. The ligand is something which targets a specific binding site or receptor, and then if you were to radio-label that ligand, you could then image where the ligand is homing into, and you can then image the binding sites themselves.

PET – pain mechanisms and research into opiates

Around '83/'84 I was approached by a young registrar from Barts Hospital, Anthony Jones, who was a rheumatologist, who wanted to possibly explore how in pain the endorphin receptors were involved. So he managed to find, with Wyeth, a drug called meptazinol, which looked promising but proved to be too non-specific. When we injected it in people you couldn't make any sense of the uptake. It was obviously much too non-specific or there was too much metabolism. And then - and I don't know how he did it - but he then got in contact with a company called Reckitt and Colman, who were producing diprenorphine, which … I think they were developing it as a drug or a potential drug. And he managed to get them to give us precursors of that, which as you would need for the radiochemistry. The precursor drug which you then attach with a radiochemical entity to make the labelled molecule. The chemistry was very difficult. Don't ask me the details but it was, and people like Jim Debooth and Vic Pike struggled hard to make enough of that stuff so that we could inject it into ourselves, and I think I was one of the first to have it into me. And then he showed - Anthony showed - the last activity of our old cyclotron in a subject before and after naloxone. Naloxone does block these opiate receptors. Now, dipenorphine is a new delta and kappa ligand. It's a broad spectrum. It isn't specific for any of the subtypes as such. However, when we were working, when he was working with dipenorphine we knew that Johns Hopkins were also working in opiates as well, and I got in contact with Henry Wagner. I said, 'Yes' – he was working on carfentinil, which was a quite something to do because it's an agonist - a powerful agonist - and it's pretty clear that with Sol Snyder working at Hopkins, there had been a lot of

input from that group into the Hopkins Nuclear Medicine Department. And they did it before we did with carfentinil - injecting carfentinil into themselves and Henry Wagner, and showing the brain uptake of how specific it was for the opiate receptors in the brain. Dipenorphine gave equally nice images, and as I say, we showed that dipenorphine was displaced with naloxone, which showed we had a displaceable signal in the brain with our old ECAT camera. And then later, when we had the new cameras - higher resolution - we then … Anthony came then on a more permanent basis and we began to do a whole range of in and out of pain studies.

PET – the dopamine reward system

So, I talked to Paul Grasby, who was destined to go to Queen Square – psychiatrist but had done a lot of brain activation work and water, but he elected to stay at Hammersmith and get more involved in radio-labelling study. I said, 'But Paul, shouldn't we be thinking about chemical activation?' And I think that - it was a mutual discussion, of course - and then they began to dream up some interesting paradigms of testing that along the reward story of the dopaminergic system. And we had ligands for the D2 receptor in the brain - the raclopride – and the question is then when you … it was known in animals, in fact, when they have a reward situation, dopamine is released into the synaptic cleft, and that should mean there would be competition for the binding of your ready-labelled probe – raclopride – so, you should get decreased uptake of raclopride if the playing is producing more dopamine in response to reward. That was the hypothesis.

Paul Grasby and Mattheus Cope, who was an epileptic doctor, actually doing research in epilepsy in the unit with ligands but very experienced in the use of his ligands, raclopride and others. They dreamed up the reward game of … as I remember, it was like a sort of an arcade game where the subject was lying in the camera and they had to shoot down certain tanks, I think, and if they succeeded they were going to be paid some money. Well, they never were paid, but I mean, but they were students and various individuals had … were asked to take part in this video reward game, and there were two conditions. There were baseline conditions of raclopride-binding and then a condition where they were playing the game - and some were more successful than others - and therefore, they were able to titrate the amount of blockade against whether these people … how successful the individuals felt they'd been. So, that was the trick, and the SPM was tracking subtle changes of those who were being rewarded most against where there less … more and more blockade of the ligand. That was the clever thing of it.

PET – developing drugs for brain tumours

We were broadening the base at Hammersmith as Richard (Fracowiak) and the activation programme was going to move, and we were going much more into chemistry. And we took up the initiative of 'Can't we used labelled drugs going into tumours - cancer drugs - to see … to look at the pharmacokinetics of these drugs in cancer?' And yeah, we had a technique. We could label the drug, and surely this must be important when you look at a new drug in cancer. Does the drug actually get to the tumour? What's the kinetics of that? Are there any normal tissues which may accumulate this drug, which may give side effects? So, we approached the Cancer Research Campaign, which was very active in this country at that time in bringing new drugs into man very quickly. They made … just do a single species, make sure it's not terribly toxic, and then into man and look at drug effects. And we found their pipeline of new drugs going into man, some of them produced by CRC - Cancer Research Campaign - itself. And one drug was called temazolomide, which was being developed for gliomas, and that drug has now since become the number one drug for brain tumours in combination with radiotherapy. It's been a big success drug but we started at the early Phase 2 where we said, 'Okay, thank you for letting us know about this new drug coming into man.' And they were testing it at Charing Cross, which was on our doorstep, so we said, 'We'll label it and we'll look at its penetration into the brain tumour.' And Pat Price was running the oncology programme at Hammersmith then - the oncologist - and we were doing the pharmacokinetics of the drug in the tumour and normal brain to show you the concentrations. And also, we were looking at … when we entered second phase was when they began to give the drug in therapeutic doses, how it would change glucose metabolism in the brain tumour. We took it much further than that. In the Phase 2 study we even took this technique where we were able to do drug studies a year before Phase 1 started, because you were giving micrograms of material. You could give - it was so safe, you could give this material, and we were able to show in collaboration with the Cambridge people, a drug distribution, as I say, a year before it went into man for the first time.

PET – microglia activation in stroke, Alzheimer's and MS

Carbon 11-labelled PK11195 was a ligand firstly introduced in Orsay, and they took a lead from a guy called Benavides, who was working for Roche, I believe, in France, and he was an expert in the peripheral benzodiazepine receptor system. Now, the microglia are the defence system of the brain. They're dormant - they may represent something like ten per cent of all the brain cells - but they are dormant. But once there's a lesion, they activate and they may even proliferate to try and encapsulate that lesion to prevent its interference with other normal tissue. And it's a generic response to when there is disease in the brain, very generic. And so this looked very exciting, and some very early work done at Hammersmith

on stroke, and patients recovering from stroke, where you've got a lot of damage clearly - and showing when we inject C11 PK11195, you really have a very strong signal in the region of the stroke due to the microglia, and they become, in many cases, macrophages, which really are trying to contain this activation. But … and Ralph Myers and others showed that it really was the microglia was giving us the signal. Now, there was a centre in Munich, a Max Planck Centre, devoted to this sort of biology, and I think Ralph Myers went to a seminar in Germany at which they were active in this area, and the junior worker there called Richard Bernati, who had been working on this - and he's also psychiatrically trained but really quite a basic biologist, and he was so interested in the fact that we had the specific ligand for microglia. Now, you have to understand that during this time, which is the mid 90's onwards, if you look at the literature of microglia, in general, the biology of microglia, it's really going up exponential. About how people perceive the microglia. Are they the precursors for Alzheimer's Disease? Are they involved or are they by-standers which are involved? But, in general, there's a lot of interest in microglia. And Richard came over and added his insight and the need … the wish to begin to explore the value of this probe in a whole range of diseases, and of course, the first one we went for was multiple sclerosis because there, there are well formed plaques of activated tissue, and there was a series of work where they actually looked at autopsy brain and looked at staining the plaques and showing that they were full of microglia and they were activated, and also the PK was binding there.

Such things like looking at early Alzheimer's disease and showing activated microglia in patients at the early stage was fascinating, and of course, as it were, suggesting how that may be associated with the plaque formation and relationships there. And that's … the jury's still out on that one, but also Richard Wise did some interesting work on a patient with stroke in showing how distant parts away from the stroke, there was subclinical damage done, but the microglia were showing it. There's a lot of work going on now … and David Brooks went on to use it in movement disorders quite extensively - multiple system atrophy. There's a lot of work within the PET field trying to get better ligands, which will perhaps give you a stronger signal, and that's an area which is developing.

PET – serotonin research

So, Ray Dolan - and he was met by people at the Royal Free - and they raised the possibility of, could we image the serotoninergic receptors because it was heavily involved in depression – serotonin and suicide. It was a system which is of interest in the psychiatric world, and Ray was somebody who felt … he stimulated our thinking about could you find a ligand for the serotonergic system. And at that time there wasn't one which was satisfactory, and yet it stimulated our chemists, particularly Vic Pike, to keep an eye open for possible

molecules. and they knew the sort of molecule needed to bind to these receptors. The serotonergic receptor has, like many others, many subtypes, and so there's more than one, but anyway … and it so happened that through the contact with Wyeth, which had been back to the old opiate days, that somehow that thread of contact was maintained. Vic was able to pick up a lead from Wyeth who was developing this as an anxiolytic drug, I think … Wyeth … as an anti-anxiety drug, primarily, I think it was. And I don't remember the details but I suspect that they had indications from laboratory animal work, because it was pretty specific … even when you inject this stuff it was tricky. And then Vic picked up the challenge of how to label it, and we were able to get it into man and show very nice images of the 5HT1A system.

PET – the burden of psychiatric disorders

Psychiatric disorders account for about twenty per cent of the National Health Service budget. Do you know that? Twenty per cent! Do you know what fraction cancer contributes to? Seven per cent. The big cost to the health service is psychiatric disorders. So, and things like schizophrenia, although you may dismiss them as not being very prevalent, they are a huge thing. If an eighteen-year-old becomes schizophrenic, that person is a sociological burden for the rest of society, as opposed to some old person with cancer. So, we're looking at large sociological impacts of understanding diseases which are not well understood. They clearly have got chemical problems in the brain with schizophrenia, because drugs do work, but we know there are some people who recover after one episode; some people are in the bin for the rest of their life, and what's the classification? How do we know when an eighteen-year-old has become … is hearing voices? What's happening in their brain? The vision would be, if we could have tools which say, 'That particular chemistry has gone wrong. Let's tailor for those people a therapy because they are of that category.' We know schizophrenia, we know dementias are a big bucket to chuck everything into, and yet there's a spectrum of conditions. Some which will respond, but you're treating them all as one big category at the moment, so if we could get to the phase of selective imaging technique - because there's no other way, I don't think - because you've got to say what's happening in … they're hearing voices these people, or whatever they're hearing. There's something going on in the brain. If you could say it's the x-subtype or sector has over-expressed, you could then tailor your drug accordingly. Now, that's a bit of a hope looking forward, but these are big sociological problems. The whole issue of ageing. Why do people get older than others? What's the microglia doing there? How is the brain breaking down? If we have … if we have tools to look at this ageing process, like microglia activation, we may have ways of beginning to titrate our cognitive therapies or whatever you're going to introduce.

PET – biologicals and the Northwick Park accident

We're now moving into an era of where … drug companies were developing small molecules for treatment, but the big emphasis now is on biologicals - antibodies for treatments. In cancer, in inflammatory disease, and eventually in the brain. Now, these are very, very powerful molecules. You will all have known about the Northwick Park accident a couple of years ago where they injected into seven volunteers, and fingers fell off and what have you. It was a huge uproar about it. They were administering these molecules, which behave quite differently in man than they did in monkeys. Now, they were injecting into these people 7 milligrams - that's all they were injecting - and they had eight people were in intensive care within hours. We can inject a thousandth of that in a PET study to see how are these new biologicals, which behave differently in man, where do they go? Do they behave differently? And it's called micro-dosing, or zero-dosing. In other words, giving drugs which have no pharmacological effect, but yet you're seeing where this drug is going. Is it homing? It is concentrating? And where you don't expect it to go. Is it going where it should go? And it's … the world is developing now for drug development, it may become unethical not to do a micro-dose before you go into Phase 1 - whether it be micro-dosing measured by a blood sample with some chemical technique - measuring how the drug is behaving - or things like PET, which are exquisitely sensitive. And when we compare the use of PET now for these FDGs tumour-staging, compared to using it to discovering new molecules - new powerful molecules - and getting more and more into man. By virtue of using these very sensitive probes, I can go into man without any worry about toxicology because I'm dealing with zero-dose. That's the vision, whether it be for the brain, or for cancer, or whatever.

Last Days at the Hammersmith – the MRC proposes to split the unit

In 1997, we had a quinquennial review by an MRC sub-committee, which went very well, given that, you know, we had lost a major section of the programme three or four years earlier than that – when Richard (Frackowiak) went, and that team. We had recovered from that. We were doing the video-activation game, we were labelling new molecules for cancer, and we were doing the brain glial activation stuff. We really were on a roll and we scored very heavily on nearly all the components - 5 Alpha star scaling. Nearly all the work done at the Hammersmith by an international group committee. But the MRC, headed by Professor George Radda, said, 'This was not necessarily strategic', and he was obviously very keen to offload the cost of that unit in some private partnership exercise. He brought into the MRC … in the first instance, he brought in KPMG, which are a very well known consultancy company, to do an option appraisal. How should a unit run? And Les Iversen was involved at that point. How should they run this centre? And the option appraisal said, 'Status quo.' KPMG spent a week there - very expensive. 'Status quo is working well.' And the MRC wouldn't accept that.

They wanted their own agenda, and they put in two people we'd never heard of before, who said it should be privatised. It should be split up. You should separate the non-clinical from the clinical, which was a disaster. Despite a long case I made against that, saying, 'This is going to destroy the whole ethos of the place, and you're trying to impose an industrial ethos on, basically, academics - Ian Cunningham and people like that. 'To try and do that at this point would be detrimental, and you would lose staff as a consequence.' And they still decided to go ahead, and I resigned on that because I knew they were going to appoint a managing director and therefore my role would go away, and I would be in the middle of something which I didn't want to be in the middle of.

Things Remembered – creating the teams

A few of the techniques which I dreamed up or refined – the steady state of oxygen is an example, and the activation work, and how to refine the technology and make it more sensitive – my relationships with industry to make me better cameras, which pushed on the science, but that's the gutsy thing. But perhaps the overriding thing is the building the team science. Building the teams. Reaching out to the clinical world, finding out what they want to do, reaching out to them and bringing them - encourage them in - to work alongside us in a symbiotic way, in an interdisciplinary, multidisciplinary … creating the team science which this field needs - from chemistry to physics to maths to operations, which are complex - to the clinical people, whether they be psychiatrists or oncologists. Getting them to work as a team. That's been the most exciting thing, and people don't realise what's involved in doing that. But when it works and it begins to fire [snaps fingers], it's powerful.To have that group singing from the same hymn sheet - and the MRC broke that.

Things Remembered – inspiring the clinical community

The best moments have been seeing my clinical colleagues standing up in the international stage and producing the data, and explaining the data, you know. Clearly, they're just the tip of the iceberg because we know what lies behind that, but for them - to see them - and they're young, often quite young, and their careers are [unclear]. But more than that, they are succinctly giving it to the audience, which they need to be giving it - neurologists or oncologists or psychiatrists. To see them - not me giving it - but to see them giving it, you know? That's when we say, 'Ah, God!'