The History of Brain Imaging in the Cyclotron Unit using PET

A Personal Methodological Perspective

by

Terry Jones

Introduction

I was hesitant about undertaking this review since the Cyclotron Unit has been about making history rather than documenting it. Nevertheless as has been pointed out by colleagues; “unless you know where you have been, how do you know where you going”. It would be quite a formidable task to adequately cover the scientific achievements over the years within the Brain Imaging programme. Hence I have taken as a theme, methodological and technical developments since they represent significant drivers of science. Through improvements in sensitivity, specificity and practicality, they introduce new measurements which enable new scientific questions to be asked. A constant theme in this history is that although there have been major steps in methodological improvement, by and large the evolution has been one of small incremental steps which, when integrated over time, represent significant advances. In this review, I will attempt to mention most of the personalities who were actively involved. I will indicate what the opportunities are for future methodological developments and what we have learnt from this historical review. The development and introduction of new radio labeled tracers and ligands are itemized. However, I clearly have not been able to do justice to the detailed chemical and technical challenges that had to be over come in making these selective probes available.

There are many who think that the Cyclotron Unit represents a tower of Babel, consisting of one large pile of activity with little connectivity between sections or plan. I hope to show from this review that there have been a number of consistent global evolutionary themes.

The first hospital based cyclotron

The story starts just after the last war when a proposal was made to install a hospital based cyclotron at

Hammersmith which would be the first facility of its type in the world. The case rested on three applications involving: (i) Studies of radiobiological effects on cells and tissues, (ii) radiotherapy advances, in particular through neutron therapy and (iii) the production of radioisotopes for medical uses. When one examines the case today, it doesn't look very strong and there was some resistance to it within the UK. This came from Cockcroft, the then head of Harwell, who said radioisotopes could be produced by the reactor and also the head of the MRC Institute at Mill Hill, who thought that with the availability of C-14, he couldn't see the need for C-11.[from correspondence between the MRC and by Dr Constance Wood- held in the Unit in 2000]. In addition, in 1948/49, the UK was going through an economical crisis because the Americans wanted their war loan returned. Nevertheless, the case was eventually approved and the cyclotron constructed in an ex prisoner of war camp, located on Wormwood Scrubs and then assembled in the current building.[see accounts in the 1980 Cyclotron Unit Jubilee book]

In 1955, the Queen opened the cyclotron facility. She was welcomed by Dr Constance Wood with Ron Post looking on.

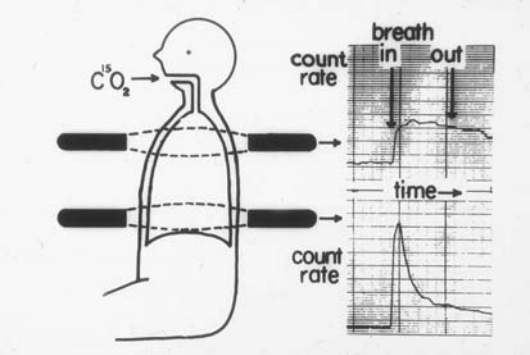
Dr Wood, the then Director of the Radiotherapeutic Research Unit had been a tremendous driving force behind this cyclotron project. Up to that time, she had already installed at Hammersmith a Van der Graaf accelerator for radiobiology research as well as the world's first linear accelerator for clinical radiotherapy. Her interest in the cyclotron stemmed from before the war when she visited Berkeley in California to meet Lawrence, the inventor of the cyclotron. The visit left a large impression on her not least by being exhilarated when driven around in Lawrence's sports car, she remained a spinster all her life. There are interesting anecdotes from the opening of the cyclotron facility. When the Queen and Prince Philip were conducted into the cyclotron chamber, their watches were collected by the engineer Ron Post to prevent them being damaged by the magnetic field. Ron noticed that the Duke of Edinburgh's watch glass was cracked and informed him of this. The Duke then flippantly said that he couldn't afford to have it repaired. There upon Ron Post, quick as a flash said, "well, you shouldn't have such an expensive wife". The cyclotron had been barely operational before the opening and there was concern that maybe it wouldn't work when the Queen came to switch it on. Evidence of it functioning was the movement of a large needle on the control desk. Hence as a backup, Ron Post was poised behind the panels of electronics with a battery and two pieces of wire, to make sure the needle at least deflected. In the end it was not needed.

The opening of the cyclotron coincided with a rather difficult situation in that Dr Wood had few scientists. She had alienated members of the Medical School through her installing the Van der Graaf on their grounds and also was prejudiced against since she had the boldness to fill wards with cancer patients and attempted to treat them. In addition, the MRC had dismissed her chief scientist, Dr Hal Gray, after which the international unit; the Gray has been named. Dr Gray, later to become an FRS, was a very prestigious scientist. He came out of the Schools at Cambridge of Bragg and Lea the famous radiobiologist. Gray and Connie Wood had fallen out over the priorities of the cyclotron's use which resulted in the MRC asking him to resign following which he moved to Mount Vernon to set up the Gray Lab. Dr Gray's senior scientists; Jack Boag, the Unit's principal physicist, and Norman Veall, the father of the use of radioisotope techniques in medicine in the UK then promptly resigned in protest. [The above account was personally related to the author by Dr Constance Wood herself and Dr Norman Veall].

The first human studies with short-lived positron emitters

In 1957, after an external beam had been extracted from the cyclotron, there was a visit to the Unit by a Dr Michael Ter Pogossian from St Louis who was on sabbatical with Gray at Mount Vernon. He had worked with the Washington University campus cyclotron which produced O-15 for his studies of rat tumour metabolism. He asked that a bag of nitrogen be bombarded by deuteron particles and promptly took a breath from this bag while holding his hand over a Geiger counter. The resulting crackling of the counter, some seconds after inhalation, alerted individuals at Hammersmith of the opportunity for using such radioisotopes for studying regional lung function. It was fortunate that at the time there was a strong lung physiology research team at Hammersmith, headed by Dr Philip Hugh Jones. In particular Dr John West, a physiologist from Australia and a house officer, Dr Colin Dollery, who later became Sir Colin Dollery and Dean of the Medical School, enthusiastically exploited the short-lived cyclotron produced radioisotopes for studying regional lung function. The measurements were quite simple, detectors were placed over different parts of the lung and following inhalation, the clearance of the tracers followed. In particular, use was made of carbon dioxide labelled with oxygen-15. When inhaled, the O-15 rapidly exchanges with water in the lung, the clearance from which gives a measure of regional pulmonary blood flow [1]. Considerable use was made of these techniques to study human pulmonary physiology, results from which were widely published. Support for these studies came from John Clark, Peter Buckingham, Gerry Forse and Norman Dyson. He explored coincidence counting and was the first to report the use of delay circuitry to monitor random coincidences [2]. By the mid sixties, most of the principal experiments on regional lung blood flow and ventilation had been completed. In addition, alternative techniques were introduced for such studies involving long lived,

reactor produced Xenon-133.

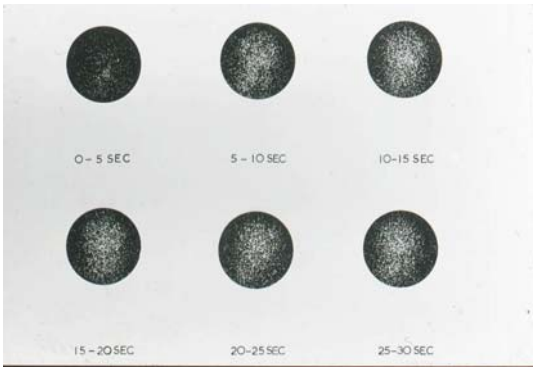


Single breath of oxygen-15 labeled carbon dioxide results in the tracer being transferring rapidly to the water pool in the lung and cleared by blood flow

Exploring how to image cerebral blood flow and metabolism with oxygen-15

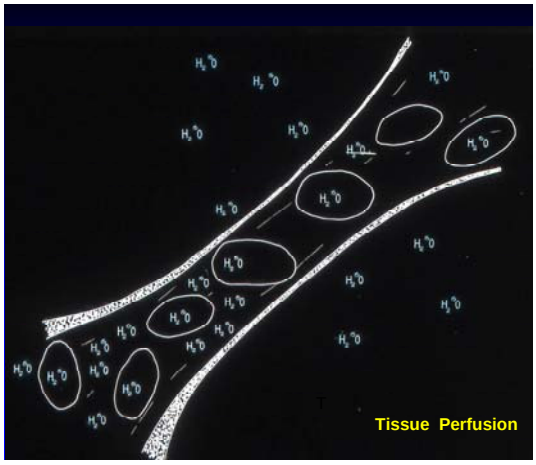
Little use was being made of the short-lived cyclotron produced isotopes in the mid sixties and the then director Mr Derek Vonberg was anxious to strengthen collaborative links with the Postgraduate Medical School. I became interested in exploring how to make use of these isotopes to study the function of organs of the body outside of the lung. At that time, I was the radiation protection officer in what had became the Cyclotron Unit and had been undertaking radiobiological studies of experimental rat tumours including measurement of tumour and normal tissue blood flow and volume using non cyclotron produced radiotracers. In the first instance, I was attracted to developing techniques for the human brain, not least because this is the most complex biological structure known to man, the most investigated and yet, the least understood. One's awareness of the opportunity to use radiotracers to study cerebral blood flow came into focus at a lecture given in London in 1967 by Dr Ter Pogossion [3]. He vividly demonstrated how, using an image intensifier system and cine recording it was possible to follow the regional distribution and clearance of Xe-133 in the human brain following its injection into the carotid artery. Also at that time, Niels Lassen and David Ingvar were reporting interesting results on the use of probes to study this clearance [4].

The studies of cerebral blood flow at Hammersmith were started by exploiting the ability to non invasively deliver a bolus of radioactive water, a freely diffusible inert tracer, into the arterial blood from a single breath of carbon dioxide labelled with O-15. There were no imaging facilities in the Unit but there was an Anger gamma camera, the first in the country, located in the Medical Physics Department. Anaesthetic bags of C15O2 were produced on the cyclotron and we had to run across the Hospital site to the Anger gamma camera. Single breathes of C15O2 were taken and the brain imaged in the Anterior-Posterior view. These early unpublished studies showed that it was possible to observe the arrival and clearance of the bolus of H215O in the brain. However, it is interesting to note that the maximum count rates recorded were only around 500 counts per second.



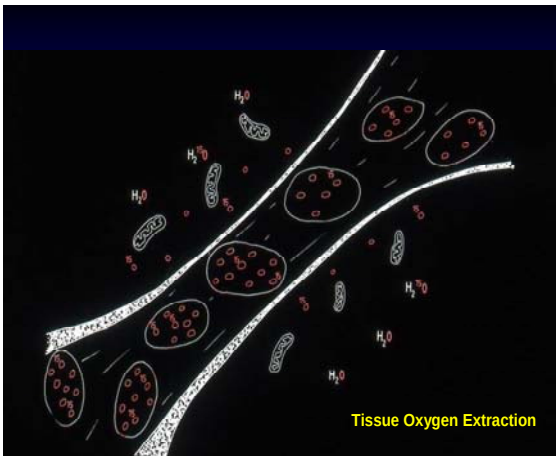
Serial images taken with a heavily collimated Anger Gamma Camera of the front of the brain following the inhalation of a single breath of $C^{15}O_2$.

This contrasts with current bolus studies of radioactive water using the HR++ PET scanner which generate hundreds of thousands of counts per second for less activity than we were giving in the early days.



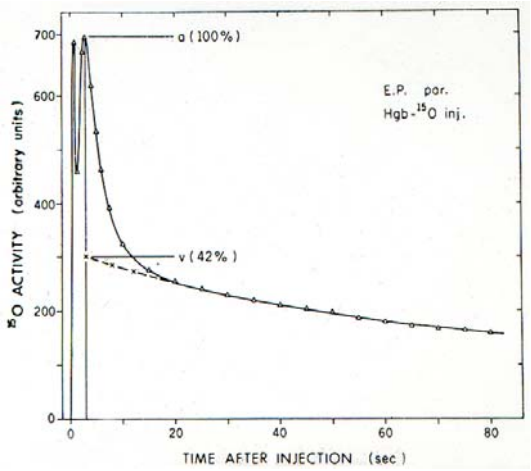
$H_2{}^{15}O$ as a tracer of tissue perfusion through free diffusion from the capillary

The real goal was to use oxygen-15 to image brain metabolism. The human brain accounts for some 18% of the body's total consumption of oxygen. Oxygen is carried to the tissues bound to haemoglobin. It then diffuses into the tissues and enters the cytochrome system to produce ATP (energy) with the oxygen becoming incorporated into water; water of metabolism.



Tissue utilisation of oxygen-15; involving its diffusion from the red cells in the capillary and conversion into labeled water of metabolism within the ATP cycle.

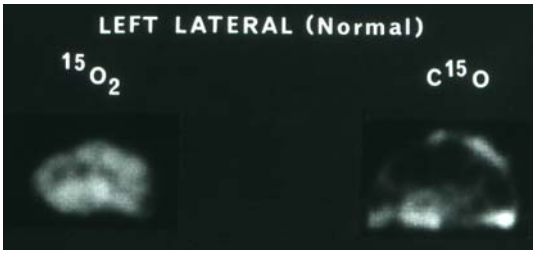
In 1968, reports were coming in from St Louis, where the second hospital based cyclotron had been installed [5].There Ter Pogossian's group were labelling blood *in vitro* with oxygen-15 and injecting it, as a bolus, into the carotid artery. From the time course of the tracer over the brain it was possible to measure the fraction of the injectate that had been extracted, by following its slow clearance in the form of water of metabolism. A second injection of radioactive water produced a measure of blood flow. The multiplication of the oxygen extraction fraction with blood flow and the arterial oxygen content gave a value for regional cerebral oxygen consumption. For this study, three probes were placed over each hemisphere of the brain.



Time course of tracer within the brain following inter carotid artery injection of ^{15}O labeled red cells. The slower clearance component is the labeled oxygen that has been utilized by the brain.

I considered these carotid injections a rather drastic way of carrying out such measurements which clearly were limited in their application. Hence, I thought it would be better to adopt the normal route of administering oxygen namely inhaling it. The concept was to continuously inhale oxygen-15 and because of its 2.1 min half-life, it would take 6 to 8 mins to reach a steady state. This state of dynamic equilibrium is reached when the arrival of radioactivity through flow and metabolic extraction equals its rate of washout and decay. The hypothesis was that during the steady state, it should be possible to record sufficient counts to form a metabolic image using what were relatively poor sensitivity imaging devices. The concept was that this steady state represented the formation of metabolic water, the distribution of which would represent that of energy metabolism in the human brain. This is analogous to how one could map the distribution of human populations in the UK by flying over the country and monitoring carbon dioxide or carbon-monoxide concentrations. These exhaust products would reflect distributions of energy consumption and hence human activity. Steady state recordings also had the attraction of avoiding the then difficult deconvolutions needed for analysing kinetic bolus studies where emphasis is placed on accurately recording the time course of the arterial input function.

One really did not know what fraction of the 15O2 steady state signal recorded over the brain would be due to the locally generated water of metabolism compared to radioactivity in the cerebral vasculature or recirculating labelled water. To investigate this, I was able to obtain, in 1972, an MRC travelling fellowship to go to the USA for a year and in the first instance spent 6 months in Ter Pogossian's laboratory in St Louis. There they had a monkey model whereby they could study brain uptake of tracers with a single probe as well as take arterial blood samples. Systematic studies of 15O2, 15CO2 and C 15O 2 breathing allowed the substraction of contributions due to recirculating labelled water of metabolism and the radioactivity contained within the brain's vasculature. Using the arterial whole blood and plasma concentrations for normalisation, the results showed that 70% of the steady state 15O2 head signal was due to locally generated water of metabolism [6]. When at St Louis, one enjoyed much fruitful discussion and further insight into the embryonic field of studying the brain using cyclotron produced isotopes from: Mike Ter-Pogossian, Ed Hoffman, Mike Phelps, John Eichling, Mark Raichle, Ken Larson, Bob Grubb and Mike Welch.

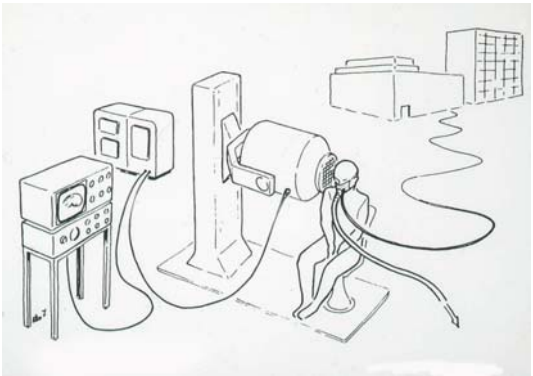


Images recorded with the MGH Positron Camera during the continuous inhalation of $^{15}O_2$ and $C^{15}O_2$

Armed with this experience, I then went to Boston for 6 months where, at the MGH, Gordon Brownell and Charlie Burnham had constructed one of the first high sensitivity positron cameras - PC1 [7]. There, I imaged the distributions of tracer in the human brain during the sequential, continuous inhalations of 15O2, C15O2 and C15O. The resulting images showed quite clearly that during steady state 15O2 breathing, the distribution of radioactivity in the brain was not significantly contaminated by a blood volume contribution since that image fitted inside the shell of the vascular image obtained during C15O breathing. This produced, to the best of my knowledge, in 1973, the first "metabolic" image of the living human brain [6]. The camera had tomographic facilities and was able to focus data on different planes. It was also possible to rotate the camera around the head to produce tomographic distributions of radioactivity in the brain. This used filtered back projection reconstructions which had been first developed for PET by David Chester at the MGH. However, the results at that stage were not very convincing.

First qualitative clinical studies of regional cerebral blood flow and oxygen utilisation

Encouraged with these experiences, I returned to the UK in 1973 enthusiastic to pursue such studies at Hammersmith. However, the neurologists were not that interested. Donald Calne was just leaving for the NIH, Nigel Legg had only just arrived and Chris Pallis was singularly sceptical. Nevertheless, I was able to attract the attention of Dr Chris Mackenzie, a radiotherapist with an interest in studying brain tumours' functional response to treatment. For this, we used the gamma camera located in the medical physics hut fitted with a 4½ inch thick lead collimator to view the lateral aspect of the human brain [8]. This required piping 15O gas some 700ft from the Cyclotron Unit to the medical physics department. John Clark laid the supply pipes in underground ducting and Peter Buckingham maintained steady state levels of supply through servo mechanism control and intercomm with the cyclotron control room. The gases expired during breathing were simply exhausted out of the window!



Gamma camera imaging of brain using oxygen-15 which was piped continuously form the Cyclotron Unit to the Medical Physics Hut

where the current MRC CSC building now stands.

Initial studies showed that not only could one image the uptake within the brain with a gamma camera and follow the effects of radiotherapy but cases of meningiona showed mismatching between the high blood flow to these tumours and their relatively low respective oxygen consumption [9].

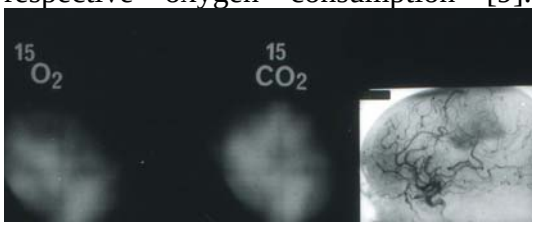


Image recorded during $^{15}O_2$ (oxygen utilization) and $C^{15}O_2$ (perfusion) of a patient with a meningioma).

At the time, Chris Rhodes and I were developing techniques to measure pulmonary edema. This was in collaboration with Mike Hughes and Ferruccio Fazio , a visiting research fellow from Pisa Italy He and I were also developing the 81Krm lung ventilation technique which has since become important for patient diagnostic studies. However, he was also very interested in the brain studies I was undertaking not least because his father, Cornelio Fazio was the number one neurologist in Italy. Ferruccio had a good former college friend Gian Luigi Lenzi who was a neurologist training in Sienna with Cesare Fieschi, from the Fazio senior school. Ferruccio encouraged Gian Luigi, who also had an experimental neuro physiology background, to come to London for 6 months in 1976 bringing the needed neurology and physiology input in this project.

Gian Luigi began to study a range of patients including those who had suffered a stroke. Here we showed mismatching at some 2 to 3 week following a stroke in that within the territory affected, oxygen consumption was low compared to blood flow [10].

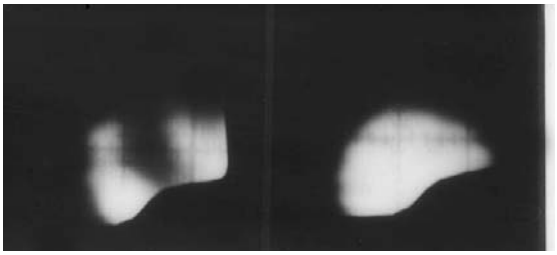


Image recorded during $^{15}O_2$ (oxygen utilization)-left and $C^{15}O_2$ (perfusion)-right of a patient recovering from a stroke resulting from an occlusion of the middle cerebral artery.

This feature of luxury perfusion we were later to document more accurately with the PET camera. Through Cesare Fieschi, Gian Luigi had an introduction to Queen Square and in particular made contact with Professor John Marshall and his research fellow Dafydd Thomas. Through Italian neurology, we entered into a long standing collaborative relationship with Queen Square the principle centre of neurology in the UK. Patients were studied with transient ischemic attack and carotid artery disease. We also investigated dementia patients who showed clear deficits of oxygen consumption and blood flow in the frontal lobes [11]. With John Lumley, a vascular surgeon at Barts, the carotid artery disease programme extended to studying patients before and after external-internal carotid artery bypass [12]

Patients with Parkinson's and Huntington's disease were also studied with John Reid in clinical pharmacology

[13]. There was particular interest at Hammersmith through Tony Pinching and Graham Hughes in using the technique to investigate patients with cerebral lupus [14]. The focus here was to attempt to distinguish between vasculitis and the effects of steriod therapy which in extreme cases can produce psychosis. It was particularly interesting to systematically follow individual Lupus patients over time. On one occasion, we were able to pick up a deficit in regional oxygen consumption some 24 hours before one patient attempted suicide. This qualitative work in lupus resulted in a Lancet publication. Anecdotal changes were also observed in cases of bipolar depression in a collaboration with Dr Benaim at the Royal Free Hospital. A number of papers were written on the various clinical groups studied with this qualitative technique encompassing in total, some 600 patients. The method appeared to offer specificity for studying regional cerebral function but lacked sensitivity due to the absence of quantitation and tomography.

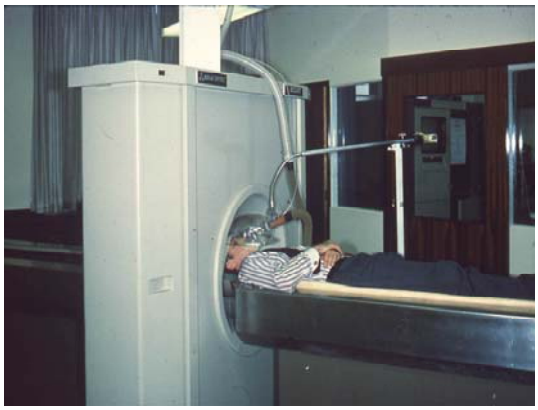
This early experience substantiated the value of metabolic and blood flow imaging and together with our links with Queen Square and our other research work in the lung and the heart, formed the body of a case for applying to the Medical Research Council to purchase a PET camera.
The proposal was to set up in the Unit, facilities to undertake programmes of clinical research based on PET studies. Prior to this, the exploratory work described had largely been undertaken on the Hammersmith site outside the Unit and had been subsumed and protected, during this evolutionary period under the umbrella of the Unit's principal justifications for MRC support. These included undertaking neutron therapy trials, radiobiology and hyperthermia research together with the production of single photon emitting radioisotopes for on and off site use. Over the following ten years, the PET programme was to expand to become the Unit's sole research activity.

The Unit's first PET scanner and quantitative measurements of rCBF and rCMRO2

In the mid seventies, reports were coming in from St Louis of the development of PET scanning using equipment specifically designed by Michael Ter-Pogossion, Mike Phelps and Ed Hoffman to accurately record tomographic data [15] In particular, this reduced the registration of background due to random and scattered coincidences as were present in the earlier Burnham planer camera. A decision had to be made as to which PET camera we would wish to purchase for Hammersmith. For this Ferruccio Fazio and I visited various centres in the States, inhaling radioactive gases and placing our anatomies in various tomographs. We were particularly impressed with the ECAT I camera which was being beta tested at Los Angeles [16]. This had been produced by the ORTEC Company according to a design by Mike Phelps and Ed Hoffman. At LA they and David Kuhl were using it to image 18FDG in the brain which had recently been introduced along with

13NH3 for perfusion. These showed impressive tomographic images.

The case was made to the MRC to purchase a more advanced version of this machine called ECAT II [17]. This was to cost £300,000 and was approved by the MRC in the summer of 1978. Eight members of the Unit visited Orsay in December 1978 to gain insight into their ECAT I scanner where John Claude Baron, who had earlier been at the MGH, had begun to use it for steady state oxygen-15 studies.



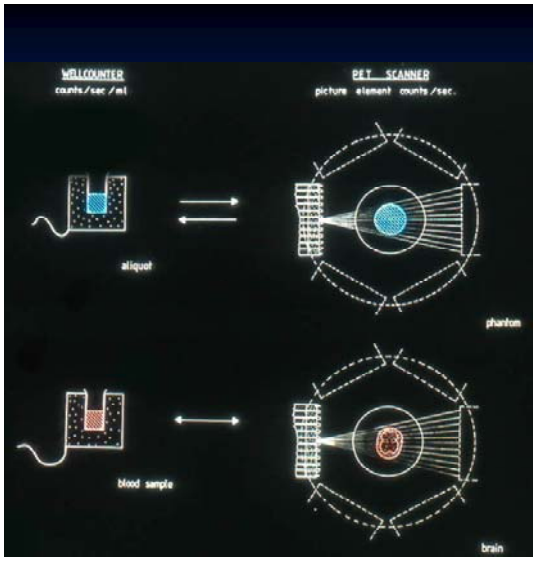
The First PET scanner at Hammersmith being used to image the brain during the inhalation of oxygen-15

The camera arrived in the early summer of 1979. It was a single slice machine, with 66 detectors arranged in a hexagon. Within this array, it was able to record some 121 possible coincidences between individual detectors. Contrast this with the 190 million lines of coincidence which are now possible with the latest generation of tomograph in the Unit. The scanner gantry had to rotate through 60^{o} and the detectors translated tangently to ensure adequate spatial sampling of the field of view. We had also asked that an automatically retractable transmission ring of 68Ge/68 Ga be included, the first of its type to easily undertake transmission measurement.

Our first foray into investigating the physical performance of the new generation of PET scanners was helped through a working visit by Ed Hoffman from Los Angeles. As a principal designer of these instruments and a former colleague when at St Louis, it was possible for us to rapidly gain insight into this new technology. Future visits by Ed when we took delivery of the next two generations of cameras provided, in 1987 and 1990, much appreciated support at the early stages of their testing.

The most revealing initial physical testing of the ECAT II involved scanning objects with quite different attenuation characteristics. These included both a brain sized phantom and a lung phantom in which we used sawdust for the lung cavities. When scanning these quite different objects using the same stock solution of fluorine-18 in the heart and the brain positions, we were excited to find, after correcting for attenuation using the ring source measurement that the pixel counts were within a few percent of each other. This meant that using a uniformly filled phantom, we could calibrate the tomograph's pixel element response against a well counter in which an aliquot of the activity, withdrawn from the phantom, was measured. Hence, whenever recording pixel counts per second in the human brain and corrected for attenuation, one could convert them to those if you had taken a sample of tissue and measured its activity in a well counter. This meant that we could undertake quantitative studies by relating blood concentrations to the

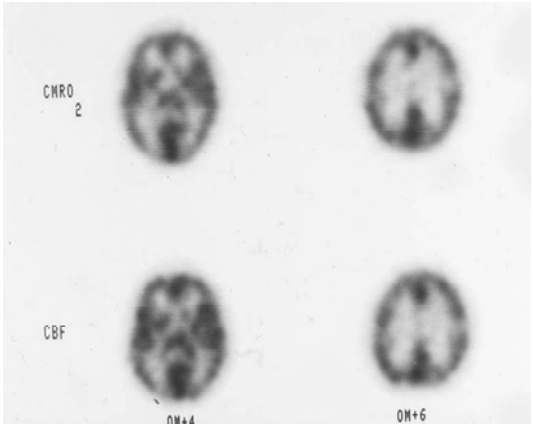
corresponding concentrations, in the human brain. Using appropriate kinetic models relating blood and tissue concentrations, absolute values of tissue function could be determined from these data. In addition, the fraction of an injected dose of activity resident in a ml of tissue could be measured.



The ability to calibrate the pixel element response to obtain absolute tissue concentrations of a positron emitting tracer

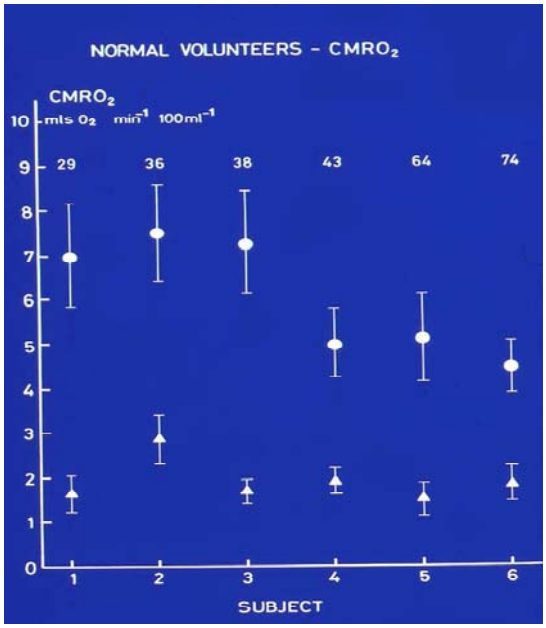
Gian Luigi Lenzi returned to the Unit for a further period to help initiate human investigations with the PET camera and in particular to undertake a study of the long term recovery of stroke patients. A very important step then occurred, namely that of Professor Keith Peters seconding, with financial support from Nigel Legg, Dr Richard Frackowiak to the Unit to help bring on the first quantitative neurological measurements with the scanner. The importance of this step cannot be over emphasised since it brought a neurological presence from the Hospital and from the UK neurology field in general. It ensured that appropriate questions were being asked and the results communicated to the neurological community in the country. In undertaking this role, Richard was heavily committed to developing quantitative methodology.

If one examines the underlying model of steady state oxygen 15 breathing, it can be seen that the signal recorded has contributions from not only the locally generated water metabolism but also from radioactivity in the blood and in particular recirculating labelled water of metabolism. By combining serial 15O2 and C 15O 2 breathing along with arterial blood sampling, in which assays are made of whole blood and plasma concentrations, it is possible to correct for the recirculating water of metabolism. Later, C15O inhalation was added to correct for the intravascular activity. After correcting for these contaminants, it is then possible to solve the underlying steady state kinetic models to derive absolute values of tissue blood flow and oxygen utilisation. Correcting the recorded data for attenuation, using the transmission source, allowed each pixel value in the image to be solved to produce absolute values of blood flow and the cerebral metabolic rate for oxygen. These were displayed as parametric images of flow and metabolism the computation of which were undertaken by Jon Heather.



Parametric transaxial images of cerebral metabolic rate of oxygen ($CMRO_2$) and Cerebral Blood Flow (CBF) at the levels of 4 & 6cms above the Oribital-Meatal (OM) line.

By the end of 1979, it had been possible to study a series of normal volunteers from whom arterial blood samples were withdrawn during steady state procedures. This required appreciable commitment by Richard to recruit volunteers and withdraw arterial blood samples through femoral artery puncture. When analysed, the normal series showed that the values for grey and white matter blood flow and oxygen consumption were of the right order of magnetude



First quantitative values recorded at Hammersmith of Cerebral Metabolic Rate of Oxygen for six normal volunteers between the ages of 29 and 74yrs for grey and white matter (lower values)

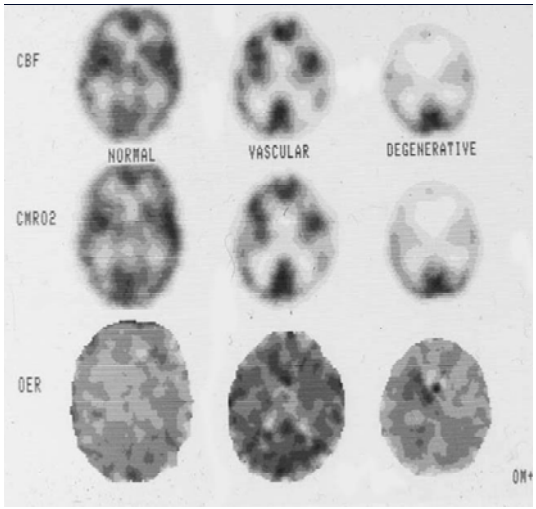
Confidence in our results was endorsed by Neils Lassen who visited the Hammersmith in November 1979. It needs to be said that we were not alone in developing the steady oxygen-15 state method to produce quantitative data. At Orsay, where they had installed a PET camera before us, John Claude Baron had begun femoral arterial blood sampling in 1978.

A further study of the accuracy of the technique came from investigations in the dog brain undertaken by Chris Rhodes, Gian Luigi Lenzi and Richard Frackowiak. This involved changing the arterial carbon dioxide concentration in the dog. An increase of PCO2 will result in an increase in blood flow in the brain due to vasodilation where as brain metabolism should not change. It was shown that as blood flow increased, the oxygen extraction ratio dropped keeping the CMRO2 constant, as should be the case [18]. This methodology was highly practical in that it did not require the formulation of tracers for injection, they were quite simply administered by breathing. Hence we had quantitative, sensitive and specific measurements of regional cerebral function available as research tools for neurological investigations [19].

Clinical research using the quantitative steady state oxygen-15 method for measuring regional brain metabolism and blood flow

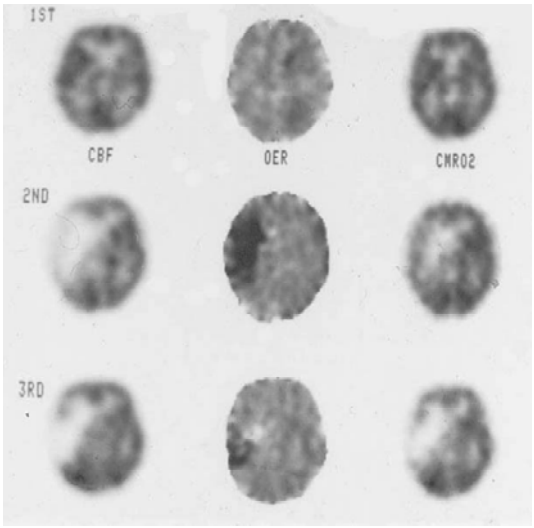
The first clinical series was undertaken by Richard Frackowiak who studied patients with multinfarct and Alzheimer's dementia. The hypothesis was that in some cases we would expect

to observe regional ischemia, a hallmark of which would be a raised oxygen extraction ratio in the presence of reduced perfusion. However, this did not prove to be the case in that the oxygen extraction ratio for both types of dementia was the same as the controls. However, it was clearly shown, in both categories of dementia patient, that oxygen consumption and blood flow were both reduced in a coupled way. Richard helped by with Carlo Pozzili also showed, for the first time, the now classical sign that in early Alzheimers, the pariatal regions are first affected [20]. Gian Luigi initiated a study following the long term recovery of stroke patients [21].



Patterns of regional cerebral deficits of CBF and $CMRO_2$ in vascular and degenerative dementia. The regional oxygen extraction ratio (OER) remains normal

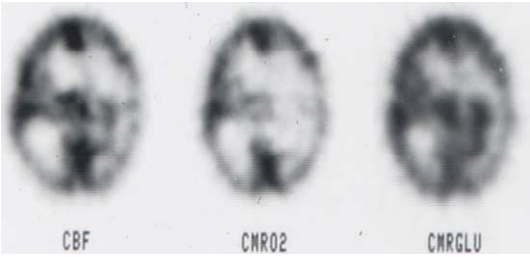
It was not until the studies into acute stroke of Richard Wise, who joined the Unit in 1980, did we see clear examples of mismatching between flow and metabolism. He and Richard Frackowiak were able to study patients with this condition within the first day or so after the stroke. This showed that the oxygen extraction ratio is raised within the periphery of the affected area indicating that the tissue was still metabolically active in the presence of reduced perfusion. However, when repeated after 3 or 4 days, it was shown that the oxygen extraction ratio fell, due to a drop in metabolism. This observation has since been constantly referred to and has provided the stimulus to try and improve cerebral function during the acute phase of stroke recovery despite it being after the ictus [22].



Patterns of regional cerebral deficits of CBF and $CMRO_2$ in the days following an acute stroke. The regional oxygen extraction ratio is raised in affected area within the first few days and returns to normal soon after.

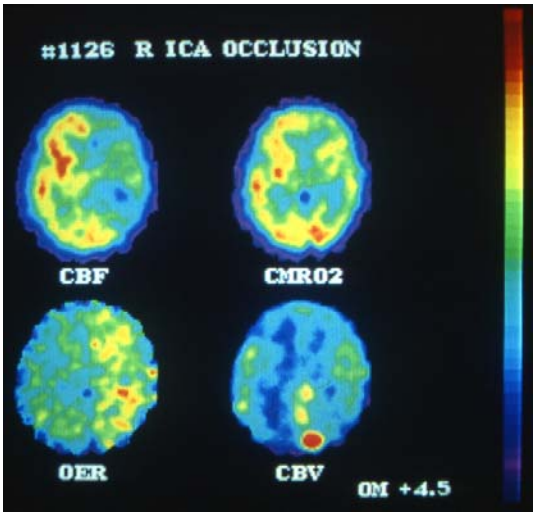
Another example of mismatching was shown in cerebral tumours where, in addition to the steady state technique for oxygen metabolism and blood flow, we had introduced the glucose metabolism method using 18FDG. It was shown by Chris Rhodes, Richard Wise, Masatoshi Itoh and Mr David Thomas from Queen Square that gliomas have relatively low oxygen consumption in comparison to blood flow and glucose utilization [23, 24]. This underlies the preferential

glycolitic activity of tumours and some 18 years after this observation was first undertaken, there is now widespread enthusiasm for using 18FDG to locate neoplasms. This glucose:oxygen utilization relationship was also studied by Richard Wise in recovering stroke patients indicated the presence of macrophages within the post affected area [25].

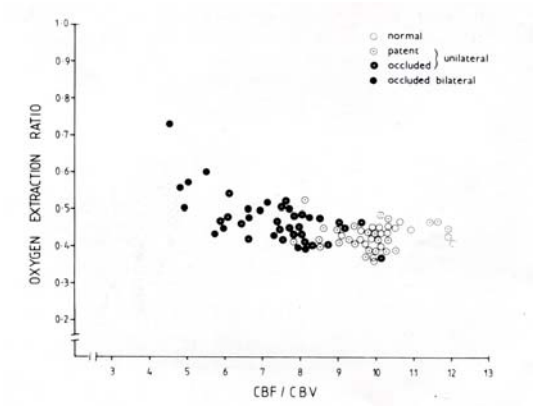


Perfusion, oxygen and glucose utilization in a grade IV astrocytoma demonstrating glycolosis.

Adriaan Lammertsma had joined the Unit in 1979/80 and in a systematic, Adriaan like, fashion improved on the steady state 15O technique [26, 27]. It was realised that, where there is low oxygen extraction, radioactivity within the vasculature would be an important contaminant in tissues He therefore introduced the breathing of carbon-11 monoxide to provide a vascular tracer and as a consequence, produced new, lower normal values for the oxygen extraction ratio [28, 29]. This extended methodology proved fruitful in the work of Jeremy Gibbs who was studying carotid artery diseased patients. It is worth noting, that Jeremy was actually funded out of one of the first commercial drug company studies, sponsored by Abbot, to investigate the metabolic effects of one of their pharmaceuticals. He showed that in extreme cases of arterial occlusion, oxygen extraction ratio was raised. However, in less severe disease, the ratio of regional cerebral blood flow divided by blood volume was decreased. This indicated that in the early stages, the vasculature of the brain dilates to compensate for the occlusion in the arterial supply in order to maintain perfusion rate. It was only when the brain's vasculature becomes fully dilated, in the presence of extensive occlusion, that the brain tissue begins to extract more oxygen as shown by a rise in the oxygen extraction ratio [30].



Right internal carotid artery occlusion resulting reduced left hemispheric perfusion (CBF) and an increased oxygen extraction ratio (OER) to compensate for reduced delivery

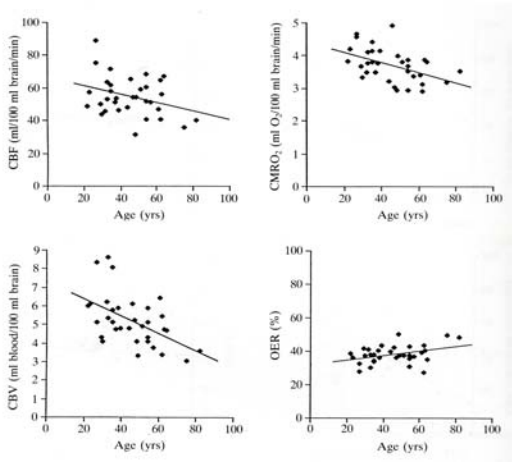


With increased severity of carotid artery disease the CBF/CBV ratio decreases. In extreme occlusive disease the OER begins to rise to compensate further for the reduced oxygen delivery

A whole series of diverse clinical research studies were subsequently carried out using this quantitative, sensitive, specific and very practical method which had evolved to using radial artery sampling through an indwelling catheter. The case for this now routine procedure was championed by Richard Frackowiak working with the local ethics committee.

Other studies, carried out using this methodology were:

Drug naive schizophrenia [31] (Graham Shepard and Stevan Hirsch), multiple sclerosis [32], hydrocephalus [33, 34] (David Brooks), sickle cell anaemia [35], autism [36], migraine, cerebral haemodynamic reserve [37] and the effects of brain revascularisation using omental transposition [38] (Sigrid Herold), mitochondrial cytopathy [39] (Richard Frackowiak), epilepsy [40, 41] (Silvia Bernardi Gallhofer and Mike Trimble). Parkinsons [42] disease and the effects of L-Dopa [43] (Nico Leenders and Les Wolfson), cerebral edema [44], and decompression [45] and dexamethazone [46] effects in brain and the effects of cranial irradiation of pituitary tumours [47] (Ron Beaney, Nico Leenders and David Brooks) and diaschesis in stroke patients [48]. These studies extended to normal ageing which showed a reduction of flow, oxygen utilisation and blood volume with age and a slight increase in the extraction ratio [49] (data compiled, at a later date, by Nico Leenders and Daniella Perani).



Variations with age in cerebral perfusion (CBF) Oxygen Utilization ($CMRO_2$), Oxygen Extraction (OER) and blood volume (CBV).

This programme of research demonstrated that metabolic imaging of the brain was firmly established in the UK through the use of this methodology. Central to this acceptance was the ability to communicate the novel data in quantitative physiological units that were easily understood by the neurology community.

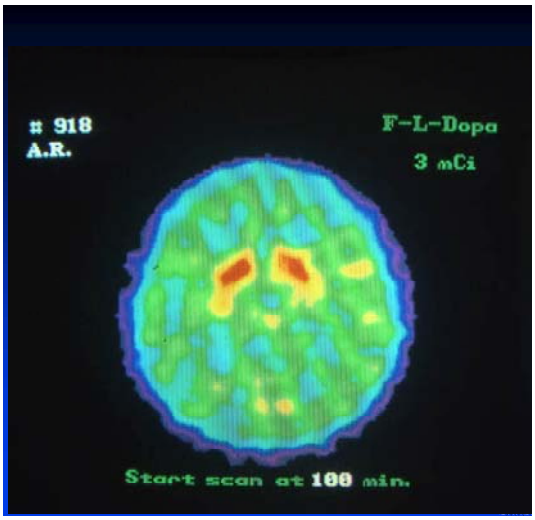
Early non flow and metabolism studies

Other techniques for studying the brain were introduced in the early eighties. The arrival of David Brooks in 1983 to undertake research on blood brain barrier transport resulted in the steady state use of rubidium-82, a 78 second half-life isotope, to investigate cation leakage across the barrier in a range of clinical conditions [50, 51]. David extended his studies to the use C-11 labelled methyl glucose which is not metabolised but provides a measure of glucose transport to investigate changes

in diabetic and brain tumour patients [52, 53]. This was one of the earliest examples of kinetic analysis which he and Adriaan Lammertsma undertook using a fitting package called BLD produced by Richard Carson in Los Angeles and later at the NIH. It provided a means for deriving the classical rate constants we now measure and use extensively. David also used this analysis when undertaking studies of brain tumour pH using the continuous inhalation of 11CO2 [54]. 11C-labelled albumin was together with 11CO – labeled red cells also used to measure the haematocrite of normal brain and tumour tissue in order to ensure the blood volume corrections made in the steady state method were accurate [55, 56]. The accuracy of the steady state blood flow method was verified by imaging the brain of cardiac patients who had 11C-labeled microspheres injected into their left ventricle by the cardiologist developing methods to image myocardial perfusion [57].

Early Neuro transmitter studies

In 1983, we began to think about being able to image neurotransmitter activity.We had in the Unit Les Wolfson, a visiting worker from New York. Les stressed that there would be considerable interest in being able to study the dopaminergic system in the brain. He had previously undertaken autoradiographic studies in rats showing the incorporation of L- dopa in the striatum. We were aware that Dr Steve Garnet at McMaster University, Canada had been attempting, over the previous years, to label L-Dopa with reactor produced fluorine-18. Although Steve appeared to have been relatively unsuccessful, Nico Leenders was encouraged to telephone him to update us on developments. This coincided with what had turned out for the McMaster group to be a breakthrough in the radiosynthesis. Indeed, a few months later they published their observations in Nature of using F-18 labelled L-Dopa in man. Nico Leenders and John Clark went to McMaster and persuaded the radiochemist, Gunter Firnau to come to Hammersmith to help Tony Palmer, set up the synthesis of 18F-L-Dopa. We soon became the first centre outside of McMaster to use this radiotracer.

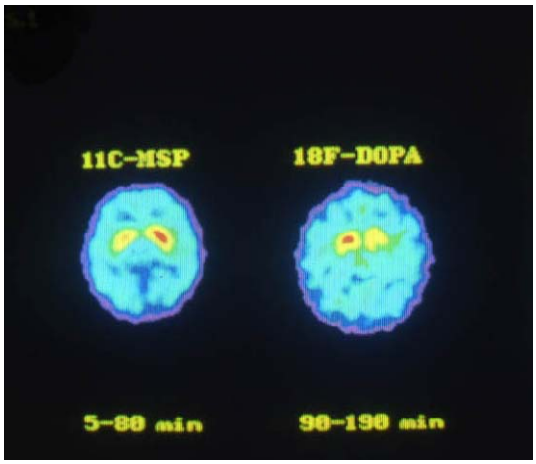


The first ^{18}F-L-Dopa scan done at Hammersmith

Encouraging results were obtained in imaging uptake of L-Dopa in Parkinson's disease [58]. This forged a very important link with Professor David Marsden, the UK's foremost movement disorder neurologist, which extended, over the coming decade when he became

head of the Institute of Neurology at Queen Square.

During this time, there was also interest in being able to measure D2 receptors in the brain. The stimulus for this came from Dr Tim Crow at Northwick Park. He had formulated the Dopamine theory of schizophrenia and together with Normal Veall and Jo Zanelli constantly met with the Cyclotron Unit staff to stimulate the synthesis of ligands for imaging the D2 site. In 1983, a report came from the John Hopkins of using 11C-methylspiperone where it had been synthesised by Bob Daniels and Bengt Langstrom when visiting there. Dave Turton in the Unit was soon able to synthesis this tracer and we were then in a position to study both presynaptic (18F-L-Dopa) and postsynaptic D2 activity using 11C -methylspiperone although this is both a D2 and seratonergic receptor marker [59]. It was interesting to undertake paired imaging studies in hemidystonic patients. These showed clear mismatching between the low uptake of 18F-L-Dopa on one side of the basel ganglia with an increased binding of 11C-methyl spiperone due to the compensatory up regulation of D2 receptors [60].



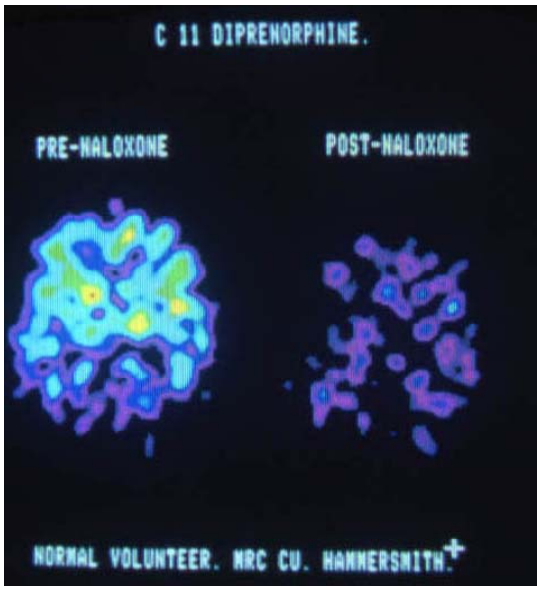
Mismatching in a hemidystonic patient between pre-synaptic (18F-Dopa) and post synaptic (11C-Methyl Spiperone) dopaminergic activity.

Sigrid Herold studied schizophrenic patients using 11C-methylspiperone, and ratioed the uptake in striatum to that in the cerebellum as a reference tissue. This required moving the patient up and down the bed during the dynamic study. No difference was seen between uptake in the striatum of schizophrenics to that of normal subjects, a finding that did not substantiate Tim's theory [61].

It should be pointed out that although today in the Unit, there are some 60 SUN work stations in use for image analysis, in the early eighties there was only one off line image analysis system which was a duplicate of the scanner consul. Time had to be booked on that workstation for analysing data. This was not quite as restricting as it might seem since most of the data was printed out as matrices of numbers on sheets of paper. These could be taken away to analyse with a pocket calculator at one's leisure! Although this may seem unpractical, it should be remembered that the PET camera was producing very few planes of data for analysis.

A novel area of neurotransmitter study undertaken was that of the opiate receptors. Anthony Jones had come over from St Bartholomews and was keen to study changes of regional cerebral opiate receptor density in the presence of pain. A search was made for a suitable ligand with a false start arising from the use of 11C- meptazinol. Anthony was then able to identify diprenorphine, produced by Recketts and Coleman, as a potential candidate. Vic Pike and Jindy Luthra

undertook some quite difficult chemistry to label this ligand and it was shown in a normal subject, before and after a blocking dose of naloxone, that we had a specific opiate receptor signal within the recorded images [62].



The last PET scan before the decommissioning of the original cyclotron which demonstrated the specificity of 11C-Diprenorhene for the opiate receptors by prior blocking with Naloxone.

A two year hiatus in the Unit's PET programme and its re-start

In May 1984, there occurred an event which resulted in an hiatus in the Unit's PET programme which lasted nearly 2 years. The old home built cyclotron was to be replaced by a modern machine and also the foundations under the pillars of the building needed replacing. These had been found to be crumbling due to the use of high alumina, fast setting cement. The case for the considerable funding needed for both the new cyclotron and building restoration came from the successful MRC sub committee visit to the Unit in 1981 when the emerging strengths of the PET programme and its perceived future longevity were made apparent. We had known about these two major changes for 3 years and therefore had time to plan for this gap in research.

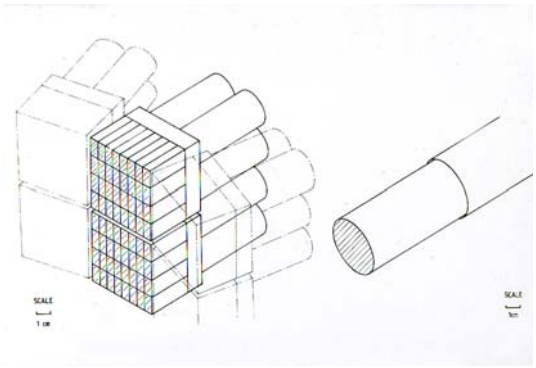
Decommissioning the original cyclotron

Underpinning the Cyclotron Unit building

Most worrying was the loss of continuity which is so central to a research institute where know how is handed on to successive generations of visiting workers. It was important to ensure that we would hit the ground running when the scanning programme restarted. This involved a strategy to place individuals at other international PET centres to gain new insights. As a result, individuals

went to Los Angeles (Adriaan Lammertsma, Luis Araujo), CTI (Jon Heather), Uppsala (Nico Leenders), Orsay (Anthony Jones, Jindy Luthra, and Vic Pike), Pisa (Terry Spinks), Lund (Chris Rhodes) and Tohoku University (Frank Brady).

We were keen that the Unit should have the most advanced PET scanning facilities, thereby realising an advantage when catching up with other centres. To this end, I visited the CTI company, a spinoff from ORTEC, in the autumn of 1984, to identify what might be the next generation of scanner technology. Ron Nutt, the vice president of the newly formed company, showed me a prototype of an idea he had, together with Mike Casey, for assembling an array of 32 BGO crystals, surveyed by only 4 photo multipliers designed to give both high axial as well as transaxial spatial resolution. This immediately struck a chord in that having experience in surveying structures with such complex 3-D anatomy as the basal ganglia, one had already been thinking of the need for such arrays. The array of detectors, was promptly called a block, a name that has stuck ever since [63].



The detector mosaic in the block compared to the detector of the first PET scanner depicting the higher transaxial and axial spatial resolution

This detector technology was revolutionary and formed the core for future generations of PET scanners. The blocks were to be arranged in a circle hence there would be no need to move the scanner to survey the brain and would be compatible with recording fast kinetic data. Retractable ring sources were also to be built into the tomograph.

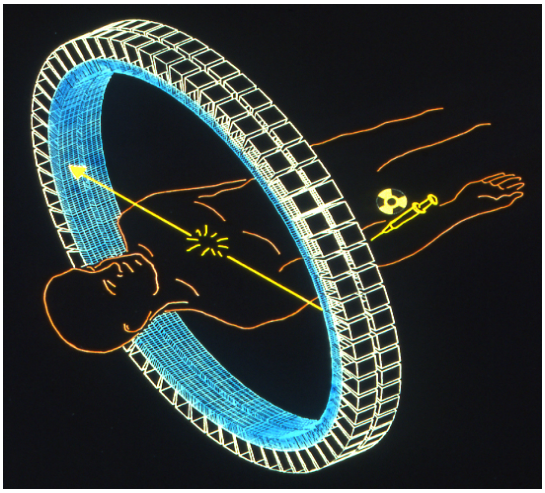
A case was made to the MRC in 1984 for installing, what would be the first of these devices. This was strengthened by the fact that Richard Frackowiak had been recruited back to the Unit to head up the neuroscience programme, a recommendation from the 1981 MRC review of the Unit. This case was approved and through stalwart support from Diana Dunstan at MRC Head Office, £2 million allocated for its purchase. The time between approval, at the beginning of 1985 and the delivery of the scanner in March 1987 indicates the level of preplanning that was necessary to ensure that the Unit would be receiving the first of the generation of the new cameras at the time of start up following the shut down. The new cyclotron was installed as were also a series of hot cells which enabled John Clark and Peter Horlock to introduce new computer controlled automated radiosynthesis. Prior to this, the radiochemistry and engineering groups headed by David silvester had to bring on line the new cyclotron and all the ancillary beam lines and target holding facilities necessary to create a flexible operational PET programme.

New administration

The build up to the retirement in 1996 of the Unit's director, Mr Vonberg, created something of a disarray since the MRC could not decide on a future replacement. At the prompting of Mr Vonberg, I was able to suggest to Sir Jim Gowans, the head of the MRC, that may be a scientific administrative person from MRC head office would be a suitable candidate as an administrative director. This was accepted and immediately unblocked the log jam on this decision with Dr Keith Gibson, a former biochemist who knew the Unit well, being appointed as administrative director. Terry Morris was also brought from head office as Keith's assistant manager. Subsequent to that Richard Frackowiak was made assistant director, clinical and I was made assistant director, scientific.

This administrative/clinical/scientific structure was extremely productive and allowed us to cut through of a lot of bureaucracy with Keith and Terry forging productive links with head office's administration; a model later taken up more widely by the MRC. One example was the purchase of a network of SUN computers. CTI had no equipment available for off line analysis and we were left to devise our own strategy for this. We were fortunate that David Townsend from Geneva was in the Unit for a period in 1987. He had heard Richard Robb from the Mayo Clinic talk about his SUN computer based new Analyse system for image processing which he was prepared to make available to academic institutes. In addition, CTI had surveyed the work station market and recommended that SUN was a "promising new company "in this field. Terry Morris was then able to make some quite "constructive deals" in purchasing the first group of Sun computers setting up the Sun lounge for image data analysis on the first floor. Finally software needed to be developed by Jon Heather to transfer CTI ECAT 931 data to ANALYZE format - JDH transfer. The work stations, operating ANALYZE and since maintained by Ralph Myers represented a considerable methodological advance for research.

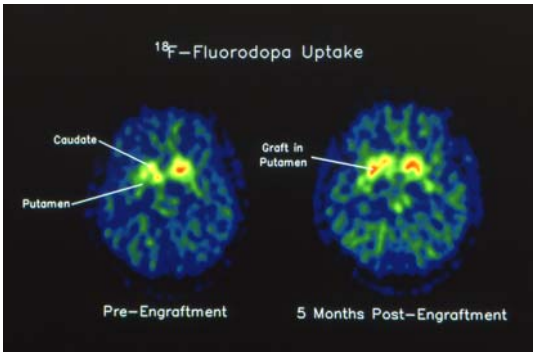
Studies with the new generation of block based PET camera



The spatial coverage with the new block based PET scanner and ability to record kinetic data

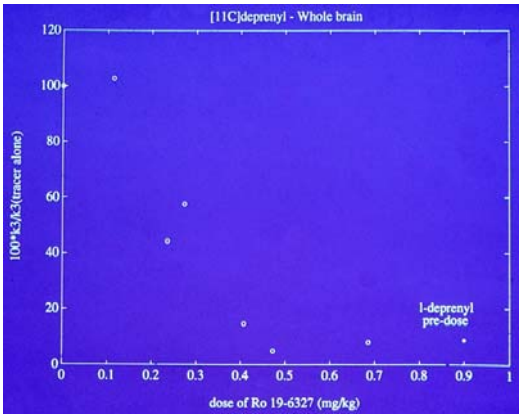
The physical performance of the PET camera was examined by Terry Spinks and Chicca Gilardi from Milan [64]. Early studies by Pippa Tyrrell, supported by Martin Rosser, of blood flow and oxygen utilisation in dementia [65] and Vitorio DiPiero in stroke [66], revealed the value of high axial and transaxial resolutions. Also, early studies of 18F-L-Dopa and 11C-raclopride demonstrated how the striatal tissue could be surveyed

in detail axially. This became extremely important in the collaborative programme set up by Richard Frackowiak, Nico Leenders and David Marsden with the pioneering foetal striatal transplant team based in Lund in Sweden. It resulted in being able to follow individual patients for months and years using 18F- L-Dopa. Because of the multiplane axial data sets taken over the striatum, it was possible when analysing serial data, to realign corresponding planes taken on different occasions [67]. The momentum behind the basel ganglia studies was provided by Nico Leenders, Guy Sawle, Pippa Tyrrell, Eric Salamon and David Brooks who had been attracted back to the Hammermsith [68].



The use of ^{18}F-L-Dopa to demonstrate viability of striatum engraftment

Our earliest commissioned dose ranging studies with the pharmaceutical industry involved the use of 11C-deprenyl, an MAO-B inhibitor. This was carried out by Chris Bench and Gary Price and indicated the future potential for collaborations with the pharmaceutical industry [69].



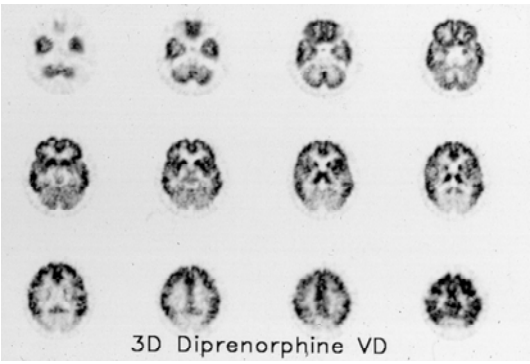
Seven normal subjects with increasing levels of drug administered finds the blocking dose

The chemists set up in the new hot cells, routine productions of 18F-L-Dopa, 11C- raclopride,

11C-nomifensine [70] and 11C-Schering. The last two, together with 11C-deprenyl, were the result of Nico Leenders' experience of working at Uppsala .

Further refinements in technology/methodology involved setting up on-line blood counting using BGO detectors which Alex Ranicar was active in establishing in collaboration with CTI. This led to introducing non stick, teflon tubing to prevent retention of tracer on the monitored blood line [71]. A great deal of consideration was given as to how we could set up a blood plasma metabolite analysis facility. Here Vic Pike and Jindy Luthra, along with Safiye Osman and Alex were active in establishing this. The newly formed biology group, headed by Jill Cremer brought extra impetus and know how to establishing these procedures [72]. A very sensitive on-line scintillating bead detector introduced by John Clark and Dave Turton, was a big advance for assaying low concentrations of labelled metabolites. The earlier work on 11C-

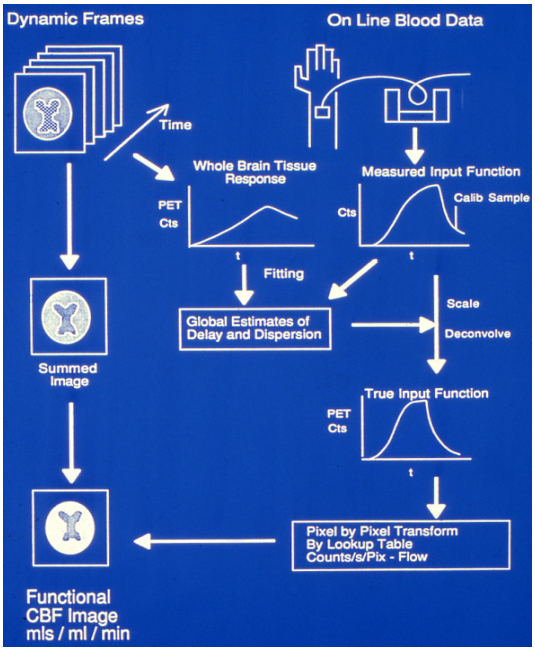
diprenorphine, which had been carried on at Orsay by Vic Pike, Jindy Luthra and Anthony Jones during the shutdown, came good in 1989. Anthony's return to the Unit was a follow on from the earlier pioneering work where a 11C-diprenorphine study was the last investigation made with the old cyclotron. With the high resolution camera, one could observe the detailed typography of opiate receptors in the human brain along with the differences in kinetics for the respective cerebral tissues of ranking opiate receptor densities [73, 74].



Parametric images of ^{11}C-Diprenophine with the new PET scanner

These data underpinned Anthony Jones' pain research and initially were extended to studies of epilepsy through John Duncan and Peter Bartenstein.

Adriaan Lammertsma and Vin Cunningham established a dynamic method for measuring regional cerebral blood flow based on kinetic recording of H215O data and the arterial input function. They refined the integrated uptake look up table method, initially undertaken by Iwao Kanno from Akita in the Unit using the ECAT II camera [75]. From this they were able to derive, functional, parametric images of regional cerebral blood flow [76].



Data recording and processing to derive functional parametric images of regional cerebral blood flow (CBF)

Andrew Dean, a medical student from Oxford was the first to stimulate interest in studies of cerebral activation and it was he who introduced us to Semir Zeki, who stimulated studies of the centre of colour vision in the cortex. Visiting workers Dr Jay Nutt from Portland, Oregon, Dick Passingham from Oxford and Jim Colebatch from Sydney were attracted to the Unit and helped initiate a systematic exploration of regional cerebral activation studies based on blood flow measurements. Using the technique of Lammertsma and Cunningham, it was possible to demonstrate changes resulting from fairly strong activations due to motor movements. However, the analysis of these were subjective, tedious and it was not possible to comprehensively examine the brain data for activation foci.

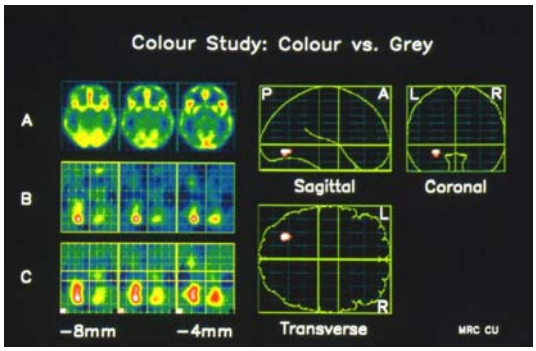
The birth of SPM

There occurred a very important step in methodology for the Unit. Dr Peter Liddle, a psychiatrist with a PhD in nuclear physics, had, since 1986, been building up the case for undertaking a study of regional cerebral blood flow and oxygen metabolism in schizophrenia. He hypothesised that schizophrenics fell into three categories which would be revealed as regional neurofunctional differences using PET and the steady state oxygen-15 method. He established himself in posts at Charing Cross and St Bernards and was able to obtain a Wellcome grant to fund this programme. Two candidates were interviewed, to undertake this research. One was a well turned out individual, who seemed a reasonable candidate. The other, although it was early summer, presented himself wearing a long camel coloured overcoat. This was Karl Friston. Peter had known Karl when they were both at the Oxford department of psychiatry and although he interviewed modestly, he clearly was the stronger candidate. Karl soon gathered data on a total of 30 schizophrenics and set about its analysis. I then received a paper to referee from St Louis where they had been pioneered regional cerebral blood flow activation studies using PET. To analyse focal changes registered during activation they had introduced a statistical approach operated within a standard anatomical framework. Although this may have helped stimulate his thoughts, Karl clearly had been thinking along similar lines to analyse his data. He was well equipped to address statistical issues since he had earlier undertaken a degree in quantum mechanics at Cambridge. He came up with the concept of Statistical Parametric Mapping (SPM) [77] which exploited the detail with which the new tomograph was able to provide high transaxial and axial data to survey the brain. This was a major breakthrough in that it analysed data sets for focal change by defining the statistical variance for the whole of the brain data. It allowed regional changes to be identified over and above the mean statistical variance for the brain.

There was some confusion and resistance in the Unit to such a radical concept. The more dyed in the wool, quantitative campaigners thought this was a deviation and healthy rapour was had when grasping the concept of SPM. It was nevertheless truly quantitative in that it defined precisely, in brain space, where activations were statistically significant. This line of analysis lead to a relaxing of the need to derive absolute values of regional cerebral blood flow and thereby avoid the need for arterial blood sampling. The reasoning was that if the focal activations were not statistically significant in the raw H215O uptake data, they would not become so in the parametric quantitative blood flow image, the derivation of which tended, if anything, to amplify noise. Statistical analysis of the primary data was a simple, yet very important shift of methodological emphasis since it made the procedure less invasive and hence more widely and readily available. Richard Frackowiak was a strong supporter of Karl's new ideas and together with Jon Heather’s computer support, helped introduce them widely within the brain research programme .

SPM mapping was used early on in the pioneering work of Semir Zeki in identifying colour centres in the brain

resulting in the Unit's first Nature paper on this subject [78].



Statistical Parametric Images (SPM) of the colour centre in the brain

The power of SPM and simplifying the means for studying focal activation attracted many workers to the Unit. This included, Richard Wise who came back for research sessions along with people like Francois Chollet, Ray Dolan, Chris Frith and many others. Chris Frith's interest in schizophrenia were to be reinforced by that of Peter Liddle and Karl Friston. It is pleasing to learn, at time of writing, that Chris has just been elected as a Fellow of the Royal Society based on his schizophrenia research which included imaging. Ray had been attracted through his interests in depression and was able to fund the work of Chris Bench. It needs to be noted that it was Ray Dolan who first made the case for studying serotonergic receptors in depression. Early attempts of this using 11C-citalopram, a re uptake blocker, were unsuccessful but later Vic Pike seized the opportunity, in collaboration with the Wyeth Company, to label the highly successful ligand -Way- 100635 to study the 5HT1A receptor [79].

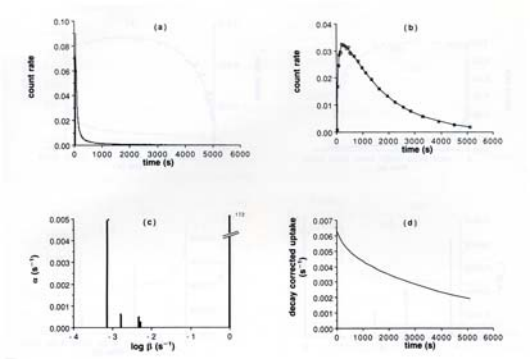
Initiating PET biology

Around 1987, another important methodological strategy was introduced by creating a basic biological support for the PET programme. The radiobiological and hyperthermia work headed by Stan Field was closed down and the biologists, Ralph Myers, Susan Hume, Randy Ahier, Luisa Manjil and Beulah Cullen, seconded to create a PET neuroscience biology group. It was also possible to attract Gary Price, a pharmacologist, to work in the team supported by the drug company MSD. The group was headed by Dr Jill Cremer who, together with Vin Cunningham, had moved across from the MRC Toxicology Unit at Carshalton. They were both very familiar with measurements of regional cerebral glucose utilisation using deoxyglucose and Jill was extremely competent at setting up the laboratory to carry out systematic *ex vivo* studies in animals. Two examples epitomised the value of having such basic biological support. These include Ralph Myers researching the nature of the PK 11195 signal in an experimental acute brain ischemia model. He demonstrated that this signal emulates from the activation of microglia and macrophages [80]. This helped develop the pioneering programme it has become in subsequent years attracting from Munich, the commitment of Richard Banati. Secondly, the detailed *ex vivo* analysis of diprenorphine in rat brains, coupled with competitive challenges to understand the recorded signal, resulted in the formulation of a kinetic model which Vin Cunningham then went on to analyse human data recorded within Anthony Jones' pain programme [81].

Analysis of kinetic data

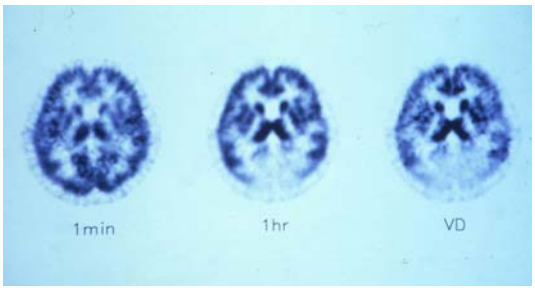
The ability to record high temporal resolution PET data with the new ring camera brought with it the challenge of kinetic curve fitting in the form of compartmental analysis. A mathematical tool box had to be selected for such generic studies. Here Adriaan Lammertsma committed the Unit to adapt Mat lab which has proved to be an important decision for formulating subsequent analytical routines including the SPM work of Karl Friston. Compartmental kinetics analyses developed by Adriaan and Vin were also extended to curve fitting whole blood plasma and metabolic data.

Vin also introduced the spectral analysis technique for analysing data which, in simplistic terms, represents a generic deconvolution method allowing the response of the tissue to be derived independently from the shape of the input function [82].



The derivation of the impulse response function of a tracer in tissue from the tissue and plasma input time courses using a series of exponential components

He was able to extract from this response, parametric images of, for example, 1min or 1hr uptake and volumes of distribution.

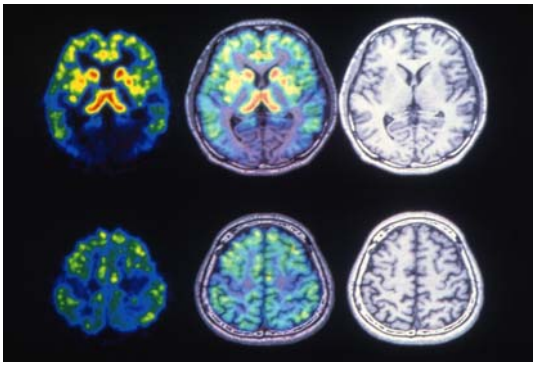


Spectral Analysis derived parametric images obtained for ^{11}C-dprenorphene

These integrated the whole statistical power of the recorded time course of activity. By offering high resolution parametric maps of opiate binding, it was possible to use this within SPM which not only Anthony Jones but also Robert Weeks, Nora Turjanski and David Brooks exploited in studying focal changes in Tourettes syndrome [83] and Huntingdon's disease [84].

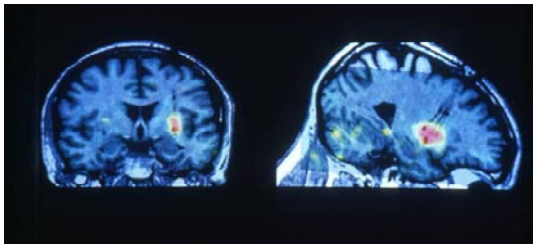
Co-registering PET and MRI

The co-registering of functional PET data with anatomy such as that offered with MRI was a large challenge. One approach, developed in Chicago by Pelezzaris; the head and hat technique, was found not to be very reliable. A new method, developed by Roger Woods at Los Angeles was implemented with his help [85]. This led to Ralph Myers setting up routines to accurately coregister functional brain images with MRI data.



Co-registering PET (^{11}C-diprenorphene) with MRI

The value of this was epitomised in Guy Sawle's study of the uptake of 18F-F-Dopa in brain transplant patients [86]. Here coregistration of a patient's individual neuroanatomy, including the tracts of the implantation needles, clearly delineated the anatomical localisation of the viable functioning graft as assessed with PET.



Co-registering 18F-L-Dopa with MRI in a patient who had undergone striatal engraftment; with the needle tracks shown

Operational support

At this juncture in this historical survey, it is important to acknowledge the contributions of unsung heroes in bringing forward methodological developments. The described new initiatives represented only the tips of the activity of the Unit since without considerable operational support, their development and exploitation would not have been possible. This includes the commitment of the cyclotron team, headed in earlier years by Geoff Burton and since 1987, by Bruce Mackay and Mike Renton in providing flexibility of service. The radiochemistry team provide what became the largest PET programme in the world with respect to the production of a wide range of radiotracers for regular patient studies. This was made possible by the automated hot cells set up by John Clark and Peter Horlock carried out operationally by David Turton, supported by the quality control laboratory headed by Steve Waters. Ian Watson has, over many years, played a central role in juggling the programme to maximise the radiochemistry output for PET scanning. To help in this balancing exercise he has been supported by a series of radiographers; Claire Taylor, Graham Lewington and Andy Blyth Together, they have met the clinical demand as well as accommodating and refining new procedures. Blood lab facilities have also been centrally important with Alex Ranicar setting up this programme, initially using gap year students and now run by Safiye Osman who heads both research and routine metabolite analysis.

Over the years, we have introduced a number of first in the field, new generation of PET scanners which have produced challenges to handling large volumes of data often ahead of what was available for computing and storage. Here Jon Heather, John Ashburner and Peter Bloomfield have played a central role in introducing new initiatives for data handling and overcoming many logistical computational problems. This

has extended through the work of Leonard Schnoor, Dale Bailey, Mike Prior and Cristina D'Oliveria in consolidating ways of handing this data through efficient computer processing, storage and networking. The introduction of the new tomographs would not have been possible without the close collaboration over the years with individuals firstly at ORTEC And then the CTI company. These include Ron Nutt, Mike Casey, Larry Byars, Bill Jones, Johnny Read, Chuck Williams Andy Holley, John Hoffman, Raymond Roddy, Mark Andreaco, Charles Watson, John Young, Mike Crabtree and Cliffreda Hitch.

The calculation of radiation doses received by subjects undergoing PET studies are essential for defining the protocols and seeking permission for the respective research programmes. Here, Ken Butler, Brian Page and John Parnell have provided the necessary estimates, supported at a distance by Terry Smith, formerly at the CRC at Northwick Park.

Last, but not least, has been the stalwart effort of the Unit's receptionists, Ivy Temple, Ann Peers, and Roy Budd in arranging the transfer and receiving of subjects brought to the Unit for PET studies. This co-ordination has been most important for the tightly arranged programme using rapidly decaying radioactivity.

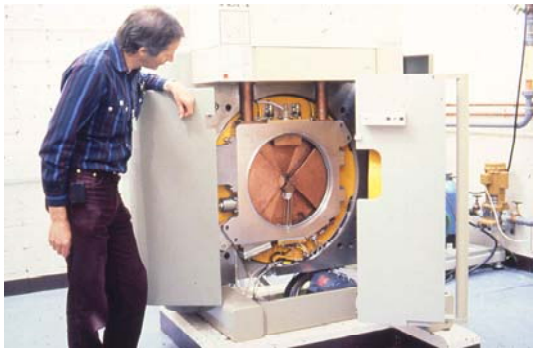
A second cyclotron solely for oxygen-15 and the H215O generator

By way of illustrating advances at a practical level, in 1991 the Unit installed a second cyclotron solely for the production of oxygen-15. It had been projected as early as 1989 that the demand for 15O was going to conflict with production of 11C and 18F by the main cyclotron. The second machine, a cyclone 3-D cyclotron from IBA, was a prototype which was installed in the Van der Graaf tower.

Delivering the 3Mev deuteron cyclotron into the Van der Graff Tower

It was financed as a result of a drug contract study undertaken by Chris Bench. Although relatively cheap, it was necessary for Bruce Mackay, Mike Renton and John Clark to invest a

considerable amount of effort in making it into an operational device for clinical use.



The 3 Mev cyclotron is quite small compared to the Unit's 40 Mev machine

This helped overcome the many logistical issues which we faced due to the demand for oxygen-15 along with the need for cyclotron produced C-11 and F-18 compounds for two PET scanners.

Another simple but effective practical advancement was the development of the H215O water generator by Henri Touchon, John Clark and Keith Dowsett [88]. The key to efficient automated transfer of H215O vapour into sterile saline for injection was the use of semi permeable membrane, which was first explored in the Unit by Adriaan Lammertsma for assaying on line blood levels of H215O during the inhalation of 15O2. The introduction of the water generator was stimulated by the group from Charing Cross of Abe Guz and Lewis Adams who were studying focal brain activation during breathing where the inhalation of C15O2 was not practical [89]. This was a very important advance in that it allowed automatic administrations of H215O to be given to subjects being PET scanned. It not only avoided handling but allowed the tracer to be administered without disturbance or arousal of the subject which was important for activation studies.

Generating and administrating $H_2{}^{15}O$ at the scanner

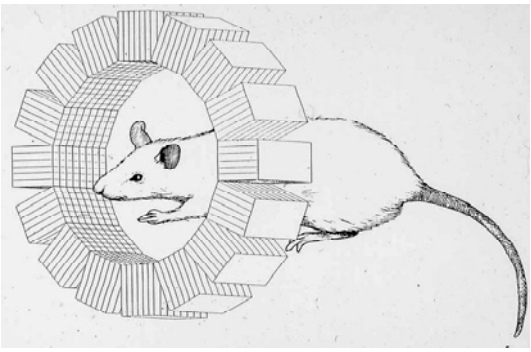
At one point, up to 120 H215O injections were being administered per week and remote handling for this became vitally important. We understand that other centres, which were handling radioactive water manually, became extremely restricted in their studies because of radiation dose limitations to the staff.

RAT PET

In 1989, a new initiative in the biology programme came about though the initiation of the RAT PET project. On a visit to Boston, I was impressed by a PET camera which Charlie Burnham had developed. This consisted of a ring of single crystals which produced

convincing images, when recording 18FDG in the rat brain. CTI were manufacturing a high resolution (HR) block detector and a pair of these were borrowed to begin to explore the value of imaging the rat brain at Hammersmith. This work was undertaken by Suren Rajeswaren and although comparatively crude non tomographic data sets were obtained, it was possible to show that one could record specific signals for example when administering 11C-diprenorphine under control and blocked studies [89].

With help from David Townsend, Suren went on to model and construct a polygon of such detectors which was assembled at CTI and installed in 1992 as the RAT PET [90, 91].



The Rat PET constructed out of standard HR block detectors from CTI

Using the available dopaminergic tracers, Susan Hume showed it was possible to delineate between specific and nonspecific tissues, such as the striatum and cerebellum [92]. It was also ponted out by Susan and Roger that there were pharmacological retraints when undertaking imaging of receptors in small animals due to the finite amounts of unlabelled drug that accompanies the radio labeled ligand [93]. The value of animal imaging became clear when undertaking a project with the Brain Repair Centre at Cambridge in collaboration with Dr Steve Dunnet. They were interested in following the viability of striatal grafts over time, Using 11C-raclopride and 11C-RTI, it was possible to show the viability of these grafts *in vivo* [94]. Stavia Blunt at the Cyclotron Unit continued on this work in a similar vein.

In order to analyse these data quantitatively, there was the challenge of identify a reference tissue. For this purpose, Adriaan Lammertsma and Susan Hume used data recorded from the cerebellum. One was concerned that the reference tissue would be contaminated by signal cross talk from the rest of the brain. Nevertheless, robust values of binding potential were obtained by this technique [95] which was later extended for use in man by Roger Gunn [96] . It avoided the need for blood sampling and improved the statistical quality of the resulting parametric images compared to using the plasma input.

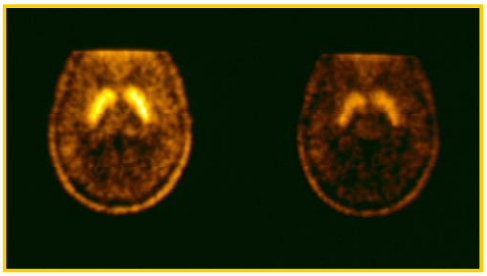
High sensitivity 3-D septa less PET

A major advance in methodology has been the introduction of septa-less, 3-D high sensitivity PET. When applying to the MRC in 1984 for the first generation of high axial and transaxial resolution block based tomographs, it was clear that the resulting images would contain limited statistical information due to the use of septa to delineate the transaxial plane. Hence in the application to the MRC, we introduced the concept that it should be possible, in the future, to

remove the septa from these cameras and capitalise on the high sensitivity available by recording all the possible coincidences between the detector elements. We were not experts in what would be a more complex method of reconstruction and took advice from Dr David Townsend who was then based at the University of Geneva where he had been working on 3-D reconstructions for a HIDAC camera. David spent periods in 1987 and 1988 in the Unit and together with Terry Spinks and Chicca Gilardi, explored the collection of the data from the 931 camera in the septa-less condition. This needed a temporary modification of the camera involving the manual removal of the septa from the field of view with help from Andy Holley of CTI. Test phantoms and some human subjects were imaged under 3-D conditions thereby defining the overall advantage of septa-less data recording along with its limitations [97, 98].

3D Imaging: 1988 - 1990

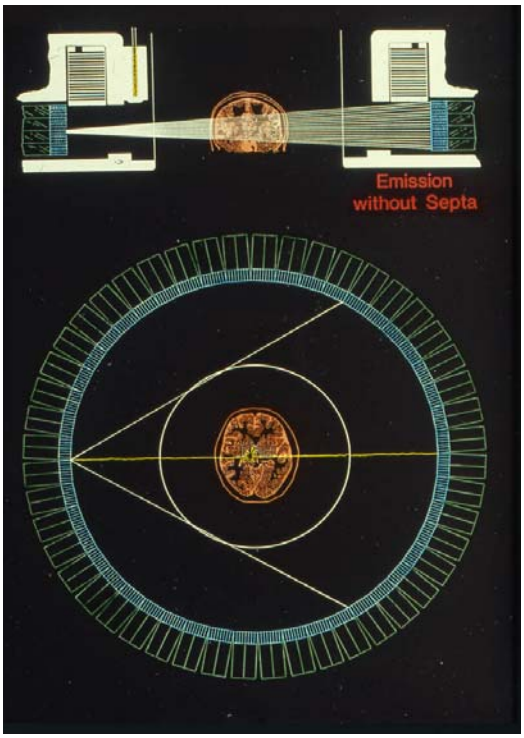
ECAT 931-08/12
Septa removed

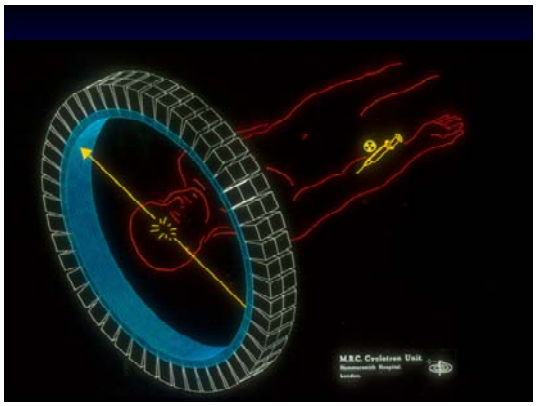


First 3D ^{18}F-fluorodopa scan
February 1988

Uptake of ^{18}F-L-Dopa in the striatum of the same subject and with the same administered activity before and after the removal of the septa from the ECAT 931

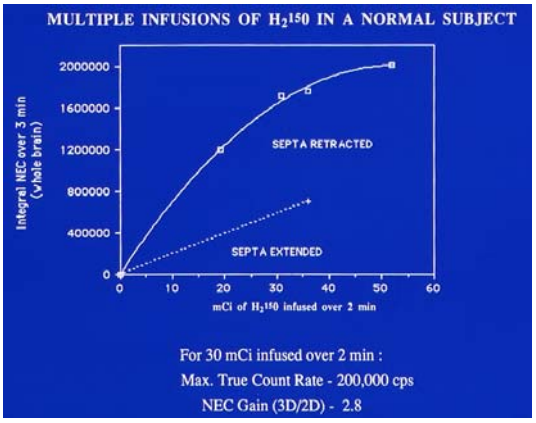
This experience stimulated us to approach CTI with a design for a tomograph with easily retractable septa. As a result, the 953B PET camera was designed and constructed and in 1990 specifically for brain imaging, introduced PET scanning onto the ground floor of the building where its physical performance was examined by Terry Spinks, Dale Bailey, Chicca Gilardi and Sylke Grootoonk [99, 100].





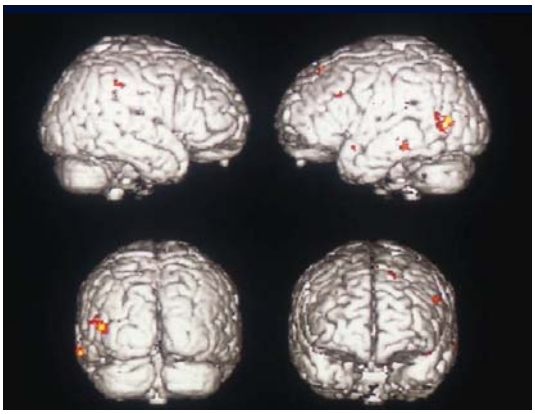
The design of the ECAT 953B dedicated brain PET scanner with retractable septa to record data with high sensitivity

Results from this camera comparing septa in and septa out obtained by Dale clearly demonstrated the advantages of 3-D for blood flow studies. It was estimated that there was a gain of a factor of 5 in effective noise equivalent counts compared to the 931 data sets recorded with septa [101]. To take full advantage of this improved sensitivity, Dale Bailey showed that data should be taken using lower doses of H215O of around 10-12 mCi [102].



The net sensitivity gain with septa retracted is around a factor of 3

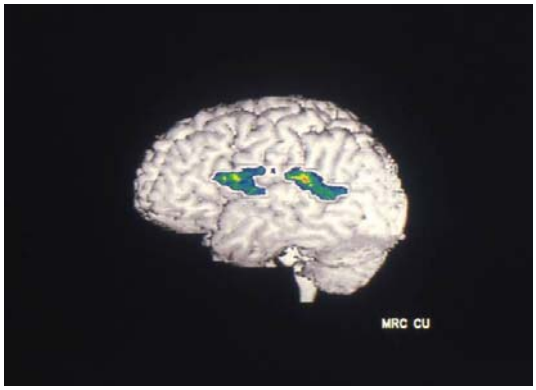
The impact of this high sensitivity data collection was widespread. In the first instance, it represented a major reduction in radiation dose to subjects. It allowed for the first time, within the permissible radiation dose, the collection of sufficient statistical data to analyse cerebral activation in a single subject. To date, it had been necessary to average data from a series of subjects to achieve sufficient statistical power. This clearly was a drawback when studying patients with brain lesions which would be in different locations. Also, variable anatomy in normal subjects resulted in a dilution of signal when averaged across individuals. It was also a protracted process to have to wait until a series of subjects had been studied before insight could be gained into whether or not the paradigm was working. The first demonstration of single subject activation was that of John Watson and Semir Zeki working with Dale Bailey and Ralph Myers who demonstrated the V5 visual activation area and its association with movement by delineating that area on the individual subjects' MRI defined neuroatomony[103].



Single subject study of the visual activation area superimposed on the individuals MRI

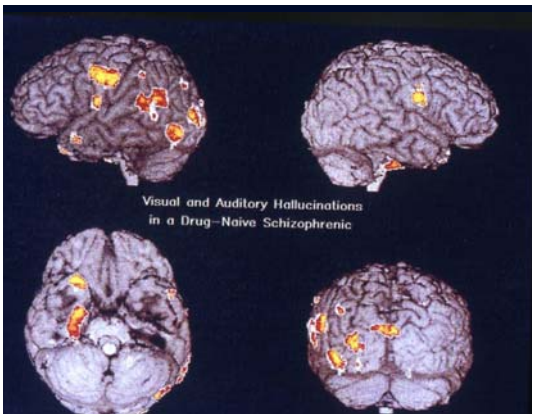
The high sensitivity also stimulated the study of more subtle cognitive changes.

The work of Chris Frith and others defining regions of inner speech and hearing of brain, although requiring subject averaging, capitalised on the sensitivity of the 3-D camera [104].



Demonstrating areas of inner speech and hearing of subjects recalling telephone numbers

This was taken further with the work of David Silberweig, and Emily Stern from New York, who observed similar focal changes in regional cerebral blood flow in individual schizophrenic patients when experiencing hallucinations [105]. This study was possible through the introduction of a novel methodological paradigm whereby the patients indicated, by pressing a button during the administration of H215O, when they were hallucinating, visually or auditorily. Both the inner speech/inner ear and the hallucination findings were separately published in Nature. However, the hallucination work required two earlier methodological papers to be published demonstrating how it was possible to capture transient events in a single subject using the defined paradigm [106, 107, 108]. Methodological support needed to record this data and to correct for patient movement came from Leonard Schnorr, Sylke Grootoonk and Jimmy Seaward a student working in his gap year.



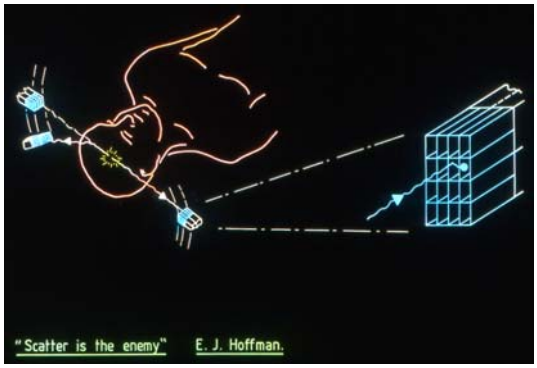
Studies of brain activation during hallucinations in a single Schizophrenic patient

With the increasing use of H215O for cerebral studies and the motivation to record lower levels of focal activation by maximising the total amount of activity administered, it became necessary to derive more accurate values for the radiation doses received by subjects being studied. For this, a novel methodological approach was adopted whereby the recorded arterial blood curve was used to model the integrated dose of H215O delivered to the respective organs and tissues of the body. Here Adriaan Lammertsma and Carrison Tong derived the respective distributions using flow models. Together with Terry Smith, Ken Butler, Leonard Schnorr and John Clark and with the co-ordinating effort of John Watson, a composite body of estimated values was derived from arterial curves recorded earlier in a series of normal subjects by Stuart Ramsey. The resulting mean dosimetry values proved to be higher than those that had been previously used and was an important step to ensure subjects received doses within the acceptable limit [109].

The expansion of H215O brain activation studies

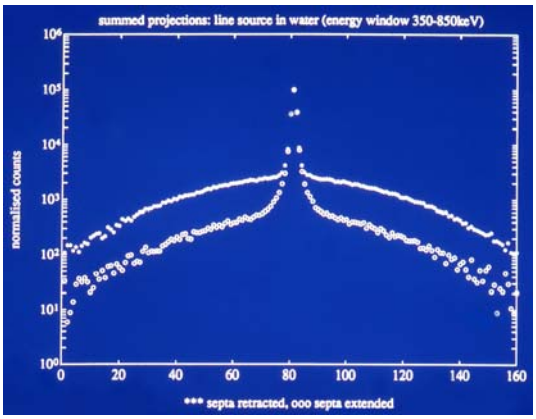
It is not possible to describe at length, the research projects associated with, the explosion of interest in the Unit in brain activation studies using high sensitivity, non invasive PET and H215O. Many visitors appeared attracted to the development and use of this methodology. Andy Holmes and John Baptiste Poline worked alongside Karl Friston. Many of the additional faces who came to exploit the methodology are still active both at Hammersmith: Paul Grasby and Harri Jenkins, in the UK: Cathy Price, Lizzy Warburton, Paul Fletcher and over seas: Cornelius Weiller, John Francois Demonet, Eraldo Paulesu, Gabriella Bottini, Banke de Jong , Gereon Fink and John Watson. The methodology also attracted the attention of the cardiologists in the Unit, Paolo Camici and Stuart Rosen to study cerebral activation during angina attacks. [110,111].

Quantitating 3-D septa less data



The challenge to realizing quantification with septa less PET data

A major challenge in exploiting the sensitivity of septa-less machines is that high levels of scattered coincidences are recorded within the data set.



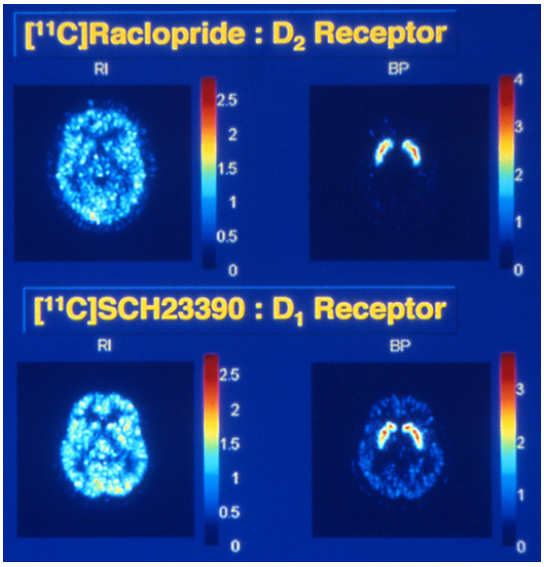
Line source placed in a scattering medium and imaged with the septa in place and then removed. Note the high scanner background (upper curve) present when there are no septa

It was therefore necessary to devise ways of removing the scatter component in order to realise quantitative, tomographic data which could be calibrated in the standard manner. Here Sylke Grootoonk and Terry Spinks worked on the dual energy window technique. This required recording a second coincidence window within the Compton region of the energy spectrum thereby providing a means for monitoring the level of scattered coincidences in the data set. Sylke studied a number of patients who were undergoing 18 FDG studies within Angus Kennedy and Martin Rosser's dementia programme Comparing the 2-D and 3-D results it was shown that it was possible to correct for scatter by this technique and thereby provide a means for calibrating the high sensitivity mode of data collection [112]. 3-D quantitative

measurements were then implemented for a range of neurotransmitter studies and extended through the introduction of a deconvolution technique to correct for scatter by Dale Bailey [113].

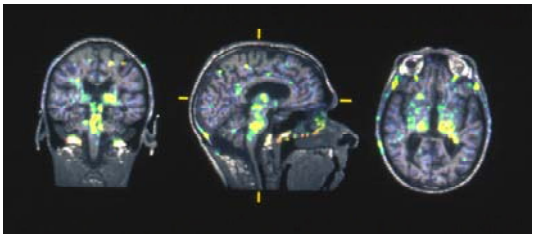
Further advances in kinetic modelling

Advances continued in kinetic modelling. Roger Gunn took further the earlier work of Susan Hume and Adriaan Lammertsma in the use of a reference tissue in the brain and introduced a technique whereby he created a series of bases functions [96]. This was a look up table approach to create functional parametric images of both the arrival of a tracer, known as an R1image and a parametric binding potential image. This was quickly introduced for 11C-raclopride and 11C-Schering.

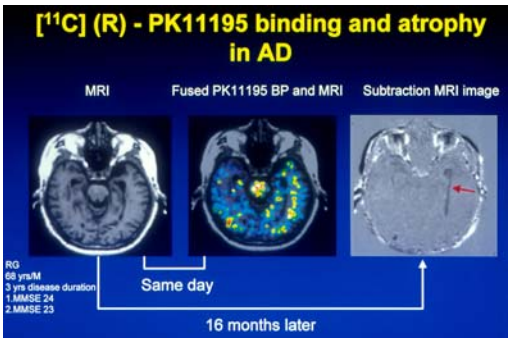


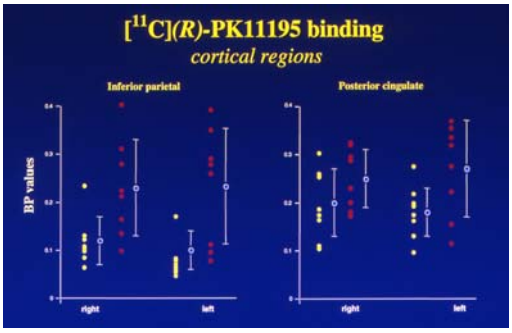
Use of the reference tissue model to derive parametric images of RI (delivery) and the receptor binding potential (BP)

The reference tissue technique was taken further using cluster analysis to identify the reference tissue region. It built on earlier work of John Ashburner and Vin Cunningham in collaboration with Chris Taylor in Manchester [115]. It has been particularly important in advancing the quantitative analysis of 11C-PK11195 by Ralph Myers, Roger Gunn and Richard Banati. Here reference tissue kinetics are identified from the heterogeneous time courses of clearance. As a result, high quality parametric imaging of the binding potential of this ligand to inflammatory lesions in the brain have been produced from what is a primarily weak signal. These have included studies of patients with Multiple Sclerosis [115], Dementia[116], herpes encephalitis and stroke, , [117].



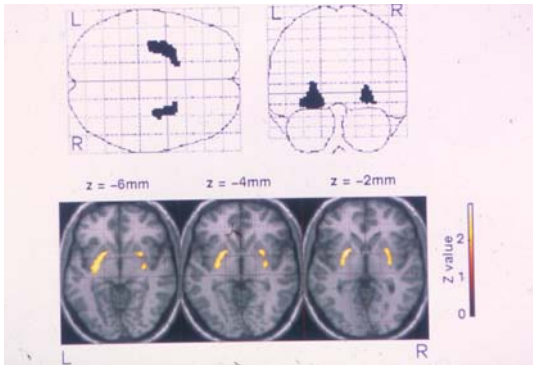
11C-PK-11195 binding in the brain of a patient with multiple sclerosis superimposed on the subjects MRI





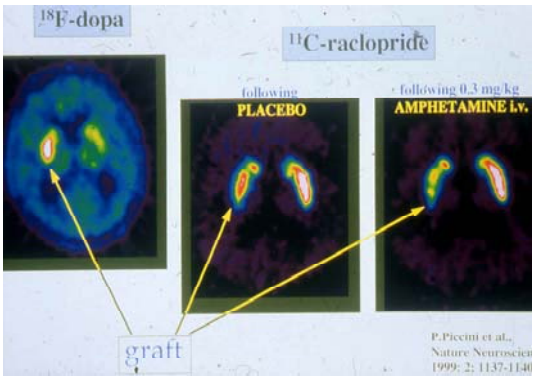
Increased ^{11}C-PK-11195 binding (microglial activity) in the brains of patients with Alzeimers Disease

Combining the high sensitivity of 3-D and the kinetic modelling of Roger Gunn's reference tissue model encouraged Paul Grasby, Matthias Koepp and others to explore radioligand displacement during cognitive activity. The video game results published in Nature [118] of the subtle displacements using 11C-raclopride was the culmination of the use of the range of developed methodological advances to document this phenomena.



Regions of increased competition for the binding of 11C-Ralopride which correlated with the degree of reward achieved in a video game

This strategy of neurochemical activation was extended recently by Paola Piccini and David Brooks in the study of striatal graft viability using apamophine challenge [119].



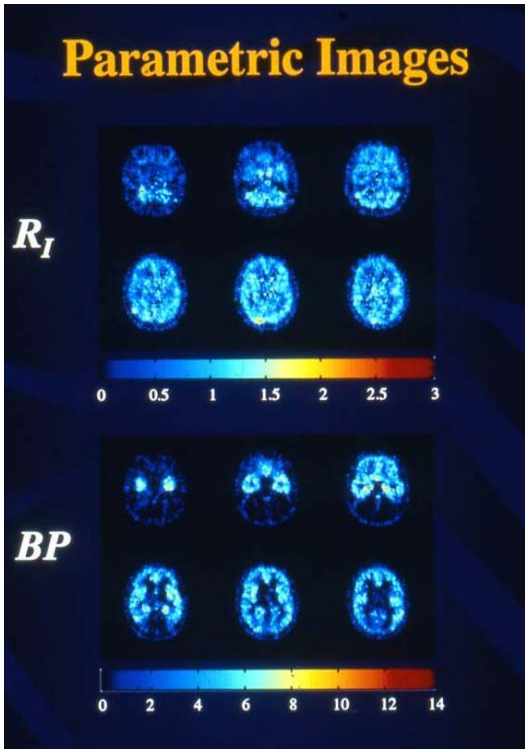
Viability of striatal engraftment by demonstrating the graft's ability release dopamine in response to an amphetamine challenge as shown by increased occupancy of the D-2 binding site; i.e. less 11C-Raclopride binding.

The study of 18F-L-Dopa uptake in the brain has benefited tremendously from 3-D high sensitivity and in particular for studying dopaminergic function outside the basal ganglia. James Rakshi and David Brooks worked with Dale Bailey to implement the PATLAK plot to create parametric images to feed into SPM. This revealed interesting pre frontal cortex disturbance of 18F-L-Dopa incorporation in Parkinson's disease patients, an observation which was only made possible by the high sensitivity quantitative recordings [120].

Imaging the Seratonergic System

A new methodologically important advance was brought about by Vic Pike in his relationship with the Wyeth Pharmaceutical Company for developing 11C-WAY-100635 a highly selective and clean ligand for the 5HT1A receptor [121]. Again striking parametric images were undertaken through quantitative 3-

D using the reference tissue method. Not only has this produced a new probe for psychiatric research. particularly in depression, but has attracted a number of commissioned pharmaceutical company dose ranging projects as well as being adapted by many PET centres internationally [122].



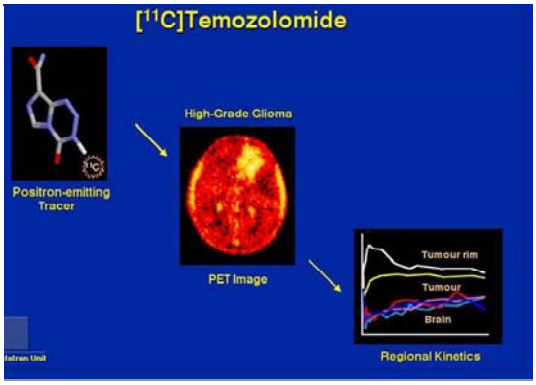
Parametric images of the delivery (R_1) and binding potential (BP) of the specific 5HT 1A receptor ligand: ^{11}C-WAY- 100635

Correcting for the partial volume effect

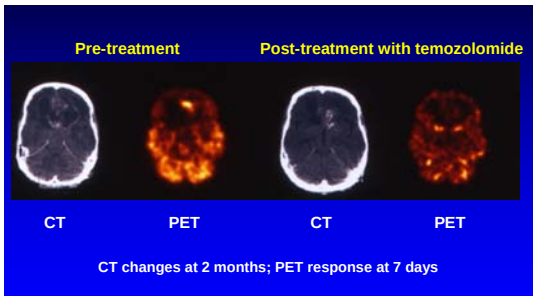
To accurately quantitate brain structure uptake, it has been clear for sometime that one ideally needs to correct for the partial volume effect using anatomy led information as derived from the MRI scanner. These corrections were pioneered in the Unit by Claire Labbe, Ralph Myers, Vin Cunningham, Matthias Koepp, Mark Richardson, Alex Hammers [123] and recently by John Aston, particularly with respect to analysing data recorded within John Duncan's epilepsy programme. They demonstrated the importance of such a correction when measuring receptor density in brain malformations which are central to epileptic foci.

PET oncology studies in the brain

With respect to introducing novel radiotracers for the brain, note needs to be taken of the work undertaken by the PET oncology group for studying the pharmacokinetics of anticancer drugs in brain tumours. C-11 temozolomide has been used following its radiosynthesis by Frank Brady and Gavin Brown. As a drug, this compound had shown clinical efficacy at Charing Cross and it was of interest to look at the dosimetry and kinetics of this molecule within cerebral gliomas [124].



The distribution and kinetics of ^{11}C-temozolomide within a glioma and normal brain tissue



The ability of ^{18}FDG to detect the pharmacodynamic (functional) effects of temozolomide on a brain glioma compared to X-Ray CT

This was complemented by studying functional changes in glioma tissue metabolism in patients undergoing treatment with temozolomide by Susan O'Reilly and Cathryn Brock. Comparison between the sensitivity obtained from repeat CT scanning has demonstrated that patients who responded to treatment, show metabolic reductions in the tumour within 7 days using 18F-FDG as a metabolic marker whereas it takes some 2 months for the CT scan to show improvements [125]. These methodological advances have been critical in attracting substantial funding from the Cancer Research Campaign into Pat Price's programme for studying the mechanism of action and effectiveness of novel anticancer agents.

The establishment of the Functional Imaging Laboratory at Queen Square

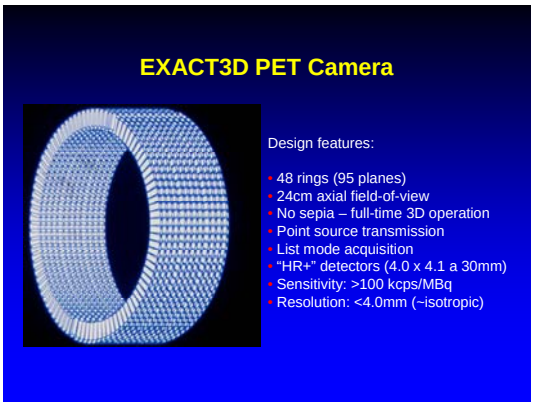
In October 1995, an important event occurred when Richard Frackowiak took a team of scientists, including methodologists and operational support, to open the new Functional Imaging Laboratory funded by the Wellcome Trust. This spin off of a Cyclotron Unit developed programme represented over £25 million of additional funding into functional neuroimaging in the UK. The location of the Functional Imaging Laboratory at Queen Square, with access to neuroscience within the Institute of Neurology and University College London, was an extremely important strategic move. It has resulted in a research laboratory whose brain activation programme has become one of the best in the world. A smooth transition was possible, between the time of announcing plans for the FIL and its eventual opening because the MRC allowed ongoing research in the Unit by Richard's group in the interim period. A point of note is that a feature of the FIL's success has also rested on methodological developments, particularly through Karl Friston's ongoing evolution of SPM which has extended into the challenging area of fMRI for brain activation.

David Brooks then headed up the Unit's neuroscience programme. While this rested heavily on his own research into movement disorders he also fostered new initiatives to expand into the gap left by the departure of Richard Frackowiak's team. Dr Richard Wise went to the FIL and returned to study stroke recovery, Paul Grasby stayed

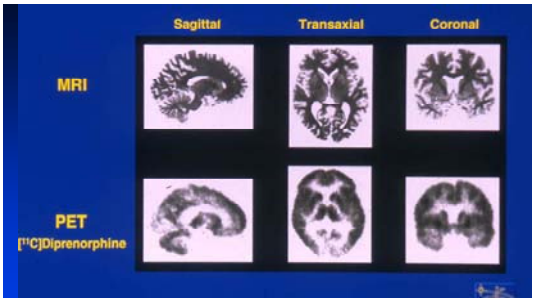
behind and David and Paul's programme stimulated new methodological developments in neuroimaging, focusing on radioligand studies which eventually led to the ligand neurotransmission activation programme. Paul's PET psychiatry programme has filled the gap along with David Nutt from Bristol who was attracted to undertake studies of addiction and anxiety using both blood flow activation and neuroligand studies. Within this programme, Andre Malizia extended his PET studies on anxiety by championing the introduction of a novel methodology to study tissue pharmacokinetics [126]. This was based on recording global head counts and from other organs in the body using the Unit's whole body counter [127, 128]. The attraction of this approach is that it requires only one hundredth of the radioactivity needed for a PET study. David's addiction work was later to reach MRC programme grant status bringing in Ann Lingford-Hughes who was already very experienced in SPET psychiatric studies.

Installing the most sensitive PET camera in the World

In 1996, a more advanced PET camera was installed again in collaboration with CTI. This had a 24cm long axial field of view as well as increased spatial resolution. It is currently the most sensitive PET camera in the world by a factor of 2 over other rivals [129].



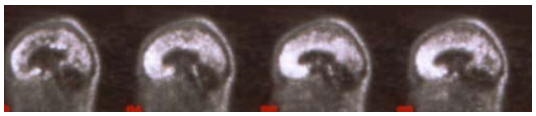
The most sensitive PET scanner



Improved quality of ^{11}C-Diprenorphine imaging with the ECAT 3D-compare with the image on page 18

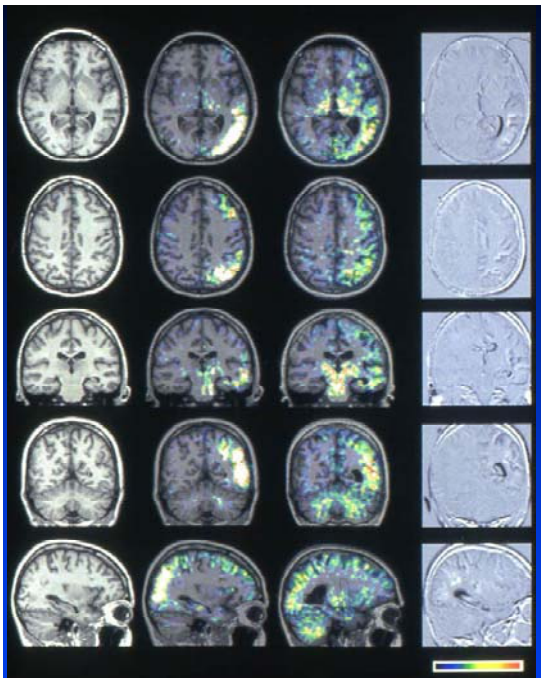
Another important methodological advance was that it provided a much more uniform response across the axial length of the human brain. This is particularly important for accurate measurements of non specific binding within the cerebellum, which the earlier camera recorded with lower sensitivity than that of the cortical mantle of the brain. An example of where this has been particularly important is in the use of C-11-WAY-100635, where not only is the cerebellum used as a reference tissue but also the counts within that region are reduced because of the low levels of non specific binding exhibited by this ligand. Impressive parametric images have been produced with high definition for recording the raphae nucleus which, in the earlier camera, was

positioned in the less sensitive region of the recorded field of view.



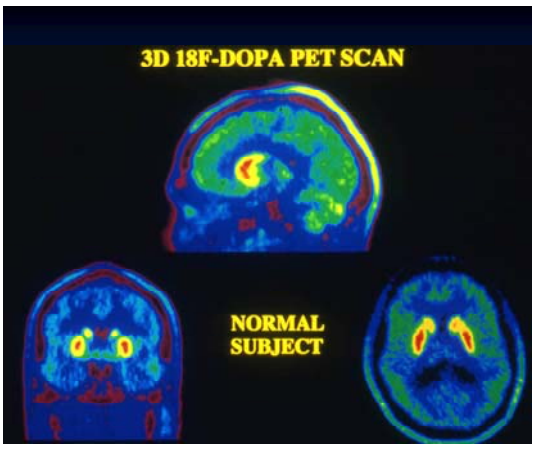
Images taken of 11C-WAY-1000635 which show how the long axial coverage of the ECAT3D ensures efficient coverage of the cerebellum and structures like the raphae nucleus

For H215O activation studies the high sensitivity for recording the cerebellum proved important in the discovery of cerebellum activation differences in dyslexic subjects undertaken by Emma Berry from Sheffield with support from Dale Bailey [130]. Interesting results in individual stroke patients have been obtained by Richard Wise and his aphasia group. Not only would it be quite difficult to study these with fMRI but also using the robustness of H215O PET activation measurements, fully capitalises on the collaboration of such patients within the one experimental setting. The sensitivity improvement with the new camera has been exploited in extending the studies of 11C-PK11195 to investigate lower levels of neuro inflammatory activity. This has included patients recovering from stroke, and with early signs of Alzheimer and CJD.



^{11}C-PK-11195 in a stroke patient within the first few days (middle column) and after six months. Note the ability to detect low level of glial activity away from the main ictus over time

The earlier work on measurement of kinetic uptake of 18F-L-Dopa in the prefrontal cortex has been extended with the new camera.



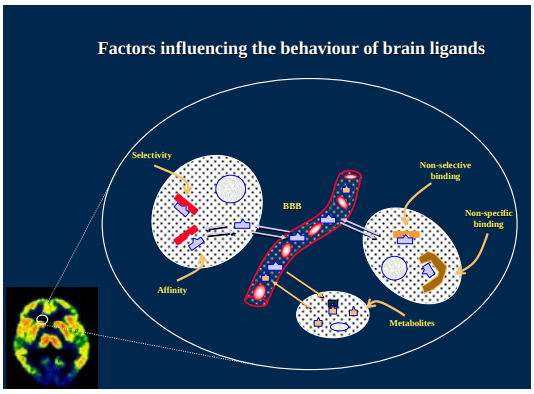
The high sensitivity of the ECAT 3D enables low levels of cortical ^{18}F-L-Dopa uptake to be measured

Here Steve McGowan, in the psychiatry group, has shown good accuracy for measuring the signal in the cortex which is an order of magnitude weaker than that in the striatum [131].

Future developments in PET methodology

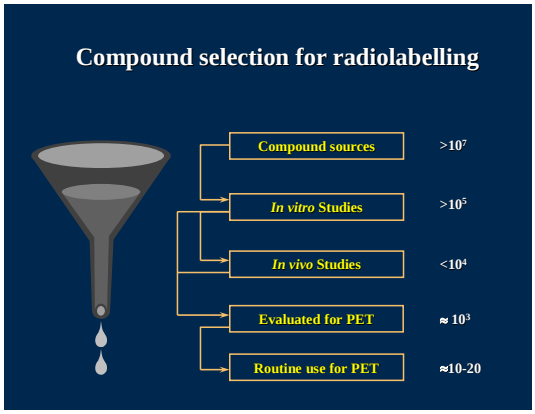
With respect to future developments foreseen in methodology, it is clear that we need to make better use of the data which we are currently recording. Detection sensitivity for the brain is, for the foreseeable future, more or less maximised and hence improvements are sought in the statistical noise associated with kinetic analysis of dynamic data to produce parametric images. Recent work for example by Federico Turkheimer in wavelet analysis bodes well for advances in this area [132]. In addition, improvements are foreseen in reconstruction techniques to strive for better signal to noise in the tomographic data. Encouraging examples have recently been shown by Kris Thielmans, Terry Spinks and Darren Hogg for a kinetic 11C-WAY study which shows how signal to noise is clearly improved using the 3-D iterative reconstruction methods developed within a European consortium. One can foresee improvements being made in the spatial resolution of the PET camera using new scintillation crystals with improved light output such as LSO being developed by CTI. In future tomographs, a factor of 3 improvement in volumetric resolution is predicted over that currently realised. Nevertheless, where appropriate, further consideration also needs to be given to the value of global brain measurements of pharmacokinetics using positron emitting ligands and tracers.

One major area for future development is the discovery and development of more selective and specific radiotracers and radioligands for molecular imaging. Despite there being huge libraries of molecules within academia and the pharmaceutical industry, there are no more than a dozen or so which have shown to be of value for molecular imaging. The main problem is not so much the specificity which these molecules have for a molecular target or a molecular pathway of interest but plasma binding, poor transfer across the blood brain barrier and signal contaminations arising from non specific binding and radiolabelled metabolites.



Ways need to be introduced of how to effectively "mine" the libraries of molecules which already exist and how to bring on potential candidates, by screening and refining their analogues as agents for *in vivo* imaging. A strategy on how this could be achieved comes from the work of Antero Ambrunhosa who, working with the radiochemists, established a data base of reported 11C ligands and tracers which have been explored for brain imaging. This compendium of some 900 compounds contains molecular structures and

pharmacological information which underlies good and poor molecules for *in vivo* imaging [133]. It is now ready to be used to interrogate libraries of candidate molecules many of which may need to be synthesised within an in-house programme or *in silico*. Ways of undertaking such syntheses and screening of molecules are being now considered following the arrival of John Thorn back who is experienced in this area.

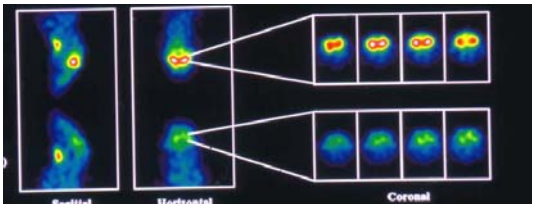


Discovery and development of PET ligands and tracers from libraries of molecules from within industry and academia

Future applications of PET

With respect to future applications, clearly the role of PET is that of a translationary medium between basic molecular/cellular discoveries and studies of diseased tissue in life. There is a tremendous amount of scientific activity undertaken at the basic level in the fields of molecular and cell biology. Also, a dominant force is the R&D undertaken by the pharmaceutical industries which worldwide amounts to $50 billion per year. However, it is worth noting that 70% of that is spent in attempting to cross the gap between basic science and *in vivo* observations through Phase I/II/III clinical studies. It is also of note that on the basic side, many animals are sacrificed amounting to 1.5 million mice per year in the UK alone. Molecular imaging as represented by PET is seen as being a way of bridging this gap. However, it is clear that the link between the current human imaging and basic environment is by no means consolidated. One means of helping to forge this link is through small animal imaging and in particular for the mouse.

Insight has already been gained that it may not be possible to derive certain kinetic data from sacrificed animal studies with the same level of statistics now possible in single animal imaging procedures. We are therefore excited that support for this is forthcoming from the recent Joint Infrastructure Fund award to bring on mouse imaging with PET and MRI based on our experience with the RAT PET and the high resolution HIDAC camera produced by Oxford Positron Systems (OPS) [134,135]. This offers 1mm resolution in experimental animals and promises to provide a constructive medium for forming scientific links with basic drug discovery, molecular and cell biology. Here there is a growing movement in the post genomic era of functional genomics to study tissue function in the context of their basic discoveries.



Striatal uptake in mice of a pre-synaptic ligand before and after receptor blockade using the 1mm resolution HIDAC positron camera

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What have we learned from this historical review?

Clearly methodological development has represented a tremendous driver in brain imaging, resulting in the generation of new knowledge on the workings of the normal human brain, focal pathophysiology and treatment effects.

It is also clear that realising new methodologies needs long term developments for them to reach maturity and this certainly has been available by the long term support from the Medical Research Council.

The introduction of new PET instrumentation rests heavily on close collaboration with the commercial developers and manufacturers. However, this invariably takes longer than predicted especially as the data output from new devices challenges the logistics to handle the accompanying increased volume of data flow and processing. The pattern seen is one of computational "catchup". While in the past, in house support has been assigned for such a process, in the future, it may be prudent to share in this introductory burden through collaboration and co-ordination between PET centres who wish to introduce the next generation of instrumentation. In the first instance, this would require deriving a consensus between centres on the design of the next generation of cameras.

Development in methodology and the introduction of improved techniques is an iterative process between non clinical and clinical people. A central feature has been clinicians, who have been interested in and prepared to share in the risk to make the investment necessary to explore new methodology with non clinical people. This has been in the knowledge that in the short term, the effort will be relatively unproductive as far as generating new scientific information is concerned with individuals being prepared to postpone scientific productivity while exploring and perfecting new methodology.

The programme has evolved through a multidisciplinary approach which has been highly conducive to generating new ideas through cross fertilisation between different disciplines in which the rapid gestation of ideas, or their rejection, has been the central feature. We have been concerned with a research activity to which, by definition, non conformists were attracted. These have been receptive to exploring new ideas and concepts bringing immense added value to a central methodologically innovative programme. However, to capitalise on the advantages of multidisciplinary and non conforming individuals and groups, constant attention is needed to ensure cross fertilisation and pollination between the disciplines to share in the new ideas and emerging results. This requires continuous catalytic networking activity. Secondly, non conformity brings with it a range of different personalities and agendas which if not harnessed can easily go wrong and result in conflict. The challenge here is to achieve consensus without stifling individuality and to constantly steer in a common direction whereby ensuring

contributing individuals receive sufficient value from the programme with a shared enthusiasm. This needs constant fine tuning at a personal/political level.

A critical mass of multidisciplinary research activity, in a rapidly evolving field, as represented by the Cyclotron Unit's programme attracts to it further researchers, many of whom come from overseas and are often self-funded . This brings much added value to the core investment and makes the tackling of difficult goals more possible through the addition of self motivated individuals.

Spin off from the Central Institute to create new start ups in imaging should be seen as natural and universal means for realising more focus and investment in the field and a way of localising selected applications, in more specialised environments. This may become ever more important as pressures on research funding continue to increase with science expanding at twice the rate of the economy. Spin offs, generating research funding from new sources may be an answer to this.

The illustrated methodological advances and scientific results represent the tip of the overall activity in the Unit. Pilot studies and prototypes have had to be refined and implemented for routine operations. Here one has to acknowledge the value of the big support team at the Unit which has embraced the new advances and matured them for routine use.

A central lesson is that one needs to be in control of ones' research activities when taking risks. If additional external bureaucratic, administrative and political problems are laid upon this, the associated loss of nervous energy results in less productivity and risk taking.

Finally, it is clear that a research institute needs to have a vision for what it wants to do and to focus on this vision and not be too diversified. It is important to focus on what it feels is important to be done and of course on something which is nearly impossible. Above all it is important to make sure it does it first.

July 2000

This review was the theme of a talk delivered at a Cyclotron Unit's Brain meeting on the 6th of April, 2000

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