

Michael Peters

Nuclear medicine at the Hammersmith Hospital was established as a separate unit by Peter Lavender in the early seventies. It was called the Radioisotope Unit to distinguish it from the pre-existing Department of Medical Physics, headed by Harold Glass who was one of the early pioneers in medical radioisotope scanners [1]. As well as providing a clinical service, the unit, which only comprised two rooms, was active in clinical research complemented by the extensive academic activities of the MRC Cyclotron Unit. Two good examples of these activities that launched nuclear medicine at Hammersmith are firstly the development by Clark, Watson Fazio and Jones of Kr-81m for ventilation and perfusion studies [2], and secondly, cell labelling.

Kr-81m is a 13 s half-life radionuclide that is the metastable daughter of Rb-81, which has a half-life of 4.7 h. To obtain Kr-81m gas, oxygen is passed through the generator. There was an enthusiastic response to the generator across the UK, and, at one point, Kr-81m/Tc-99m ventilation/perfusion imaging was the second most frequently performed imaging procedure in the UK after bone scanning. Whilst Kr-81m remains the optimal ventilation agent for lung scanning, it is not so widely appreciated that Lavender and his colleagues also administered Kr-81 in solution to measure tissue perfusion. To obtain Kr-81m in solution, isotonic glucose is passed through the generator. For example, Harvey-Turner and Selwyn infused Kr-81m into the aortic root of dogs and continuously imaged regional changes in myocardial perfusion in response to transient coronary artery occlusion [3]. The distribution of pulmonary blood flow in humans was also imaged by continuous intravenous infusion [4]. Kr-81m was given both by inhalation and infusion to study ventilation-perfusion ratios and regional lung function in adults [4, 5] and children [6]. When combined with the longer half-life Kr-85 (a lung gas volume marker), regional lung

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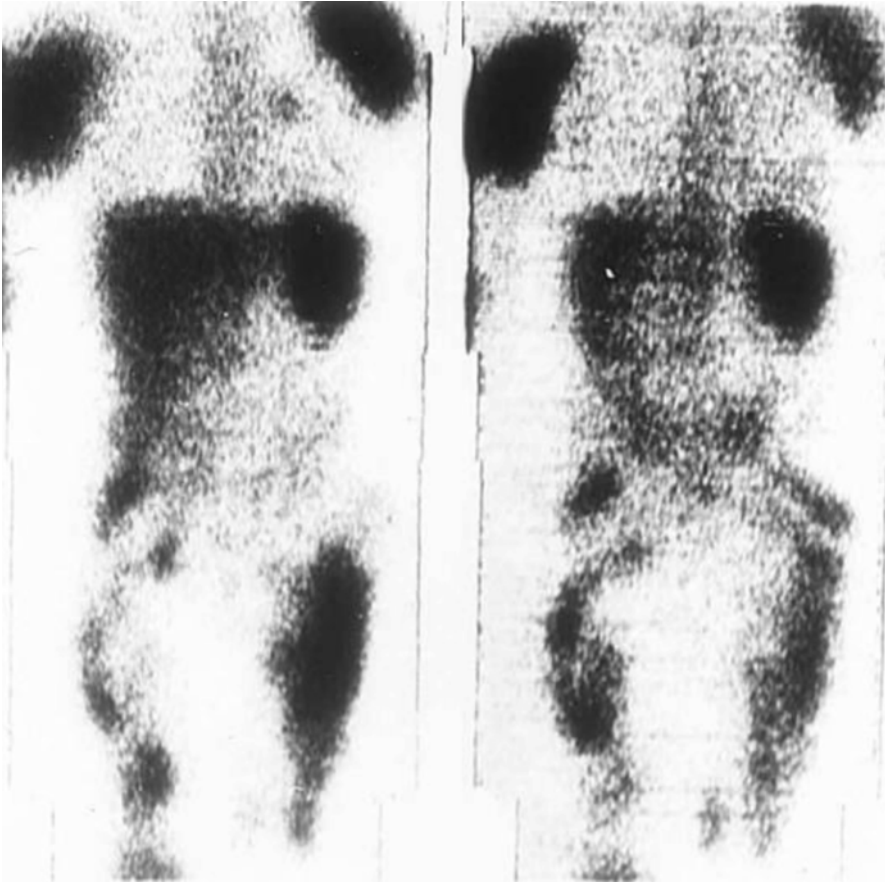
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**Fig. 12.1** A patient with multiple sites of sepsis imaged with In-111-labelled leucocytes (From Ref. [8])

function per unit volume could be assessed. Lavender used Kr-81m/Tc-99m SPECT in the early eighties to study pulmonary physiology [7] but did not feel that it offered any great advantage over planar imaging for diagnosing pulmonary thrombo-embolic disease.

The second example of innovative collaboration between Hammersmith nuclear medicine and MRC Cyclotron Unit was the development of cell labelling by Thakur and McAfee. John McAfee came to the Hammersmith for a 6 month sabbatical with the specific aim of working with Matthew Thakur to develop cell labelling for clinical imaging. Cr-51 had already been developed for cell labelling but is not suitable for gamma camera imaging, only surface counting. Testing several combinations of lipophilic chelating agents and radiometals, Thakur and McAfee came up with In-111 and hydroxyquinoline (oxine). The first full paper on leucocyte scanning for sepsis, based on 15 patients, was published in 1977 ([8]; Fig. 12.1).



**Fig. 12.2** The cyclotron being installed in the MRC building at the Hammersmith Hospital in 1956

There was great hope for performing labelled lymphocyte studies too, until it was soon found that lymphocytes are radio-sensitive and destroyed by labelling with amounts of In-111 required for imaging. I arrived at the Hammersmith in 1979 to undertake a 3-year Cancer Research Campaign-funded project on labelled lymphocytes but with this discovery quickly turned my attention to labelled leucocytes and platelets. In those days, Amersham International was not selling In-111-oxine, so it had to be prepared in-house (by a radio-chemist, Malcolm Kensett, in the MRC Cyclotron Unit). Once a patient had been identified, I would order the In-111-oxine, go to the MRC to collect it, take the patient's blood, go to the Haematology Isotope Unit to label it, then take it back to the Radioisotope Unit to inject it and image the patient. The Haematology isotope unit under the leadership of Mitchell Lewis, provided a tertiary service for ferrokinetics, using Fe-59 and Fe-52 (a positron emitter), and red cell survival and surface counting studies using Cr-51-labelled red cells. The unit also supported studies involving labelled cells, including In-111-labelled platelet kinetic studies by Klonikakis et al. [9], In-113m-labelled red cells and platelets, and studies on the clearance rates of labelled red cells modified by heating or antibody coating, undertaken by several workers from the Department of Medicine studying reticulo-endothelial (RE) function.

The Medical Research Council funded the building of a medical cyclotron on the Hammersmith site in 1954 (Fig. 12.2). This stimulated much research into

cardiopulmonary physiology and neuro-pathophysiology in collaboration with the clinical staff of the Hospital. Pairs of scintillation detectors (front and back) were used first (with coincidence counting of positron emission), then planar gamma camera imaging, and finally positron emission tomography. The first studies were carried out in the late 1950s by West and his colleagues [10–12] using the short-lived positron emitting isotope, oxygen-15 (half life 2.1 min) as  $C^{15}O_2$  and  $C^{15}O$ . Lung water distribution was studied with  $H_2^{15}O$  [13, 14], pulmonary perfusion with infused  $^{13}N_2$  in solution [15], pulmonary haemorrhage with inhaled  $^{11}CO$  [16], and ventilation with neon-19 [17]. Rhodes and Hughes [18] summarized pulmonary studies using the positron camera. There was also much interest in studies of inflammatory conditions using F-18-fluorodeoxyglucose ( $^{18}FDG$ ) [19, 20], and in imaging beta-agonist receptors in the heart and lung [21, 22].

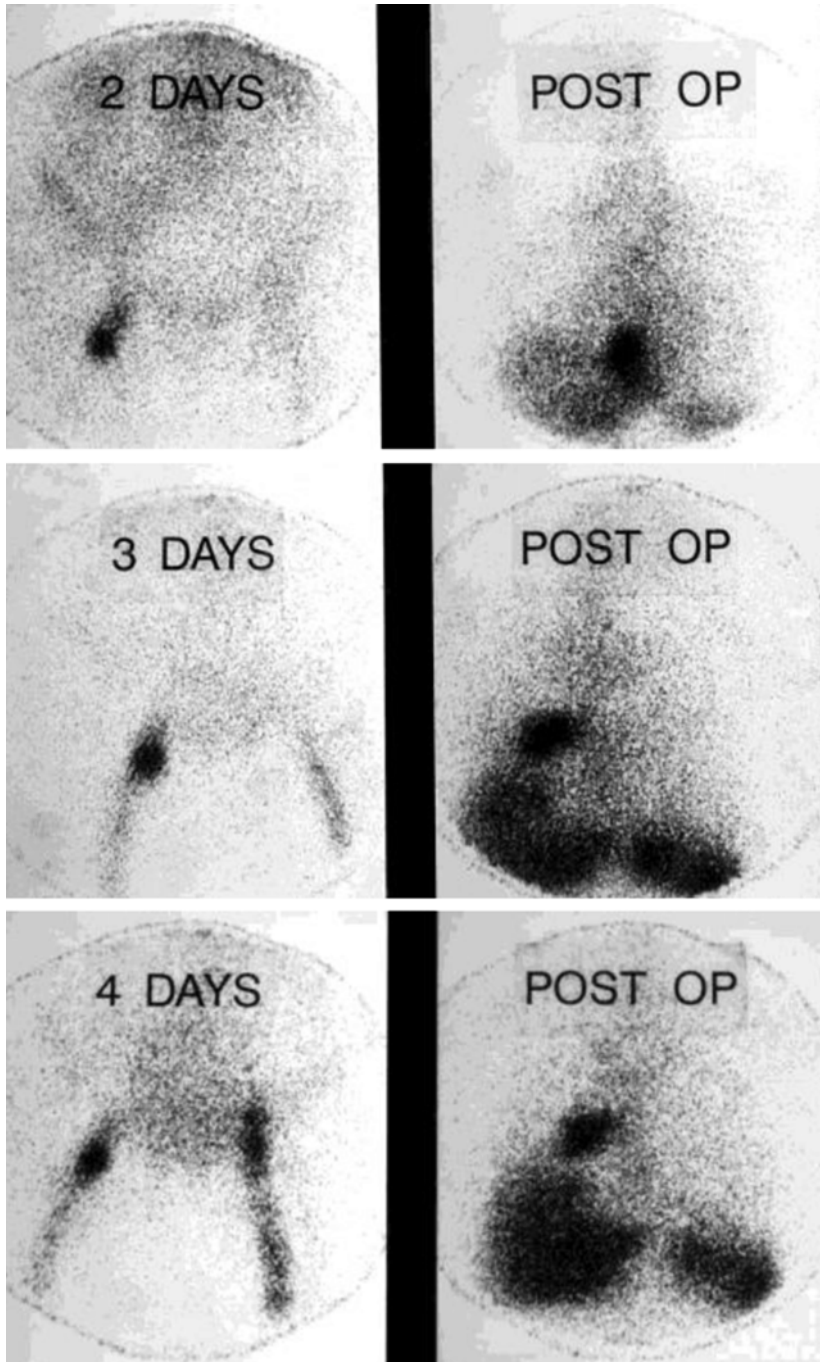
Research activity elsewhere in the MRC Cyclotron Unit included the development of  $^{18}FDG$  for imaging the brain (Terry Jones and Richard Frackowiak) and myocardium. Camici et al. were one of the first groups to image Rb-82 uptake in the myocardium of patients with coronary disease and show increased FDG uptake in ischaemic regions [23].

Many pioneers in nuclear medicine worked at Hammersmith. One of the earliest was Charles Galasko who in bone scintigraphy showed in 1968 that 12 of 50 patients with apparently ‘early’ breast cancer on clinical, radiological and biochemical grounds had positive scintigraphy and developed metastatic disease in the first 5 years following mastectomy [24]. Joseph Pflug was a pioneer in lymphatic function studies and was one of the first to use lymphoscintigraphy. Aga Epenetos, an oncologist, was one of the first to develop radiolabelled monoclonal antibodies for imaging cancer. Having worked with Keith Britton at St Bartholomew’s and Walter Bodmer from the then ICRF, Epenetos continued his work at the Hammersmith. Also collaborating with ICRF, Lavender used a very effective monoclonal antibody to the platelet fibrinogen receptor for imaging thrombus ([25]; Fig. 12.3).

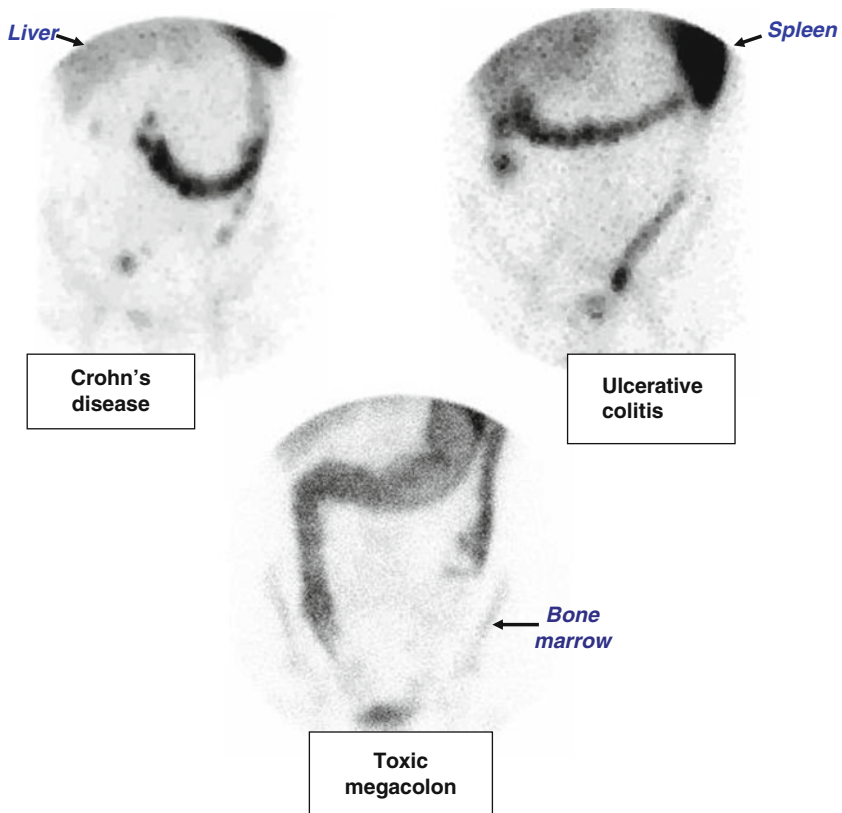
Dominic Haskard came to Hammersmith from Guy’s Hospital around 1990 and developed very effective monoclonal antibodies to vascular adhesion molecules for imaging inflammation [26]. Sadly, however, none of these labelled antibodies made it into regular nuclear medicine practice.

Having developed In-111-oxine cell labelling, workers at the Hammersmith, again in collaboration with the MRC Cyclotron Unit (Danpure and Osman), then explored other chelating agents and discovered tropolone [27], which, now that GE do not offer In-111-oxine, is the standard agent for In-111 cell labelling. We then went on to develop Tc-99m-HMPAO for leucocyte labelling [28]. Saverymuttu demonstrated the extraordinary ability of In-111 and Tc-99m-labelled leucocyte scintigraphy to quantify and image inflammatory bowel disease (Fig. 12.4) and published numerous papers on its applications in gastroenterology.

Other, generally unfunded work, on patient volunteers established the normal whole body kinetics and physiological margination sites of granulocytes, and, in particular, dismantled the erroneous notion that the vast majority of intravascular granulocytes are pooled in the lungs [29]. It was clearly demonstrated how in systemic inflammatory diseases, such as pancreatitis, IBD and vasculitis, circulating granulocytes become primed, lose deformability and undergo prolonged transit through the pulmonary vasculature. This is in contrast to hold-up in the lungs of



**Fig. 12.3** Images in a patient who 2 (*top panel*), 3 (*middle panel*) and 4 (*bottom panel*) days before receiving a total hip replacement. The In-111-labelled antibody P256 was administered shortly after surgery. Note the development of thrombus in the femoral veins and the movement of an embolus from the right ventricle to right pulmonary artery (From Ref. [25])



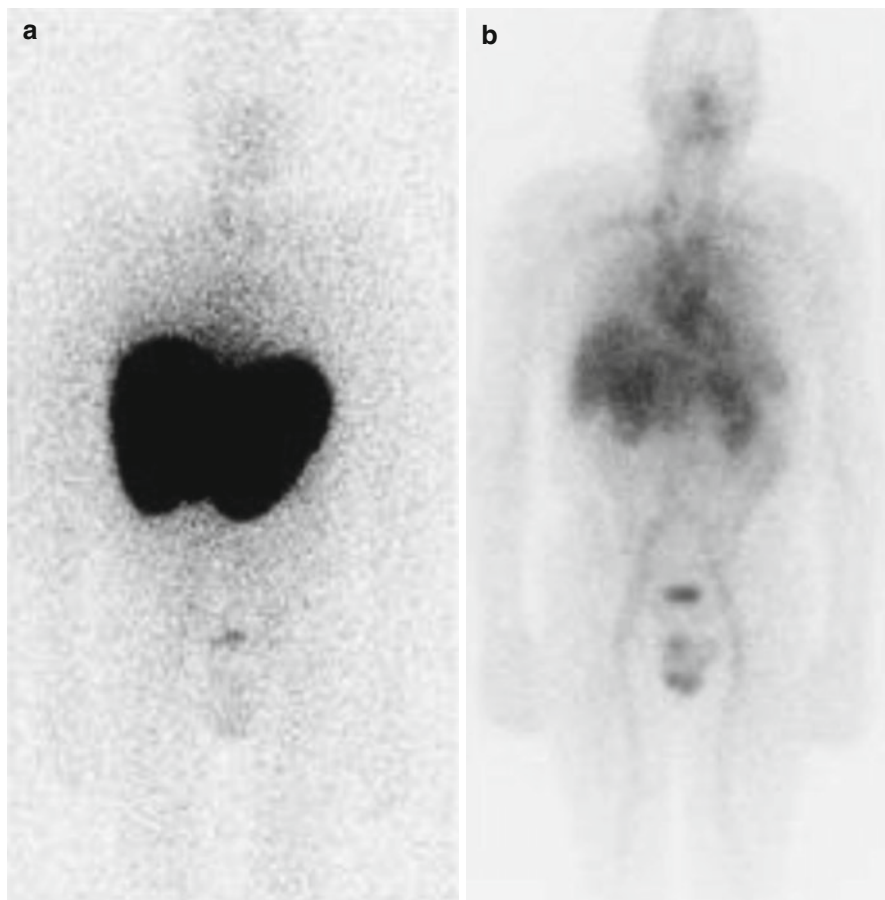
**Fig. 12.4** Inflammatory bowel disease imaged 1 h after injection of Tc-99m-HMPAO-labelled leucocytes

granulocytes artificially activated by the labelling procedure and associated with very low intravascular recovery. This work led to quality control guidelines for leucocyte labelling.

Another major nuclear medicine landmark in the history of the Hammersmith radioisotope unit was the development by Mark Pepys and Philip Hawkins of I-123-labelled serum amyloid protein (SAP) for imaging amyloidosis [30]. This work was dramatically successful and led to the establishment of a separate unit in the hospital with its own gamma camera and technical staff, such was the weight of referrals from all over the country. So, at one time, there were five separate nuclear medicine units on the Hammersmith site! I remember Pepys and Hawkins opening champagne in the Radioisotope Unit when they had just witnessed heavy hepatic uptake of labelled SAP in a patient with amyloidosis (Fig. 12.5). I wondered if the celebrations might be premature, having learned that in general when a tracer is not functioning properly it is liable to end up in the liver, but this was clearly not the case!

The spirit of research collaboration at the Hammersmith Hospital fuelled many interesting research projects using radionuclides. For example, the early advances in





**Fig. 12.5** Hepato-splenic amyloidosis (a) compared with normal distribution of I-123-labelled SAP (b) (From Refs. [29])

interventional radiology allowed us to inject In-111-labelled platelets directly into the splenic artery of patients having arterial catheterization and show conclusively that platelets pool in the spleen and are released after a mean residence time of about 10 min. Plasma exchange for the treatment of immune complex disease was shown to be associated with improved RE function as measured by the splenic extraction efficiency of radiolabelled antibody-coated red cells, using simultaneously injected In-111-labelled platelets to measure splenic blood flow [31]. Before then, it had been thought that RE function could be quantified by the clearance rate of heat-damaged red cells until we showed that the clearance rate reflected splenic pooling and was therefore, like platelet equilibration between blood and spleen, a measure of splenic blood flow. Early studies on pulmonary epithelial permeability using inhaled Tc-99m-DTPA [32] and pulmonary endothelial permeability using intravenous In-111-transferrin [33] were performed by Royston and his co-workers. Davies

and Walport demonstrated for the first time the whole body kinetics of I-123-labelled immune complexes [34].

In the mid-nineties, rotaPET was acquired by what had now been re-named the 'Nuclear Medicine Department'. This was a partial ring detector consisting of two separate segments and was used predominantly for FDG imaging of cancer but also clinical F-18-DOPA brain imaging. The department was involved in early clinical work with In-111-pentetritide and showed how amino acid infusion blocked renal tubular uptake of the agent [35]. In research, Harrington and Stewart demonstrated the targeting of tumours by In-111-labelled stealth liposomes containing chemotherapeutic agents [36]. In collaboration with 'Tiny' Maini from the Institute of Rheumatology, the therapeutic effect of TNF $\alpha$  blockade was shown to reduce dramatically leucocyte uptake in rheumatoid joints [37]. Muhammad Mubashar was one of the first workers to image P-glycoprotein expression in breast cancer [38]. As one of the first centres in the UK to develop interventional radiology, the Hammersmith Hospital was a referral centre for conditions such as pulmonary arterio-venous shunts and much work with the Department of Respiratory Medicine [39] was performed to quantify these shunts before and after therapeutic embolization. Finally, elegant work performed in collaboration with George Hall, an anaesthetist with an interest in exercise physiology, demonstrated in trained athletes undergoing maximal brief exercise how platelets and all leucocyte subtypes pool in the spleen with similar residence times [40]. Contrasting the behaviour of red cells versus leucocytes and platelets in response to exercise, he showed that the spleen is essentially an erectile organ – permanently erect!

In the time I was at Hammersmith Hospital (1979–1999), the Hammersmith campus was probably the leading medical research hospital in the UK, and enjoyed a reputation based on a fantastic multidisciplinary approach and spirit of collaboration, co-operation and clinical support. Clinical research in nuclear medicine that goes beyond the evaluation of the latest novel radiopharmaceutical or imaging hardware critically depends on support from the clinicians, and this support was second-to-none at the Hammersmith.

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**Michael Peters** I did my pre-clinical training at St Mary's Hospital Medical School where I received a BSc in physiology in 1967. I then transferred to Liverpool University and received MB ChB in 1970. In 1972, I was appointed as lecturer in physiology in the medical school at Liverpool. This is where I discovered my interest in the use of radionuclides to study human physiology and did an MD in the use of Xenon-133 to measure hepatic perfusion. Uncertain of what I then wanted to do, I went to Australia and became a GP for 4 years, doing many different jobs and discovering the attractions of the country. I returned to England in 1978 a few weeks before my mother succumbed to breast cancer, and after a year in general practice in Liverpool I secured a clinical research fellowship at the Royal Postgraduate Medical School to work on In-111-labelled lymphocytes. There I met my mentor, Peter Lavender, and the great Robert Steiner. There followed 3 years of intense research on In-111 cell labelling and then the funding ran out so I joined Glaxo Group Research as a Research Physician. My big break came in 1984 when Isky Gordon and Peter Lavender created a senior lectureship in radiology split between RPMS and the Institute of Child Health. These two great functional radiologists convinced me of the importance of integrated imaging, a view later cemented by the introduction of PACS at the Hammersmith Hospital in the mid-nineties. In 1988, I became full time at RPMS and then, with Peter's retirement in 1991, ran nuclear medicine at Hammersmith single-handedly until 1999 when I was appointed Foundation Professor of Nuclear Medicine in Cambridge. At this time, Cambridge Medical School was growing rapidly under the leadership of Keith Peters, a man I greatly admired when he was Professor of Medicine at RPMS. I spent 6 productive years in Cambridge, working with Edwin Chilvers (respiratory medicine) and Arnie Purushotham (breast cancer), before moving to the new medical school in Brighton. The first appointments made in Brighton were Jon Cohen as Dean and Kevin Davies as Professor of Medicine, both ex Hammersmith colleagues, so whilst Cambridge was jokingly called Hammersmith North, Brighton became known as Hammersmith South. I should have retired 5 years ago but I am still working full-time and enjoying the research as much as ever. The three high points of my career were election to the fellowship of the Academy of Medical Sciences in 2002, award of a DSc from the University of Liverpool in 2009 and invitation to give the Annual Lecture at the spring meeting of the BNMS in Brighton in 2011.