A History of Nuclear Medicine in the UK

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The use of radioisotopes in the UK can be traced from the first tracer study carried out by George von Hevesy. Von Hevesy was born in Hungary studied in Germany and came to work with Ernest Rutherford in Manchester in 1911. His task was to separate Radium D from lead. He suspected that his landlady was reusing food left on his dinner plate. He put some ^{212}Pb into the left overs and some days later used a radiation detector to detect it confirming that his landlady was in fact recycling his food (Fig. 2.1).

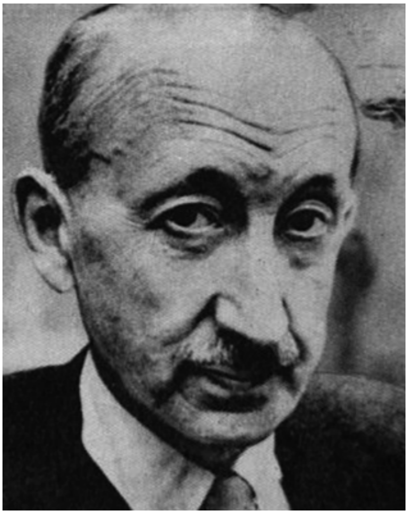

Fig. 2.1 Georges von Hevesy

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The early use of radionuclides in the UK was hindered by the McMahon Act in the US prohibiting the export of radioisotopes made in reactors until 1947. However as one of the peaceful uses of atomic energy UK government money was being poured into the Atomic Energy Research Establishment at Harwell to produce radioisotopes. Already in 1947 J S Mitchell listed most of the radioisotopes that would be used as tracers. The first isotope conference sponsored by Harwell was held in Oxford in 1951 Fig. 2.2 [1]. By 1954 colloidal gold bismuth 206 and phosphorus were being produced for therapy and iodine 131 iron 59 chromium 51 for human diagnostic procedures. With the support of the Medical Research Council medical radioisotope units managed by physicists were being formed. At the Hammersmith Hospital the first therapeutic dose of P-32 was used in November 1947 to treat a young girl with a glioma [1, 2]. By 1954 Professor Sir David Smithers at the Royal Cancer Hospital London listed treatments on 96 patients using ^{32}P, ^{131}I, ^{24}Na, ^{82}Br, and ^{198}Au [3]. The non-therapeutic use of radioisotopes concentrated primarily on human physiology. In 1957 John West studied lung perfusion with oxygen-15 produced by the first recently installed cyclotron at the MRC unit at the Hammersmith Hospital. Other in vitro studies included those on whole body water, blood volume and red cell turnover, calcium metabolism, cardiac and renal function.

The original reference book was that of Veall and Vetter 1958 entitled Radioisotopes in Clinical Research and Diagnosis (later edited by Belcher and Vetter). Counting was done using home-made circuitry with Geiger Counters. Norman Veall devised a circular array of Geiger counters to count urine in a

Fig. 2.2 Norman Veall

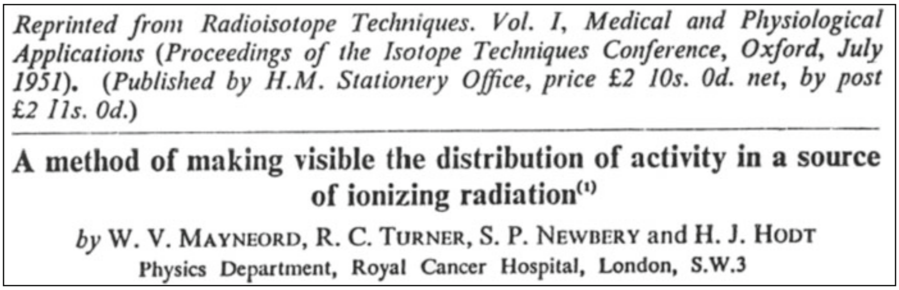
Winchester bottle. These were eventually replaced by scalers and ratemeters made by E K Cole in Southend and Isotope Developments Ltd Aldermaston which later became part of Nuclear Enterprises Edinburgh. Norman Veall is remembered by the Norman Veall medal presented to a clinical scientist annually at the BNMS.

A key development of in vitro studies in the UK was made by Roger Ekins at the Middlesex Hospital London who in 1960 enabled the quantitative determination of thyroid hormones in blood samples using radioactive isotopes and specific binding proteins [4]. Radioactive B 12 was produced by J M Bradley at the Hammersmith Hospital with high specific activity cobalt-56 with the help of Glaxo. Direct evidence of B 12 absorption in the ileum in 1959 by found by Booth and Mollin who studied the distribution of radioactivity in the intestine after oral administration of radio labelled B 12. using a Geiger counter during a laparotomy [5].

In 1949 Ansell and Rotblat in Liverpool made the first radioisotope image in the UK of a patient with a retrosternal goiter [6]. By 1955 the precursor of imaging used hand held Geiger counters to plot iso-contours of iodine 131 activity in the thyroid gland. Russell Herbert also in Liverpool used a small calcium half inch diameter tungstate crystal on an early photo multiplier tube to improve the sensitivity. Early single and multibore lead collimators improved the resolution.

An early scintillation detector designed for brain studies with Iodine 131 fluorescein was made in March 1951 by Belcher and Evans at the Royal Cancer Hospital (now the Royal Marsden Hospital) in London. The photomultiplier tube had to be cooled by liquid nitrogen to reduce the background noise. To avoid the possibility of frostbite, the patient's skin and the crystal were separated by a long Perspex light guide!

Also in 1951 rectilinear scanning was being developed to make iodine 131 thyroid imaging easier. The first device in the UK was made at the Royal Cancer Hospital London in 1951 to image initially radionuclide sources and then the thyroid gland. The Mayneord scanner displayed images on a Cathode Ray Tube, used Geiger counters, collimator, background subtraction and a clever raster scanning mechanism (Fig. 2.3).



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A method of making visible the distribution of activity in a source of ionizing radiation(1)

by W. V. MAYNEORD, R. C. TURNER, S. P. NEWBERY and H. J. HODT
Physics Department, Royal Cancer Hospital, London, S.W.3

Fig. 2.3 A copy of the paper by Mayneord et al. of the first UK radioisotope scanner presented at the 1st Harwell sponsored Oxford conference in 1951

The scanner was preceded in 1950 by that shown by Ziedes des Plantes at the London International Radiological Congress [7]. Benedict Cassen in the US also published his paper on a thyroid scanner in Nucleonics 1951.

Professor Val Mayneord inventor of the first UK radioisotope scanner and his wife Audrey met with Professor Ian Donald inventor of the ultrasound scanning in the Nuclear Medicine and Ultrasound Department at the Royal Marsden Hospital in Sutton Fig. 2.4.

The first home made whole body scanner with a colour print out was built in 1957 at the Hammersmith Hospital by Mallard and Peachey [8]. Also home-made was the first UK digital whole body SPECT scanner in Aberdeen. The first commercial Tri-D scanner was installed in the Royal Marsden Hospital Sutton in 1963. It lacked adequate collimation and soon after a 3″ Picker rectilinear scanner was purchased. In the days before ultrasound I-131 labeled albumin was used to

Fig. 2.4 Professor Val Mayneord inventor of the radioisotope scanner and his wife Audrey with Professor Ian Donald inventor of ultrasound scanning. In the background is Professor Kit Hill, Head of the joint department of Medical Physics Institute of Cancer Research and Royal Marsden Hospital Sutton

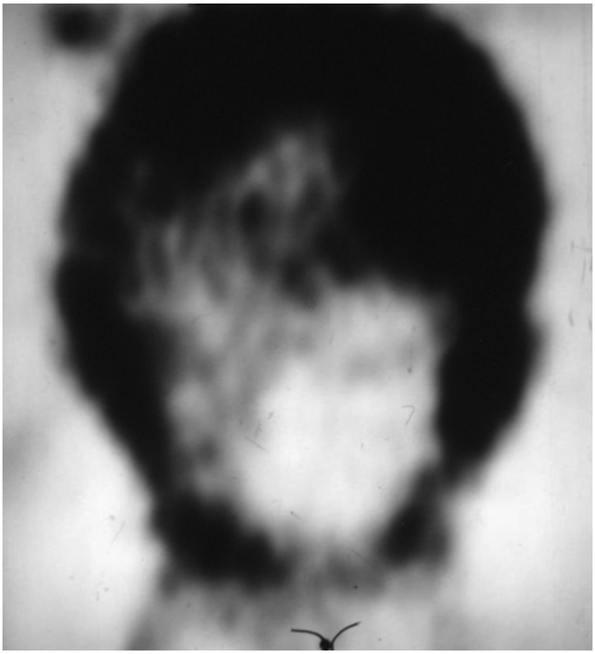

Fig. 2.5 A photoscan of abdomen showing the placenta taken with a 3″ Picker Magnascanner using I-131 labeled albumin

demonstrate the position of the placenta! Fig. 2.5. Those were the days in which anything was possible. The burdensome legislation governing the use of radioactivity was yet to come.

In the mid 1960s Glass and Westerman installed the UK's first Anger Gamma Camera at the Hammersmith.

A local firm Ekco Electronics Ltd in Southend constructed an Anger type gamma camera in 1964 using 9 photomultipler tubes and a 5 in. cryatal. It was not a great commercial success.

In 1977 another local firm J&P constructed the first UK tomoscanner with the assistance of David Keeling and Andrew Todd-Pokropek. It was placed in the Middlesex Hospital London for evaluation. Tl 201 scans using it were published in 1979 from the UK and France.

In the early days of renography Marcus Hall a radiotherapist at Canterbury Hospital developed a technique to eliminate blood background activity [9]. A computerized version of this technique was later developed by Britton and Brown in 1970.

1967 was a good year for innovation. The first paper using F-18 produced by the MRC cyclotron unit for rectilinear scans of bone showed a massive improvement in sensitivity from strontium-89 was published in 1967. With a half life of 109.8 min

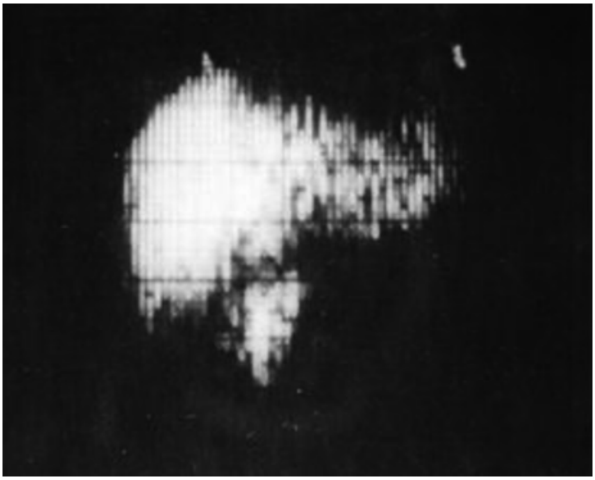

Fig. 2.6 Se-75 methionine pancreatic scan imaged on an Intertechnique computer

it was fortunate that the traffic flow and the number of traffic lights between Hammermith and Royal Marsden in Sutton was quite low [10]. In the same year Norman Veall published with Steve Garnett the still used technique for the measurement of Glomerular Filtration Rate [11]. Initially devised to improve tumour detection in brain scanning a ratio subtract device was constructed in the physics workshop in the Institute of Cancer Research in Sutton Surrey in 1967 [12]. Later the device was used to eliminate the liver uptake of seleno-methionine in pancreas scanning [13]. The same technique was performed on an early digital computer by Intertechnique Fig. 2.6. It is interesting to reflect on how exciting such awful images were. In fact this was a good example since many pancreas images consisted of about 15 dots.

In 1969 Roy Parker with his colleagues from the Atomic Weapons Research Establishment developed the first semiconductor camera [14]. Using a cooled germanium detector clear images of a rat's tiny thyroid were shown at an IAEA Medical Radioisotope Scintigraphy meeting in Vienna long before the invention of the current solid state cameras. Kromek in the UK is currently advancing CZT technology to provide similar high resolution solid state SPECT camera imaging without the need for cooling.

Fazio and Jones at the Hammersmith reported in 1975 on the use of the generator produced 13 s half life ^{81m}Kr for gamma camera imaging of regional lung ventilation. The 190 Kev gamma ray emission complimented ^{99m}Tc 140 Kev emission there by enabling simultaneous ventilation; perfusion imaging. The ^{81}Rb/^{81m}Kr generator was developed by Clark and Watson who responded to the demand for this 4.7 h half-life generator across the UK. As a result at one point ^{81m}Kr/ ^{99m}Tc based ventilation: perfusion imaging was the second most frequent imaging procedure in the UK after ^{99m}Tc bone scanning.

As the krypton generator was delivered to the individual hospitals only once or twice per week it was important for patients to have their suspected pulmonary embolus on those days only! 1977 saw the first use of I-123 hippuran for gamma camera renography by O'Reilly and colleagues in Manchester [15].

Following the demonstration of dopamine receptors in the brain by Henry Wagner in 1983 Imaging Dopamine Receptors in the Human Brain by Positron Tomography using 3-N-[^{11}C]methylspiperone. Steve Garnett et al. who had left Guys Hospital for McMaster Canada had imaged F18 fluoro-dopa with their home built brain PET scanner to show the distribution of dopamine in the basal ganglia published in Nature in 1983 and John Crawley in the UK demonstrated dopamine receptors in human brain with *77*Br-p-bromospiperone the benefit of Br-77 being its 57 h half life [16]. In 1985 Peter Ell and his colleagues at the Middlesex Hospital published the world first cerebral blood flow image using the Amersham produced Tc99m labeled HM-PAO [17].

In the early 1980s, studies with the UK's first commercial PET scanner at the MRC's Cyclotron Unit at Hammersmith demonstrated the Warburg effect of anaerobic glycolysis of human tumors by showing that gliomas preferred to metabolize glucose (^{18}FDG) to oxygen (^{15}O). It was also reported for the first time by Nolop that lung tumors have a high uptake of ^{18}FDG. This set the scene for the introduction of clinical PET world-wide where ^{18}FDG Lung cancer PET imaging was the first procedure to be reimbursed in the USA. Also the enhanced uptake of ^{18}FDG in breast cancer was reported by Beaney at that time. It should also be noted that the first use of FDG was in the UK by Bessel et al. who explored its use as an anti-cancer agent [18]

The introduction of Sr-89 by Amersham International (Metastron) led to a study of a treatment for painful bone metastases from prostate cancer by the Southampton Group in 1991. A randomized trial of 32 patients showed the benefit of the treatment against stable strontium [19]. In 2002 a grant from the National Institutes of Health enabled the Royal Marsden/Institute of Cancer Research group to test the feasibility and toxicity of high activities of Rhenium-186 hydroxyethylidene diphosphonate, with peripheral blood stem cell rescue in patients with progressive hormone refractory prostate cancer metastatic to bone [20]. It was hoped that the high activities would ablate the metastases as well as relieving bone pain. The long term results of that study are being evaluated.

More recently in 2013 the Royal Marsden published a multicentre Phase 3 study on the use of Re-223 for the palliation of bone pain on the effect on overall survival from metastases from castration resistant prostate cancer. The result showed a significant improvement on overall survival [21].

The first administration of radioiodine for thyroid cancer in the UK was given by Sir Eric Pochin in 1949. While the results from the use of radioiodine thyroid cancer have been excellent as early as 1964 Pochin was already recording untoward side effects from its use. There remains controversy on the balance between giving high activities to ensure total eradication of any residual disease and giving low activities to minimize the risks and shorten isolation in the hospital.

A first UK wide randomised HiLo study compared the effectiveness of 30 and 90 mCi of I-131 for post operative ablation of residual thyroid tissue. In the paper published in the New England Journal of Medicine in 2012 the results of the HiLo study opened the possibility of a complete change in practice reducing the post operative ablative administered activity [22]. Following the success of that trial a new UK nation-wide study comparing the administration of Iodine 131 with none in low risk patients is being carried out.

The UK can be proud of its long record of the development of radionuclide studies. Its input has ranged from the introduction of new radionuclides and techniques, the development of new equipment, and the use of radionuclides in a wide variety of diseases. It is fortunate that the innovation and research continues with the development at Kings of Ga-68 compounds which should widen the use of high resolution PET imaging both in the number of applications and its spread to centres distant from the cyclotrons.

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Ralph McCready I graduated from Queens University Belfast with a BSc in Physiology and my medical degree. As a houseman I worked in the Royal Victoria Hospital for Dr Frank Pantridge who invented the defibrillator. I was fascinated by his catheter laboratory and decided to study physiology in radiology. I moved to Guy's Hospital London to study for an MSc in Radiation Physics and Biology together with a Diploma in Medical Radiological Diagnosis (DMRD). My next position was an S.H.O in the Radiology Department of the Hammersmith Hospital where I used to assist Professor Steiner at the beginning of interventional radiology. During a locum in the newly opened Royal Marsden Hospital in Sutton I was offered a research position in the Institute of Cancer Research in the Isotope Unit by Dr E.O. Field. Early publications included mediastinal lymph node scanning in 1967 and F-18 imaging of bone metastases also in 1967.

Eventually I became a Consultant in Nuclear Medicine in charge of the Nuclear Medicine and Ultrasound Department for over 40 years. With Nuclear Medicine and the Medical Physics departments at either end of the same corridor I was fortunate to be able to take part in many projects involving innovations in nuclear medicine, ultrasound equipment magnetic resonance spectroscopy and radiopharmacy. It was privilege to work with Nigel Trott, Bob Ott and Maggie Flower, Martin Leach, Kit Hill and Glenn Flux amongst others. In 1973 I was awarded the Barclay Prize by the British Institute of Radiology for my contributions to the British Journal of Radiology. I was awarded a DSc in the Faculty of Science of Queens University in 1987. In 1974 I was elected to a Fellowship of the Royal College of Physicians London and in 1975 was conferred a Fellow of the Royal College of Radiologists London. I was conferred an Honorary Fellowship of the Faculty of Radiologists, Royal College of Surgeons, Ireland in 1992 and in 2004 was made an Honorary Member of the Japanese Radiological Society. In 1978 I was a vice president of the European Nuclear Medicine Society the chairman of the task group on Education and Training of the EANM 1988–1991 which preceded the European School of Nuclear Medicine.

Now retired I still enjoy publishing and presenting at National and International meetings. I am a Professor Emeritus at the Institute of Cancer Research London and an Honorary Consultant at the Royal Sussex County Hospital in Brighton, U.K.