HISTORICAL ARTICLES

The Contribution of Medical Physicists and Doctors in Aberdeen to the Evolution of Modern Medical Imaging - SPECT, PET and MRI, 1965-1992

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Abstract
From the beginnings of medical imaging with radioactivity, an account is given of the development in Aberdeen of Computed Tomography (CT) scanners in Nuclear Medicine, and their clinical value, leading to present-day gamma-cameras. The introduction and clinical use of the cyclotron and Positron Emission Tomography (PET) imager in Aberdeen, has led to a national programme for the cancer patients in Scotland. Early animal work with electron magnetic resonance, which developed into a programme towards nuclear magnetic resonance of water, and then to a quest to build the first clinically-useful whole-body MRI, is described. Successful diagnostic images obtained with it have led to the present-day worldwide use of the MRI technique.

Keywords
Medical Physics, Medical Imaging, Nuclear Medicine, Nuclear Medicine Tomography (SPECT; PET), Magnetic Resonance Imaging (MRI) Spin-Warp Imaging, PEDRI

Prologue

The author was appointed in 1965 to the first Chair of Medical Physics in Scotland at the University of Aberdeen, and to head a Department, jointly funded by the University and the NHS, which provided all the medical physics and bio-medical engineering services to the hospitals of the North-East of Scotland, and to Orkney and Shetland. In the University of Aberdeen, the Diploma in Medical Radiology course was begun in 1966, at the request of Dr L.A. Gillanders, Head of Radiology, to train junior radiologists. An M.Sc. course in Medical Physics was introduced in 1967, which was the forerunner of such courses worldwide, which was to train and inspire graduate physicists in medical applications.

The author had entered hospital physics in 1951 in Liverpool, taking part in the early use of artificial radio-activity (Iodine-131) in medicine for the measurement of thyroid function, and the very beginnings of 'imaging' the gland by moving a collimated Geiger counter in steps across the neck[1, 2]. This nuclear medicine imaging depends on the difference between normal and abnormal tissues, leading to different concentrations of the radio-actively labelled tracer. In 1953 the author moved to Hammersmith Hospital, London, where, in 1957 the world-first whole-body radio-isotope scanner was built[3], which was used for thyroid, liver, pancreas and kidney tumour imaging. It was used also to detect brain tumours, with the patient's head between two scintillation counters, which detected the positron-emission, coincident gamma-rays from a cyclotron-produced, positron-emitting radionuclide (As^{72}),[2, 4] which showed increased concentration in the tumour. This series achieved an 80% clinical accuracy, and was the forerunner for PET (Positron-Emission Tomography), when tomographic imaging later became possible.

The first European gamma-camera was built, in collaboration with EKCO Ltd of Southend, which could form images of gamma-ray distributions in the body without any scanning movements. It had only seven photomultiplier tubes and a 5-inch detector! Crude images of brain tumours could be obtained in 20 minutes, about half of the time needed for the scanner, using I^{131}labelled HAS.[5] These images were quickly digitised using two multi-channel analysers, to create the image pixels, and the first digitised gamma-camera 'image' was shown at the First International Congress of Medical Physics in 1965.[2,6] Also at Hammersmith, the first steps towards MRI were taken in the late 1950s and early 1960s, when it was discovered that samples of animal tumours gave a different size of electron magnetic resonance signals from their normal tissues.[7, 8] This ready-made natural contrast between a tumour and its surroundings could lead to a new form of imaging and the author's quest towards MRI had thus begun in the early 1960s. This potential new imaging method was reported to the same Congress in 1965 and discussed in his Inaugural Lecture in 1966.[9, 10, 11]

When the author moved from London to Aberdeen in 1965, a furniture removal van transported the body scanner; the gamma-camera; and the electron magnetic resonance spectrometers to Aberdeen.

Nuclear Medicine Imaging in Aberdeen – 1965 Onwards

A radio-isotope clinic for thyroid disorders and polycythaemia had been begun in Aberdeen by Professor Alastair MacGregor and Dr James Crooks (who later became Professor at Dundee), the physicists being Dr Tom Buchanan and Alistair McIntosh. To this was now added the first "radio-isotope scanning service" for thyroid disorders (with I^{131}); liver tumours (with Au^{198} colloid), and brain tumours (with I^{131} labelled HAS). Dr Sally MacDonald, a radiologist, enthusiastically took on clinically the diagnostic imaging field, and this collaboration laid the foundation of Nuclear Medicine imaging as it is today in Aberdeen, with a Consultant in Nuclear Medicine investigating over 10, 000 patients a year with about 40 different diagnostic tests, of which 30 are imaging ones.

The first gamma-camera was replaced in 1967 by one of the first commercial gamma-cameras, built by the Edinburgh company Nuclear Enterprises Ltd., a company which made a big impact on the field of radio-active measurement (and ultrasound imaging) for over 40 years after World War Two. It was exciting when this gamma-camera was connected online in 1969 by Dr Peter Undrill, an early computer expert, to a small computer (DEC PDP81) and a primitive digital display system. Thus began modern digital medical imaging.[2] This new camera, with digital imaging, helped to image the very elusive pancreas more clearly, using Selenium-75 labelled methionine, which localises in the pancreas and liver, and digitally subtracting an image of the liver alone, obtained with technetium-99m colloid.

Nuclear Medicine tomography – SPECT

This same computer and display system also made it possible for us to pioneer single-photon emission computed tomography (SPECT or SPET).[12] Transverse slices could be imaged across the body – until then the only views were AP, PA and laterals. The transverse section image of the tumour has a greater contrast, and a better chance of detection.

Tomography was first carried out by Dr Dave Kuhl in 1964 using an analogue technique.[13] The Aberdeen team built the first digital CT for Nuclear Medicine from 1967 to 1969[12] (this was some 5 years before the technique was applied to x-rays by Godfrey Hounsfield[14], which revolutionised x-ray diagnosis, and for which he shared a Nobel Prize). The scanner which we built was nicknamed ASS for Aberdeen Section Scanner[12], where two opposed scintillation counters made passes across the patient at a series of angles around the patient, all in the plane of interest. The mathematical method of reconstructing the image from the information gained from each pass, was originally developed by Radon[15] in Vienna in 1917, and is known as 'back-projection'. Tumours seen not very positively on AP and lateral views were clearly detected and localised on the CT view (Fig. 1), and the addition of this view from 1971 onwards, gave an improvement in brain lesion detection to 92%, halving the false negatives.[16] This scanner, and the improved version[17] (ASS Mark II – which was only dismantled in 1993), and the gamma-camera version built in the mid-70s[18], became the method of choice in Aberdeen for brain tumour detection for some years. It was used also to aid radiotherapy treatment planning, and in a clinincal trail to evolve a more positive diagnosis of epilepsy.[19] SPECT was in regular clinical use in a Aberdeen with ASS a couple of years before x-ray CT was announced in 1973, but when that did eventually arrive in Aberdeen in the early 1980's, x-ray CT became the method of choice for brain lesion detection, due to the much greater detail in the images.

A commercial version of ASS was produced by an UK company and a US company for a while, but the major multinational imaging companies really took SPECT up in a big way from the mid-1980's onwards, following our gamma-camera version[18], and these now form the main workhorse of modern Nuclear Medicine facilities, producing superb images, AP's and laterals as well as CT's. Using ASS II, and these cameras, Professor Peter Sharp (the author's successor) pioneered the use of a radioactive drug (HMPAO) to image blood flow in the brain, which is used, for example, to distinguish between Alzheimer's dementia and Huntington's chorea.[20]

Teaching hospitals worldwide and better general hospitals, all have a Nuclear Medicine service carrying out about 15, 000 tests per million population, having a significant effect on patient management, half using SPECT. The effort to pioneer SPECT in Aberdeen was considerable, with 18 physicists in total from 1967 to 1987 (not all simultaneously!), and 5 different medically-qualified staff involved in their clinical interpretation and use, particularly Dr F.W. Smith (now Professor), the Consultant in Nuclear Medicine during most of that time.

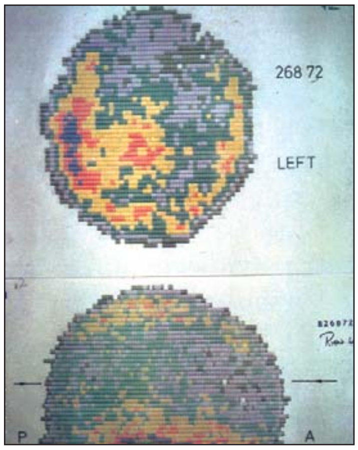

Figure 1

Nuclear medicine tomography – PET

The early brain tumour work described above had been carried out with a clyclotron-produced isotope, and although reactor-produced radio-isotopes are the backbone of Nuclear Medicine, the cyclotron is ideal for producing the short-lived isotopes of oxygen, carbon, nitrogen and fluorine which can be used to label compounds and pharmaceuticals to study living processes in the body. These isotopes emit positrons, which can be imaged as described above. By the 1970s, largely due to Dr Ter-Pogossian at St. Louis, using arrays of small detectors around the patient, the images were becoming of sufficient detail to be of real potential for clinical research and diagnosis – it was becoming known as Positron Emission Tomography (PET).

At that time, a cyclotron and PET imager costed over £1.5m plus a building with special radiation protection. After a public appear for funds, and with the help of the MRC and the local NHS, in the early 1980s, a second-hand cyclotron (moved by the Army!) and PET imager were installed in a modified old farm building at Woodend Hospital, Aberdeen. The PET was used for a series of research studies into brain, heart and bone disorders and into malignancy, leading to a valuable test for breast secondaries and their response to chemotherapy.[21] Following successful efforts by Peter Sharp, the John Mallard Scottish PET Centre was opened in 1998, by the then Scottish Minister of Health, in a new building at the Aberdeen Royal Infirmary, with a fine-resolution PET and self-shielded cyclotron. It has been used for 14 different projects, including anti-cancer therapies, multiple sclerosis, hip replacements, breast cancer metastases, hibernating myocardium, pre-operative planning for brain tumours, and investigation of brain functions. Following initiatives by Peter Sharp, the value of PET has been recognised by the Scottish Executive, in the October 2005 announcement of an overall programme of PET installations to improve treatment for Scottish cancer patients.

Magnetic Resonance Imaging (MRI)

The author's quest towards imaging with magnetic resonance was boosted when two post-docs – Jim Hutchison (physicist) and Meg Foster (biologist) were recruited – and they became husband and wife. They played a vital role, and throughout the development in Aberdeen, a biological programme to understand the resonance signals, went hand-in-hand with the physical and technological development of the imager. Following the early work on animal samples, [7, 8], a spectrometer was built to try to obtain electronic magnetic resonance signals from mice[22], but the radiation frequency necessary was too much absorbed in soft tissue, and was also scattered too excessively to be useful in a human. In addition, these electron signals originate from free radicals in the tissues[8], which are of low concentrations. (It is to be noted here that the goal of imaging free radicals in the body at this time continues to be pursued in Aberdeen by Professor David Laurie, using a double resonance technique know as Proton-Electron Double-Resonance Imaging (PEDRI[45]))

In the early 1970s we changed from electron to nuclear magnetic resonance (NMR), in particular to that of the hydrogen protons in water. We were influenced by Damadian's measurements of the NMR parameter T1 (spin-lattice relaxation time) of water in tissue samples[23], not unlike our early tissue sample work. For this NMR, the lower radiation frequency necessary has much less absorption and scatter, which, together with lower magnetic fields and the much higher concentration of water protons, made it a much more practicable possibility for human imaging, than electron magnetic resonance. We found that T1 times were longer for malignant tumour samples than for normal tissues, but less so than Damadian had found: the difference - about 10% - appeared to be related to the water content of the tissues.[24, 25] Meg Foster showed that the T1 of animal liver was about 1/10 that of pure water (3.5sec@24MHz), with the spleen being 60% longer, and white brain was about 40% less than grey.[26] Thus, NMR imaging of water protons might distinguish between the organs and between grey and white brain (not possible hitherto by external imaging), as well as possibly showing tumours and inflammation. A rabbit T1 image, and even a human sectional image were drawn predictively[26, 27] – it turned out to be surprisingly accurate!

In 1973 in USA, Lauterbur (Nobel Prizewinner 2003) made the key proposal to form an NMR image.[28] In addition to the standing uniform magnetic field required to create the magnetic resonance within a sample, a uniform magnetic field gradient was to be added. By obtaining a series of resonant frequency spectra around the sample, by applying the magnetic field gradient at different angles around the sample, an image can be reconstructed by computed tomography.

Since we were already to the fore in computed tomography, and had all the computer programmes to hand, we were very quickly able to explore this, and the first image of a whole mouse (Fig2) was obtained in March 1974.[29] It was outlined by proton concentration signals, and the liver and brain were localised within it by the average T1 values at each point. To our astonishment, we saw also on the image, the long T1 values from an area of inflammation in the newly dead mouse.

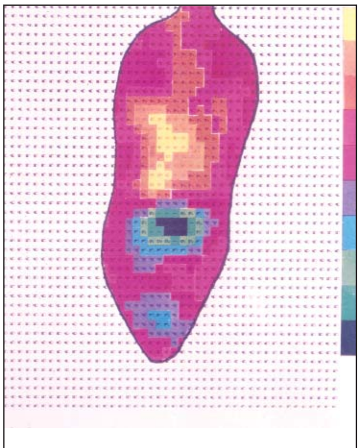

Figure 2

MRI - Milestones on the road to clinically useful images.

For a brand-new imaging technique to prove its worth clinically, the scanner experience had shown that it must be capable of imaging any part of the body: also the mouse image had shown that it must display T1 as well as proton content. The magnet needed to image a body trunk was very large and a field strength uniformity of 1 in 10^4 was vital. Permanent magnets and iron-cored electronmagnets were considered but weight (6 tons) and eddy current problems led us to adopt an air-cored electromagnet. A vertical standing field, (at 90° to the radio frequency, and the supine patient), gave a favourable gain in signal/noise (=$\sqrt{2}$), but to achieve adequate cooling and that uniformity, we dare not go above 0.04T.[26, 27] The magnet was built for us as its very first one-off by Oxford Instrument Ltd., and to buy it, and build by ourselves the radio frequency and the three gradient coils (x, y, z), and all the electronics, we needed about £30k. It took 18 months to obtain this (from the MRC). It soon became clear that the CT method was far too slow for clinical imaging, and pulse-sequence methods, related to those in laboratory NMR spectgroscopy, needed to be evolved.

Dr Hutchison introduced the inversion-recovery pulse sequence to proved T1 weighted images.[30] It became necessary to expand the team, and a young go-getting American, Bill Edelstein, joined us from the University of Glasgow; it was now seven strong including the Ph.D. students. By 1979 images were being obtained from ourselves (Fig 3), which showed identifiable organs, but they were badly spoiled by interfering artefacts due to body movements such as heart beats, making them of little use for clinical purposes.[27]

Whilst our whole body machine was being built (far too slowly!), other teams were making progress towards MRI, spurred on by the Aberdeen mouse image, so the author has been told. There were three teams at Nottingham: one led by the late Raymond Andrew, who produced the first image of a wrist in 1977[31]; one led by Peter Mansfield, who patented the method of selectively exciting and defining a slice in 1974[32], obtaining a finger image in 1974 and a cross section of an abdomen in 1978 using an electromagnet with a horizontal field, and who later concentrated on echo-planar fast pulse sequences[33] (for which many believe that he shared the Nobel Prize in 2003); and one led by the late Bill Moore, who built a whole-body imager in the early 1980's[34]. There was also a team led by Ian Young at GEC, London, who first imaged a human head in 1978[35]. Dr Young is an Aberdonian, and was awarded a D.Sc. (Hon) by Aberdeen University in 1992. There was also Raymond Damadian's team in New York, who produced the first human thorax section in 1977[36]. Although these were all of laboratory interest, none of them had the clarity and detail necessary for diagnostic clinical work.

At times from 1974 to 1980, we wondered whether we were mistaken to struggle on to make our whole-body imager capable of imaging T1 as well as proton content, since the other teams appeared to be leading the way. However, in the end it proved to be absolutely right. The movement artefacts in the images were not eliminated until early 1980, when the first of the two-dimensional Fourier transform methods was introduced[37, 38], nicknamed 'spin-warp'. This gave us, for the first time, an accurate distribution of the signals in the two dimensions of the plane across the patient, allowing for body movements. Also, an interleaved set of gradient and radio frequency pulses gave us a proton content image and a T1 image.

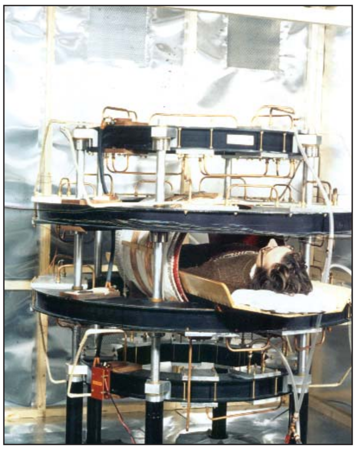

Figure 3

Spin-warp was the real breakthrough for MRI. Realistic images of ourselves showed startling anatomic detail of soft tissues, and this period also allayed fears of short-term damage from the various fields applied to the body. The first patient was imaged in late August 1980 (Fig 4), and showed both primary and secondary malignancy, including a metastasis in the spine, not suspected before in that patient.[39, 40] The images were first shown publicly at an IAEA Conference in Heidelberg in September 1980.

The Early Days of clinical MRI

Our prototype machine, in a research laboratory, was quickly in full use to investigate patients, selected and cared for by Dr F W Smith (Consultant in Nuclear Medicine), who explored its clinical potential. Patient facilities had to be created and very soon MRI was found to be diagnostically useful for many things, including multiple sclerosis (Fig 5), for which it is now the method of choice. It gave superb contrast between different soft tissues and unlike x-rays and radio-activity, it is unlikely to cause any long-term hazard, because the quantum energy of the radiation used in MRI is 9 orders of magnitude lower. Over 900 patients were imaged with this prototype over the next 2 or 3 years, and many papers were published of world-first clinical explorations of the areas that now find wide application in MRI practice.[41, 42] There was excitement in medical circles, some likening the breakthrough to the discovery of x-rays in 1895. We had a frenetic period of national and international lectures, and editors welcomed our papers.

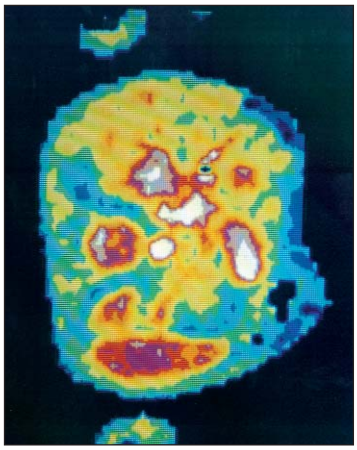

Figure 4

The multi-national medical imaging companies crashed in, pouring in megabucks to develop improved machines, and we lost some members of our team, notably Edelstein to GE in New York taking all our know-how. Our prototype was so busy with patients, that in order to improve it we needed to build another machine. Nobody in UK was prepared to fund this, except Asahi of Tokyo (in return for the know-how), and we built a Mark II prototype, which was installed in the Aberdeen Royal Infirmary in 1982 in a new room provided by the Grampian Health Board. This had the same configuration and twice the standing magnetic field strength (0.08T): it gave much improved images, and over the next ten years imaged over 9, 000 patients. Fortunately, with the help of the British Technology Group, patents had been taken out (at the time, this was not fashionable in academia), and the royalty sharing agreement has brought £17.2m to the University of Aberdeen.

It was clear that this new technique was here to stay. To satisfy personal requests for a machine – notably from Edinburgh radiologist Jonathan Best – and in an attempt to try to keep some of the manufacturing in Scotland, the author set-up a small company (M&D Technology): it was undercapitalised, the NHS did not buy, so it was beaten down eventually by the superior models now coming on stream from

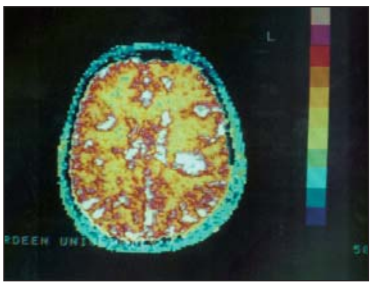

Figure 5

the multi-nationals (with superconducting magnets and over £1½m, each), but the one built for Edinburgh is now in the National Museum of Scotland, and the one for St. Bartholomews Hospital, London in the Science Museum, London. Asahi, with its vast resources, sold 145 almost identical machines in the Far East!

MRI with Superconducting Magnets

Ian Young made the next major stride forward by installing at Hammersmith Hospital in 1981, a machine with superconducting magnet (the first from Oxford Instruments) providing a horizontal field of 0.15T. This gave much better stability, and due to the higher field strength, more detailed images, more akin to x-radiographs. The competing multi-nationals quickly adopted them, in spite of their great expense, and by 1984, fields up to 0.5T had become available[42], and there were many hundred imagers in use in the USA, Japan and Germany, whilst the UK, which had developed MRI, had barely 10! Ironically, this meant that papers from Aberdeen were being rejected as "not state-of-the-art". In the hands of skilled clinical teams worldwide, MRI was applied to a vast range of clinical problems, and readers of this Journal will be familiar with the impact of MRI upon their respective specialities, and new consolidations of its diagnostic value, and new applications are the subject matter of many national and international conferences and journals.

Machines with magnetic field strengths of up to 1.5T are now becoming commonplace with fantastic detail in the images. 3.0T machines are becoming generally available in teaching hospitals, and 7.0T imagers are presently being installed as research tools. A machine for heads at 9.4T is under development.[43]

There are now a few hundred MRI imagers in the UK, and it is estimated that worldwide there are now about 25, 000 machines carrying out about 60m investigations each year, all still using methods originally evolved in Aberdeen. The 25th anniversary of the first MRI patient was celebrated this September at King's College, Aberdeen, with public lectures and a one-day conference, which brought together again many members of the original team. It is appropriate that this Scottish contribution to modern medical imaging should be recorded now in this Journal.

References - see website **www.smj.org.uk**