SEVENTY-FIVE YEARS OF ADVANCES IN PHYSICS AND ENGINEERING APPLIED TO MEDICINE IN EDINBURGH; 1936 -2010

Peter R. Hoskins[1], Anthony T. Redpath[2], David I. Thwaites[3], William H. Nailon[4], David Gow[5], Vassilis Sboros[6], Pankaj Pankaj[7]

[1]Emeritus Professor of Medical Physics and Biomechanics, Centre for Reproductive Health, University of Edinburgh, Edinburgh, UK
[2]Retired Consultant Physicist, Oncology Physics, Western General Hospital, Edinburgh, UK
[3]Emeritus Professor of Medical Physics, University of Sydney, Australia, and hon. Professor of Oncology Physics, University of Leeds, UK
[4]Professor of Oncology Physics, Oncology Physics, Western General Hospital, Edinburgh, UK
[5]Retired Consultant Medical Engineer, SMART Centre, Astley Ainslie Hospital, Edinburgh, UK
[6]Associate Professor of Acoustics, Heriot Watt University, Edinburgh, UK
[7]Professor of Computational Biomechanics, Institute for Bioengineering, University of Edinburgh, Edinburgh, UK

Abstract:
This paper reviews the main developments concerning the application of physics and engineering to medicine in Edinburgh from the 1930s to 2010, with brief mention of activity post 2010 for the purposes of continuity.

Keywords: Medical Physics, Medical Engineering, Bioengineering, Edinburgh

I. INTRODUCTION

Medical Physics in the UK mainly started with scientific support for the use of ionising radiation for diagnosis and therapy in the early years of the 20th century. However, physicists and engineers had been involved in medicine in many areas prior to this, including optics, electrophysiology and biomechanics [1, 2]. The Edinburgh Medical School was founded in 1726 and from its inception, teaching was influenced by the Newtonian scientific approach. Medical students attended lectures on physics in the university Natural Philosophy (Physics) department from at least the 1820s, with formal courses on physics principles for medicine (and 'medical physics') being presented from at least the early 1830s and a physics lecturer specifically appointed into the School of Medicine in the 1880s [1]. This was Alfed Daniell who taught to his own 1882 'Principles of Physics' textbook, later (1896) publishing a more focussed text, Physics for Students of Medicine. His successor, Dawson Turner, published a widely-used text, 'Manual of Practical Medical Electricity' in 1893, updated in the 1902 edition to add Röntgen Rays and Finsen Light, radiology having begun in Edinburgh in October 1898, so bringing us to the modern medical physics era.

The first half of the 20th century saw the growth of hospital physics and the first medical physics and medical engineering departments in the UK being established. The professional body for medical physics, the Hospital Physicists Association (HPA), was formed in 1943 with 53 members. One of those was Charles Murison, the first full-time hospital physicist employed in a Scottish hospital, who had taken up post at Edinburgh Royal Infirmary (ERI) in 1936, working single-handedly to support radiotherapy.

By 1957 there was established activity in Edinburgh in both medical physics and medical engineering, involving both the NHS and University. However, in comparison to other major teaching hospitals, Medical Physics had been slow to develop in Edinburgh. Dr (from 1966, Professor) John Greening (1922-2015) was appointed in 1957 to set up a joint NHS/University Department of Medical Physics and Medical Engineering (DMPME), which he led until his retirement in 1986. This initially combined the existing activities in medical instrumentation and radiotherapy physics, with sites at the ERI and the Western General Hospital (WGH). Subsequent growth in DMPME involved activities in rehabilitation engineering, nuclear medicine, ultrasound, MRI and biomechanics. Outside of DMPME a significant growth to 2010 was the rise of bioengineering, which is also discussed.

Separation of NHS and University activities took place in many departments across the UK in the 1990s and 2000s, often resulting in jointly funded departments splitting up. DMPME split into an NHS unit and an academic unit in 2002 and the latter was itself closed in 2012. By 2010 the original DMPME had undergone gradual fragmentation, mainly into clinically led centres. In addition, the early days of the DMPME had seen much clinical research undertaken within the NHS, often with little or no external funding. However, by 2010, a significant part of research was carried out by University staff with grant funding. At the time of writing, physics and engineering activities applied to medicine in Edinburgh are spread across many geographic and organisational areas, with the history also fragmented and in danger of being forgotten

It is hoped that this article will help keep alive the memory of the internationally leading work in applications of physics and engineering to medicine in Edinburgh over the 75 or so years prior to 2010.

II. RADIOTHERAPY PHYSICS

Although there would likely have been university physics involvement in the medical applications of X-rays and radium from soon after their discovery, Radiotherapy Physics existed formally from 1936 when Charles Murison was appointed, as noted above. He had worked for Metropolitan-Vickers on their pioneering work on continuously-evacuated 250 kV X-ray tubes and brought that experience to the orthovoltage X-ray treatment facility at ERI. There was also a radium unit at the ERI, since 1903 [3], formalised in 1929 as one of a network of National Radium Centres. When the DMPME was established, the Radiotherapy Department and its physics support had recently moved from the RIE to the new Oncology Department at the WGH. The new radiotherapy facility included a 2MV van de Graaff unit and a Metropolitan Vickers 4MV linear accelerator (linac), an 'Orthotron', installed in 1955. This was one of the first five linacs in the world to be used for radiotherapy, all in the UK [4]. Murison and others at the WGH were significant contributors to the development of practical methods of dosimetry and for radiotherapy planning and treatment using these new linacs [5]. To support the new facility, a team of physicists and mechanical engineers was recruited, beginning the expansion of Radiotherapy Physics in Edinburgh. Further accelerators were added, with increasing complexity requiring the employment of electronic engineers. In the 1980's a cyclotron was installed, with a separate team of physicists and engineers, providing a facility for neutron radiotherapy for several years [6]. By 2008 there were 7 linacs in the Oncology Department and approximately 35 physics and engineering staff. The NHS Radiotherapy Physics group were split out from DMPME in 1992 and incorporated into Oncology, as the Oncology Physics Department, headed by Tony Redpath, although academic links were continued within the university DMPME. Over the period covered by this review, significant developments were made in radiotherapy dosimetry (section III) and from the early 1970s in computer applications for treatment planning and delivery, led by Redpath and outlined here.

A. Development of an early computerised 2D planning system

A Digital Equipment Corporation PDP8 computer system with 16K memory and a floating point processor was purchased by the Radiotherapy Department in 1973, aiming to computerise and replace all the manual treatment planning processes. Redpath and Vickery wrote software for external beam planning in high-level language (Fortran IV) rather than assembler code, allowing it to be understood by physicists working in radiotherapy [7].

The treatment planning process is well defined, with its objective to achieve a high and uniform dose to the target while minimising the dose to organs at risk (OAR). A quadratic programming optimisation algorithm was incorporated into the planning software to achieve this [8]. The input data for the algorithm was calculated and its execution time was instantaneous, which was far superior to lengthy manual planning. None of this was available in other Oncology departments worldwide and by request the software was distributed to around 70 centres. It was used as a standard in several countries and was known as 'The Edinburgh Software'. It attracted commercial interest and was sold by two companies, Nodecrest (UK) and Varian (USA), running on the latest currently available hardware. It was the second most used treatment planning software worldwide for many years.

Redpath developed software for checking external beam calculations, using independent machine data from the initial calculation [9]. It worked for any treatment machine and required a small number of parameters to be set for the specific machine. If initial calculation and independent check disagreed by more than 5%, a warning was displayed, providing a final quality assurance check. This software was also distributed to centres in the UK.

Software was also written to reconstruct in 3D and calculate dose distributions for brachytherapy treatments using needle and seed implants [10]. Treatment of cervix/uterus using caesium sources with optimisation of the source positions was also included and vaginal applicators for this treatment were also designed.

B. Early computer-controlled beam data collection

Commissioning a linear accelerator for clinical use involves collection and processing of beam data. Manual collection was extremely time consuming. An automated system was developed in 1974 by Redpath, Bottrill and Nieman. The water tank's drive system was modified using stepping motors linked to a planning computer, to drive the detector remotely under software control. Detector signals were measured using analogue-to-digital converters on the computer [11]. Any X-ray beam size could be measured automatically in minutes at the points required to model it in the planning system. Software was developed to smooth and normalise the data and for transfer to the planning system database. This enabled beam commissioning measurements for a treatment machine to be performed in a day instead of weeks, as well as improving data accuracy and consistency. Redpath

then used beam modelling techniques to reduce the extensive measurement of all the beam data on a treatment machine, by developing software to generate the data using a small number of measured parameters per machine [12].

C. Treatment simulation and an early simulator-based CT system

In 1984, Redpath and Wright interfaced a Grinnell (GMR-275) image-processing computer to the image intensifier on a conventional treatment simulator to capture transmitted images and developed a set of image processing filters that could be applied to the images to enhance their quality [13]. This was designed to be performed in real time by the simulator radiographers.

CT scanners were then in their infancy and not available for radiotherapy planning. This project also developed a CT facility on the simulator [14]. A shaped filter was designed and fitted to the simulator head, to reduce the signal intensity in the transmitted image so that the dynamic range of the image intensifier was not exceeded. The signal reaching the intensifier was collimated by a 2cm slit. The simulator was rotated through 360º in a minute and the transmitted profiles captured every 1º. Software was written for the Grinnell processor to perform the image reconstruction for the slice, which took less than a minute. Although the images were not CT scanner quality, they were more than adequate for 2D planning, as internal structures could be delineated and the spatial accuracy was excellent and superior to previous methods [15]. This technique was taken up by commercial companies.

D. Development of a 3D planning system and dose calculation algorithms

The move to 3D planning took place with the wider use of CT scanners in radiotherapy. Redpath developed a 3D planning system, known as Virtsim, on a PC, such that any dose calculation algorithm could be 'plugged in'. Various useful features were incorporated, including: dose-volume histograms for any organ, beam's eye view, digital radiographs after the beam exited the patient, beam shaping using multileaf collimation and dose calculation in 3D with display on three orthogonal planes [16]. The software was distributed to several radiotherapy physics departments in the UK. It was ported to a UNIX workstation and sold by a commercial company in the UK (Nodecrest). In parallel, Redpath developed several 3D dose calculation algorithms [17-19]. The method used was based on the radiation properties of an X-ray beam and modelled the scatter distribution within a heterogeneous medium. Redpath and Thwaites tested the algorithm against measurement in a variety of heterogeneous situations, with the final version going through three modification stages with each one increasing accuracy. The time needed to calculate a 3D distribution was acceptable for treatment planning.

E. Intensity Modulated Radiotherapy (IMRT)

The availability of multileaf collimators on linear accelerators in the early 1990's allowed beam portals to be shaped with increased conformality. This enabled 'inverse planning', where the 3D patient dose distribution was specified and the shape of the beam portals and the beam intensity at any point within the portals determined. This could be treated as a classic optimisation problem. Redpath adapted a simulated annealing technique to find a solution where the objective was to obtain a uniform dose to the target volume subject to OAR dose constraints [20]. The variables used in the optimisation were the beam intensity at pixels in a map defining each of the beam portals, which led to a significant number of variables in the optimisation process, typically around 4000, with the algorithm requiring 10^6 iterations to converge. Because simulated annealing is an iterative technique, convergence in an acceptable time can be difficult. However, this took approximately 1 minute to execute and the algorithm was incorporated into Virtsim. In addition, Redpath developed a model to determine output factors for conformal megavoltage X-ray beams. It worked for dynamic wedging and for both static and dynamic multileaf collimated beams [21]. In breast cancer treatment using tangential opposed wedged beams, the shape of the breast means it is not possible to achieve a uniform dose distribution throughout the target volume. Redpath and Carruthers used Virtsim to calculate intensity modulated beams instead of using wedges. Patient studies demonstrated that noticeable improvements in dose uniformity could be achieved [22].

F. Adaptive radiotherapy for bladder treatment

Radiotherapy of the bladder presents a difficult problem due to movement and deformity, including of the target volume. The development of Virtsim (including IMRT) provided a tool that was not available on commercial planning systems, as it allowed the software to be modified to investigate specific problems resulting from conformal bladder radiotherapy. This led to collaboration (2003-2008) between Redpath and Muren (Bergen,

then Aarhus), arising from the latter's 2002-03 sabbatical in Edinburgh, with the major projects summarised below.

The clinical target volume (CTV) was outlined on a set of repeat CT scans taken weekly throughout treatment. After CT image registration, the superposition of these volumes produced an envelope in which the target volume was always present. Margins were applied in all 6 directions to enclose this envelope. In radiotherapy, isotropic margins were typically applied to the planning scan. Redpath developed an optimisation algorithm, again using simulated annealing, to determine the optimum margins required to minimise the high dose volume outside the envelope. The overall values of all 6 margins were determined from analysing 19 patients. Bladder movement and margins required were seen to be largest in the superior direction [23].

A study on 45 patients investigated if a concomitant IMRT boost dose to the tumour volume on all fractions was feasible [24], to give a 20% boost above the prescribed non-involved bladder dose. The optimisation was adapted to maintain the uniformity of dose in the non-involved bladder and fulfill the dose constraints on vital structures. This was found to be feasible in over 50% of patients and the approach was clinically adopted.

CT image guided radiotherapy (IGRT) was also used to investigate if shifting the isocentre in all of the 6 possible directions could reduce the margins required. The optimisation algorithm adjusted the margins, aiming to achieve full coverage of the target volume while minimising the high dose volume outside the target volume [25]. A marked reduction in the size of the margins from their commonly used isotropic values was shown. The target volume was reduced by approximately 30% and a reduction in dose to vital organs was also achieved.

A major challenge in radiotherapy for bladder cancer is to control and account for bladder motion. In an attempt to control bladder volume variation, a series of 20 patients were given fluid intake restrictions on alternative weeks of treatment. Weekly CT scanning was performed and the isocentre shifts required to obtain full target coverage were determined, using the available optimisation technique. The potential for a large margin reduction was shown if the bladder volume is controlled [25]. This work significantly improved the setup for bladder cancer treatment.

G. A uniform framework for objective assessment and optimisation of radiotherapy images: IQWorks

A 2010 PhD (Reilly) developed software and both hard and virtual phantoms, to perform quality assurance on digital imaging equipment in radiotherapy [26]. Named IQWorks, this expanded as a collaborative national and international project to provide medical physicists with automated image analysis software for use with DICOM test images in many other imaging areas, including CT, mammography and digital radiography [28].

III. Dosimetry

A. Fundamental radiation dosimetry

John Greening had begun significant research in London in fundamental radiation dosimetry for diagnostic radiology, radiotherapy and radiation protection, notably in the theory of cavity chambers. This was continued in Edinburgh [29-32]. He had a particular interest in low energy kV beam dosimetry [33] and a 1960s PhD programme (Tony Redpath) included calorimetry [34], ferrous sulphate dosimetry [35], ion chambers [36] and solid state devices [37]. In 1966, Redpath designed and built a calorimeter to determine microwatt energies of 10-30 kV X-ray beams, measuring temperature rises ~10^{-3} ºC/min [34]. It was used to calibrate the other dosimeters listed above for clinical dosimetry use. He was seconded to The Christie Hospital, Manchester in the early 1970s to develop a similar system to measure the dose output from a 14 MeV therapy neutron generator [38], where temperature rises an order of magnitude lower presented even greater measurement challenges.

Greening supervised Alan Nahum's 1975 PhD, arising from existing radiation dosimetry work in Edinburgh. Nahum developed one of the earliest Monte Carlo (MC) codes for applications in medical physics, modelling radiation transport for MV photon and electron dosimetry [39-41]. This pioneering work laid one of the key foundations for MC methods to develop into a major tool for radiation research and dosimetry and for its many later applications in clinical dosimetry worldwide.

The above work is folded into Greening's widely-used textbook on radiation dosimetry [42]. Greening was a member of the International Commission on Radiation Units and Measurements (ICRU) for 16 years, developing international recommendations for the safe and consistent application of radiation, particularly for clinical dosimetry and radiation protection. During his ICRU activity (1966-81) he was involved in Reports 12-39.

David Thwaites joined DMPME (Radiotherapy Physics) in 1980, direct from PhD and post-doc work on light ion stopping powers [43] and continued this analysis for materials of interest for dosimetry and medical and biological applications [44, 45]. Outcomes of this work were incorporated directly into ICRU recommendations for proton and He ion stopping powers [46] and those of other light ions [47], as source data for particle therapy, for other ICRU reports and for many practical and research applications.

B. Clinical radiotherapy dosimetry and dose protocols (codes of practice)

The neutron therapy facility mentioned in section II saw significant neutron dosimetry work by Jerry Williams and others, leading to his role in producing the European recommendations for neutron dosimetry [48]. Similarly, Edinburgh's first clinical electron beam linac was installed in 1980, beginning a programme of work on electron dosimetry and electron beam treatment applications, aiming to improve accuracy and consistency of clinical electron beam use for radiotherapy. This included ion chamber dosimetry, chamber correction factors, phantoms and measurement methods [49-52]. This was led by Thwaites and the work fed directly into new UK electron dosimetry protocols for clinical use, based on the National Physical Laboratory's air kerma primary standard [53] and then on its calorimeter-based direct-dose-to-water primary standard [54], as well as into national recommendations on secondary standard instruments to be used for clinical dosimetry [55].

C. Consistency of radiotherapy doses nationally and internationally, intercomparison and audit development

National and international radiotherapy dosimetry protocols (codes of practice) aim to ensure consistency of dosimetry between centres and between countries, so that radiotherapy delivery and patient outcomes are consistent and experience can be transferred with confidence between different places and within clinical trials. However, there is still potential for practice variations in application of protocols. Dose intercomparisons can check this. An early international example was a comparison between Edinburgh (John Law), Houston, USA and Umea, Sweden in 1970 [56]. The centres exchanged dosemeters (ion chambers, LiF and ferrous sulphate) for mutual measurements of stated doses. These agreed typically within 1%, providing confidence at that level. The implementation of different dosimetry protocols can also be directly compared in detail in a few centres [57]. Remote dose output checking systems, mainly using thermoluminescence dosimeters (TLDs) were begun in the late 1960s by the International Atomic Energy Agency (IAEA) to support low-and-middle-income (LMI) country radiotherapy facilities, but limited in scope. Also in the late 1970s, the USA began TLD-based dose checks, initially to support clinical trials [58, 59]. In the 1980s, systematic national dosimetry intercomparisons began in some countries, involving on-site visits and more extensive measurements.

A UK national megavoltage photon dosimetry intercomparison was organised and run from Edinburgh (Thwaites) in the late 1980s [60]. It was planned by an Institute of Physics and Engineering in Medicine (IPEM) working group and used ionisation chambers and specifically-designed phantoms to independently measure beam calibration reference doses, non-reference dosimetry parameters and multi-field treatment-planned dose deliveries, involving on-site visits to all UK radiotherapy centres. This was followed by a similar national electron dosimetry intercomparison, with measurements carried out by Nisbet [61]. The results gave significant confidence in UK clinical radiotherapy dosimetry, showing ratios of stated doses to independently measured doses very close to unity and with small standard deviations for the time. Various minor issues were identified for improvement and also one major issue. The latter was a miscalibrated Co-60 radiotherapy treatment unit, arising from an error at the time of a source change. This had resulted in patient overdoses at that centre which were not identified until the dosimetry intercomparison visit's measurements. This had significant impact on quality initiatives in radiotherapy (next section). The intercomparison methods were applied outside the UK [62].The general methodology and regional structure that was developed led to the establishment in the early 1990s of the on-going national radiotherapy dosimetry audit network [59], with Edinburgh continuing to lead the Scottish+ group and developing a range of other innovative audits [63]. This pioneering work and subsequent expansion have been summarised [59, 63]. It led to Thwaites joining IAEA radiotherapy dosimetry audit development groups from the early 1990s [64], to support the growth of radiotherapy (and of its complexity) in LMI countries, with significant progress taking place during the period of this review and Edinburgh acting as a testing site [65]. Remote audits were gradually expanded in scope from beam calibrations in reference conditions for megavoltage photon beams, to dose parameters in non-reference conditions and for electron beams. Later (post-2010) this led into audit methodology for remote testing of advanced radiotherapy treatment parameters, with the whole system summarised in a comprehensive IAEA document [66], and also guidelines for on-site dosimetry methods to investigate identified issues and to support whole radiotherapy centre clinical audit [67].

D. Quality management in radiotherapy, accuracy analysis and in vivo dose verification

The Co-60 beam miscalibration identified in the megavoltage dosimetry intercomparison led to significant attention being given to quality and accuracy in UK radiotherapy and eventually to the introduction of formal quality management systems in all departments. These same principles were subsequently incorporated into European guidelines on structure and methodologies for radiotherapy quality management and comprehensive quality assurance [68, 69]. This also led into an Edinburgh programme of work on analysis of accuracy required and achievable in radiotherapy, over the period from 1989-2018. The work (and interim references) in the period up to 2010 is summarised in a 2013 analysis [70]. This also included a systematic programme of in vivo verification of patient delivered doses, begun in the mid-1990s using diode dosimeters and developing novel

methodology and practical approaches [71-73]. The outcomes of this work were also incorporated into European guidelines [74].

E Other: Mammography dose and risk-benefit, image quality, small field radiotherapy dosimetry

Other significant dosimetry developments in the period of interest include John Law's work over 30 years or so. Law's work covered mammography system evaluation and quality control and mammographic image quality, aiming to minimise dose and improve quality [75], and consistency in mammography doses and the evaluation of dose-based risk versus benefit of breast screening [75, 76]. This work initially supported the Edinburgh breast screening trial, a pilot study begun in the late 1970s before the UK national breast screening trial commenced in the 1980s, and then continued to inform the national system.

Edinburgh acquired a linac-mounted cone-collimated stereotactic radiosurgery system in the mid-1990s, which began a programme for clinical stereotactic radiosurgery treatment of brain lesions and a linked small field dosimetry programme. This investigated linac head and phantom scatter factors, small field dosimetry systems and methodologies, treatment planning dosimetry and dose delivery verification, much as part of a PhD (McKerracher) [77, 80]. Its biggest immediate dosimetry impact, besides preparing the clinical service, was in its investigation and evaluation of small field detectors/dosimeters [81, 82].

IV. Medical instrumentation

The first biomedical engineer in Edinburgh was David Simpson (1920-2006). He undertook a PhD, 'The development of a method of following changes in the radio-opacity of the small bones of the hand' and then worked in the Department of Surgery from 1952. He developed a series of instruments including clinical blood pressure monitors [83-85], a skin resistance measurement device [86], fetal pulse rate monitor [87], an AV shunt for repeated haemodialysis [88] and a warning device for intravenous therapy [89]. He was an early advocate of patient monitoring stations in which several parameters (temperature, heart rate, pressure etc) were displayed simultaneously [90-92]. In 1962 following the thalidomide disaster Simpson was asked to set up a prosthetics unit, (see section V below).

Jim Neilson undertook his PhD on ECG analysis graduating in 1962 and worked in this area till his retirement. Work involved development of methods to continuously record ECG data from the patient on audio tape and then to analyse the ECG data by computer [93-96]. The work was patented [97, 98] and a spin-out company 'Reynolds Medical' was set up in 1972 to develop 24 Hour ECG recording and analysis [99-101]. The Pathfinder ECG analysis was the world's first commercial automated ECG analysis machine and was released in 1980. The patient wore an ambulatory device which recorded their ECG onto audio tape, a standard 90 minute tape operating at a much slower speed to allow 24 hours of recording. The audio tape was analysed by the computer to detect arrhythmias and other cardiac events. In Edinburgh the device was extensively used in cardiology research [102-106]. Reynolds Medical continued to operate until 2006 at which point the company was bought by OSI systems (Hawthorne, USA). At the time of writing the modern version of the Pathfinder device remains available to buy.

V. Rehabilitation engineering

A. The development of prosthetic limbs following the thalidomide disaster

In the late 1950s and early 1960s the drug thalidomide was prescribed to pregnant women to help with morning sickness and sleep. The drug led to the birth of thousands of babies with severe deformities, including severe stunting of arms and legs. Thalidomide was withdrawn in 1961. In Scotland some 100-150 children were affected. David Simpson was an established biomedical engineer and was asked to set up a unit to build prosthetics for the affected children. The 'Powered Prosthetics Unit' was set up in 1963. The unit moved to its long-term home at the Princess Margaret Rose Hospital in 1965.

Artificial limbs were attached to a frame which was contained within a harness or bodice. Movement of the prosthesis was achieved pneumatically [107-110]. An important realisation by Simpson was named 'extended physiological proprioception (EPP)' [111]. The idea was that, from the perspective of the child, the prosthesis becomes a part of the child's arm or leg. The child would seek to control the movement of the prosthesis in the same way that a person is able to control the movement of a tennis racket when striking the ball. The child would use what movement they had to control the movement of the leg or arm. Over the following decade a series of arm and hand prostheses were developed of increasing sophistication by Simpson and his colleagues [112-118].

The original Powered Prosthetics Unit evolved into the Bioengineering Unit with a wider remit around general support for rehabilitation.

B. Developments leading to the i-hand and i-limb

David Gow joined the Bioengineering Unit in 1984 and continued the work on prosthetic arms. The gas power source was replaced with an electrical source, movement was controlled by rotation of threaded shafts. While this was an improvement over the gas-powered arm, the full arm could only be built in an adult male version, plus the hand was relatively unsophisticated [120].

In the early 1990s there were limited powered solutions for a prosthetic hand. Gow developed a partial hand in which a small motor rotated a spiral shaft ('worm') which in turn was connected to a wheel. Movement of the wheel resulted in flexion of the digit. A partial hand was produced with separate motor/worm for each digit, consisting of 2 digits and a thumb. This was referred to as 'ProDigits' and patented [121]. This approach over time was scaled up to produce a full hand connected to an arm, called the Edinburgh Modular Arm System (EMAS) [120], which was also patented [122]. Much of the development of these devices had been performed within an NHS routine service setting, so the engineers involved were doing this work typically within 20% of their time, and at times with little institutional support. In 2003 Gow helped set up the company 'Touch Bionics' to further develop the technology and provide a sales platform. The prosthetic arm was called the 'i-limb' and the hand called the 'i-hand'. Touch Bionics was sold to Ossur Hf (Iceland) in 2015. These prostheses have proved very successful and have transformed the lives of thousands of patients throughout the world.

David Simpson and David Gow were internationally leading figures in rehabilitation engineering. An excellent review of the career, life and work of both is provided in the book 'Making Hands' [123] and in the web resource produced by Lothian Health Services [124].

VI. Nuclear medicine

Nuclear medicine encompasses a range of diagnostic and therapeutic techniques involving radioactive isotopes. Impetus for this area increased after WW2 with the availability of a range of isotopes produced by cyclotrons. These could be used locally or be packaged for delivery to centres without a local cyclotron. For imaging of patients the invention of the gamma camera in the 1950s was a key event. Developments in nuclear medicine were undertaken by Peter Tothill (joined DMPME in 1960, was Head of DMPME 1986-1988), Mike Smith (DMPME 1974-1986) and Jim Hannan (joined DMPME in 1975 and was Head of NHS Medical Physics 2002-2011).

A. Gastric Emptying

This technique, introduced in 1966, involves ingestion of radioactive isotope and imaging using a gamma camera. In Edinburgh, techniques were developed to monitor the early period of emptying using two different markers to simultaneously monitor solid and liquid emptying [124]. These are important issues for the effects of gastric surgery [126]. Methodological studies investigated the effect of different variables on emptying including posture [127], depth of the isotope from the camera [126] and the use of radioactive inert particles or radioactive digestible material [128]. The techniques were widely used in clinical studies [129-132].

B. Calcium and bone mineral measurement

Loss of bone mineral with age, especially following the menopause, can lead to fracture. Bone mineral is lost across all bones, but key areas for fracture are the spine, hip, wrist, knee, foot and ankle.

In Edinburgh methods for measurement of bone mineral content were developed based on irradiation of the patient with a radioactive source, with detection of the radiation after passing through the patient. The radiation is absorbed by the soft tissues and bone. As the bone mineral content decreases so the absorption by bone will be less. Single-photon techniques involving a single radioactive element were developed for measurements in the forearm and hand [133-135]. Dual-photon techniques were developed for measurements in the spine [136, 137].

The use of radioactive sources was superseded in the early 1980s by the use of X-ray sources. DEXA (dual energy X-ray absorptiometry) scanners became widely available in hospitals, with machines available from several manufacturers including Lunar, Hologic and Norland. Extensive assessment was undertaken, including comparing different commercial manufacturers [138-140] and scanning arrangements [141], investigating precision and accuracy using phantoms [142], and investigating the effect of body fat and weight [142-146].

Measurement of whole-body calcium was undertaken using neutron activation analysis. This involved irradiation of the patient by neutrons generated from a cyclotron, followed by detection of gamma rays in a whole-body counter [147]. Stable calcium-48 was turned into unstable calcium-49 by activation, which during decay produced a gamma ray. Several clinical studies were undertaken in osteo- and rheumatoid arthritis [148-151].

A review of the measurement of bone mineral and calcium was published by Tothill in 1989 [152].

C. Cardiac and pulmonary function

Techniques were developed for estimation of ventricular volume and cardiac output [153-156]. These involved injection of a radioisotope bolus, recording of gamma camera activity, and fitting of a gamma variate function to the activity-time curve. The cardiac output was estimated from the ratio of peak activity divided by the area under the curve. Modification of the bolus method was undertaken for measurement of the pulmonary blood volume, involving simultaneous monitoring of the activity time curve in the pulmonary artery and left ventricle [157]. These methods were used in a series of clinical studies on patients with pulmonary and cardiac disease [158-161].

VII. ULTRASOUND

Diagnostic ultrasound imaging involves high frequency (1-20 MHz) ultrasound waves which are transmitted and received using a hand-held device applied to the patient's skin. Ian Donald and colleagues (Glasgow) developed the first 2D ultrasound scanner for use in obstetrics [162]. This involved collaboration with Tom Brown, an engineer working for Babcocks, a company which worked on industrial flaw detection using ultrasound. In Edinburgh the Ultrasound section was led by Norman McDicken (1940-2024) who joined DMPME in 1972, becoming Professor and Head of DMPME (1988-2002). Other principal investigators relevant here are Steven Pye who joined as a PhD student in 1982 and was Head of the NHS Medical Physics unit (2011-2020), Peter Hoskins who joined in 1984 becoming Professor in 2012, Carmel Moran who joined in 1991 becoming Professor in 2018, and Vassilis Sboros who joined in 1996 becoming Associate Professor at Heriot Watt University in 2024.

A. Instrument development

Following his work in Glasgow, Brown worked in Edinburgh from 1970-73 on one of the first 3D ultrasound systems using a stereoscopic approach [163]. This was commercialised by Sonicaid as the Multiplane Scanner, however this was not commercially successful, and the product was discontinued in 1979.

Early ultrasound systems relied on manual scanning of a single element transducer in which the image was built up over several seconds. McDicken's group developed a series of ultrasound systems utilising mechanically swept transducers for real time imaging. The original rocker system developed in Glasgow involved a single element which was pivoted to and fro, giving a maximum frame rate of about 20/second. The follow up system developed in Edinburgh had 4 transducers mounted on a wheel enabling a higher frame rate suitable for fetal and cardiac imaging [164, 165]. These systems were commercialised by EMI (Emisonic 4262) and Nuclear Enterprises. The latter system was used in early studies of gastric emptying and motility [166, 167].

Other developments included visualisation of biopsy needle tips on the ultrasound image [168, 169], automatic gain control for B-mode imaging [170-172] and image processing for speckle reduction [173, 174].

B. Blood velocity measurement

Doppler ultrasound concerns the measurement of blood velocities using the Doppler effect. The history of Doppler ultrasound relevant to clinical practice centres around the development of real-time spectral Doppler (blood-velocity time waveforms), and real-time colour flow (2D images of blood flow) [175]. However, this technology is simple; it only measures a single component of blood velocity, that along the ultrasound beam, and it concentrates on measurement of maximum velocity. Blood flow may be highly complex, especially in disease such as atherosclerosis. Advances in Doppler ultrasound have been concerned with techniques for estimation of 2 or 3 velocity components and 2 or 3 spatial dimensions, and techniques which improve measurement accuracy.

For Doppler beams generated using a linear array the Doppler aperture is much larger than for pencil probes. It was shown that this leads to systematic overestimation of the maximum velocity [176-178] which occurs as a result of geometric spectral broadening [178]. The typical overestimation is 20-30%, but this is angle-dependent and machine dependent. It was shown that this creates the potential for mis-categorisation of patients for carotid surgery [177]. As the error is dependent on the geometry of the transducer it can be corrected using a string phantom to estimate the error as a function of depth in order to create a look up table of correction values. This method was used in subsequent work in Edinburgh to measure maximum velocity, and related quantities such as wall shear rate and volumetric flow, with high accuracy [178-181].

Calculation of blood velocity magnitude involves alignment of an angle cursor with the vessel wall, assuming that blood travels parallel to the wall. However, blood flow may be complex and velocity vectors may not be parallel to the wall. By measurement of 2 components of blood velocity it is possible to estimate both blood flow direction and magnitude automatically without the operator having to align a cursor. A dual-beam colour vector Doppler method was developed for estimation of the velocity magnitude and direction [182]. This was used to provide early evidence for spiral flow in arteries [182]. Vector Doppler systems were developed to provide angle-independent estimation of blood velocity in a stenosis phantom using spectral Doppler [178] and colour flow

[183]. A prototype commercial vector Doppler system was developed with ATL Ultrasound (Seattle, USA) which was trialled in phantoms [184] and normal volunteers [185] showing that spectral Doppler data was angle independent.

C. Ultrasound phantom development

Ultrasound phantoms are essential for the validation of Doppler ultrasound measurements of blood velocity. By the late 1980s there were established recipes for tissue mimics for B-mode imaging, but little work on phantoms for Doppler ultrasound. McDicken reported a flow phantom in which a gear pump was used to propel the blood mimic [186]. This phantom was extended [187] in which the gear pump speed was controlled by a computer enabling a wide range of realistic pulsatile flow waveforms to be obtained. Further progress required consideration of the acoustic properties of the materials which need to be tissue equivalent. Specifications for the components of a flow phantom were defined by IEC 61685 (2001). A blood mimic which met these requirements was developed by Ramnarine [188, 189] involving the use of nylon particles to mimic the red cells. This became the international standard blood mimic and is commercially available (Shelley Medical Imaging, Canada).

For a vessel mimic, the best commercially available material was C-flex, a rubber based material (Cole Parmer, Illinois, USA). This had the correct acoustic velocity but high attenuation. The problems of distortion of the Doppler beam led to the development of flow phantoms with no vessel, so called wall-less phantoms [190]. An acoustically matching vessel was created using PVA cryogel [191]. This material is prepared as a gel which undergoes hydrogen bonding following freezing and thawing. By adjustment of the number of freeze-thaw cycles the acoustic and mechanical properties can be controlled.

Non-planar carotid phantoms were created using a rapid prototyping technique. Clone phantoms were created. One phantom was transparent for use with optical measurement techniques including LDA and PIV [192]. The other phantom was manufactured using a wall-less approach for ultrasound [193].

Reviews by Hoskins discuss the specifications required for flow phantoms [194] and their design and use [195].

D. Cardiac imaging techniques

Tissue Doppler imaging (TDI) concerns the visualisation of moving tissues, especially the myocardium, and was developed by McDicken in a collaboration with Acuson (Mountain View, USA) [196]. TDI is similar to colour flow imaging of blood, but instead the colour image is related to the velocity of moving tissues. Adjustments are made to the machine settings to account for the lower velocities of the myocardium and the much higher Doppler signal strength compared to blood. In addition to 2D imaging it is possible to acquire TDI data along a single line and display this as a function of time [197, 198]. From the 2D TDI velocity data it is possible to estimate how much the tissue has stretched or compressed (strain) then from this the strain at each pixel as a function of time (strain rate) [198]. The TDI technique was patented by Acuson [199] and is available as standard on commercial ultrasound machines.

Intravascular ultrasound (IVUS) involves acquisition of ultrasound images from within the artery (or heart) using an ultrasound transducer mounted on a catheter. For coronary artery imaging the catheter is inserted into the femoral artery and pushed upstream to the heart. IVUS imaging is undertaken at frequencies of 20-40MHz for which the axial spatial resolution is 100-200μm. Radiofrequency (RF) data was acquired from atherosclerotic plaque excised from coronary arteries. A number of different features of the RF data were investigated for their ability to classify different regions of the plaque according to the histology; eg. ‘lipid’, ‘loose fibrotic tissue’, ‘dense fibrotic tissue’, ‘calcium’ [200-202]. These methods were incorporated into a commercial IVUS system for classification of plaque in-vivo (Volcano Corp, San Diego, USA).

E. Contrast agents

Early work in the field focussed on generation of basic science knowledge, engineering solutions (in signal and image processing) and assessment of clinical utility in cardiovascular disease and abdominal radiology. In the 1990s there was an emphasis on in vitro investigation on microbubble physical behaviour with a view to understand how to use ultrasound scanners in the diagnosis of cardiovascular disease and the variabilities associated with the administration of microbubble contrast agents [203-206].

In Edinburgh this work led to experimental physics investigations [207-210] which fed into theoretical investigations [211, 212]. The most important achievement was the first evidence that individual microbubbles produced scatter that could be detected by ultrasound imaging equipment [213]. This made Edinburgh one of the few research centres that investigated the acoustics of single microbubbles, undertaken using a novel acoustic setup for the measurement of single microbubble echoes. Using this methodology there followed fundamental research including acoustic studies on microbubble resonance [214], on decay/memory effects [215, 216], and on bubble behaviour inside capillaries [217] or next to a boundary [218]. These studies were key to understanding

microbubble scatter evolution in a real imaging setting, thus leading to signal processing research [219] and subsequently the development of in vivo ovine tissue model as a vascular regulation model and in order to generate new image analysis on perfusion quantification [221]. This research had a number of impacts, most importantly it paved the way to the generation of a new ultrasound field namely super-resolution ultrasound, where single microbubbles were tracked using image analysis tools in order to delineate their host vessels, thus creating very high resolution ultrasound meta images that are similar to those found in other fields such as super-resolution microscopy, astronomy and defence sensing.

VIII. MRI

MRI was the last of the major medical imaging techniques to gain widespread clinical use. Its origins can be traced to the discovery of magnetic resonance by Isidor Rabi (Columbia, USA) in 1938. The first MR image was produced in 1973 by Paul Lauterbur (Stony Brook, USA). Peter Mansfield (Nottingham, UK) developed echo-planar imaging, reducing imaging time to seconds which allowed future developments such as diffusion and functional brain MRI. John Mallard (Aberdeen, UK) developed the first MRI whole body scanner from which the first whole body image was produced in 1980 [222].

In Edinburgh a low field (0.08T) MRI system (M&D Technology, Aberdeen) was installed in 1984, under the leadership of radiologist Jonathon Best, with Mike Smith responsible for MRI physics. Developments included gated acquisition for cardiac imaging [223], methods for measurement of brain water [224], blood velocity imaging [225], and demonstration of pulsatile flow in cerebrospinal fluid [226].

Work on brain MRI was led clinically by neuroradiologist Joannna Wardlaw at the Western General Hospital [227]. A 2T Elscint MRI unit was funded from 1996, with the Brain Research Imaging Centre for Scotland opening in 1998. This system was replaced in the early 2000's by a 1.5T GE system that remained in operation until 2018 performing a wide range of clinical and technical development studies, principally focused on structural brain MRI. In the 2020 paper [227] Wardlaw comments that research using these units has changed stroke clinical guidelines worldwide, scanned >30,000 patients and led to >£120M research funding. There has been considerable physics support for these activities; prior to 2010 this was Ian Marshall (joined DMPME 1980, Head of the Academic Medical Physics Unit 2006-2012) and Mark Bastin (joined 1997). There were technical developments in MR spectroscopy [227-230], diffusion tensor imaging [231-236] and measurement of brain temperature [237, 238]. In addition to stroke, these methods were used in a range of clinical studies, including brain tumours [239], schizophrenia and bipolar disorder [240], and cognitive ageing [174], including via imaging of the Lothian Birth Cohort (LBC) of 1936 and discussion also of work on the 1921 LBC [241]. These techniques have all been further developed post 2010 and continue to be used in many clinical studies.

The use of MRI to measure blood velocity and wall shear rate are noted in section IX below.

IX. BIOMECHANICS

The term 'biomechanics' in the UK is often interpreted as part of rehabilitation engineering, usually involving gait analysis. The term used here is the wider international definition; 'the study of structure and motion of biological systems'. At the patient level this includes aspects of blood flow, the behaviour of arteries and the musculoskeletal system, surgical interventions and prostheses. Biomechanics is highly cross disciplinary and most work involves interactions between physicists/engineers and clinicians/biologists. Any one project will usually use 2-3 technologies, drawn from medical imaging, computational modelling, material science, metrology and others.

A. Heart valve development

Artificial valves were developed in Edinburgh by Norman McLeod [243-245] working in the Department of Physics with the initial version patented in 1970 [246] and an updated version in 1985 [247]. They were of a tilting design and tested extensively in a flow phantom and in animals, but were not commercialised for use in humans. Testing in a flow rig [248] used milk, with its clotting being used to mimic the build-up of thrombus on the valve surface [249-251]. This method was subsequently used to investigate commercial artificial valves [252].

B. Arterial biomechanics

A simple model of blood flow is that the velocity direction is parallel to the vessel wall, as noted in section VII.B. Flow in arteries may be complex; characterisation of a 3D flow-field requires 7 components; 3 spatial (x, y, z), 3 velocity (v_x, v_y, v_z) and time. In the 1990s ultrasound, MRI and computational fluid dynamics (CFD) had

sufficiently matured to enable the measurement of complex flow fields in-vivo and to estimate new flow-field quantities such as wall shear stress (WSS) which may be useful in clinical diagnosis.

Early work on colour flow vector Doppler involved sequential collection of data with the beam steered to the left followed by the beam steered to the right with vector compounding performed off-line. The initial application was the first ultrasound demonstration of spiral flow in the femoral artery of volunteers [182]. A single spiral shows as adjacent D-shaped regions of flow towards (in red) and away from the transducer (in blue). These techniques were used to demonstrate spiral flow in a cohort of volunteers [253]. Stonebridge went on to develop a prosthetic bypass graft which induced spiral flow, manufactured by Vascular Flow Technologies (Dundee).

Marshall developed MRI techniques for the measurement of the flow-field in carotid phantoms and the first MRI measurements of WSS [254-257]. It was shown that there was excellent agreement with the flow-field estimated using CFD. However estimated WSS was in error due to the difficulty in estimating the exact location of the vessel wall, and in estimating small velocities near the wall. Flow-field data was acquired in normal volunteers, from which standard flow-time waveforms were provided for the common, internal and external carotid arteries which have been widely used as input data in CFD studies [258].

For abdominal aortic aneurysm (AAA) rupture carries a 90% mortality rate and surgical repair is considered when the maximum diameter is greater than 5.5cm. It is known that diameter is not an accurate predictor of rupture and that there is a need for alternative measures. Studies initiated by Hoskins and Whyman investigated the use of AAA stiffness in rupture prediction. Stiffness was estimated using a combination of measured blood pressure and aneurysm wall motion measured using ultrasound. It was shown that stiff AAA are associated with increase in collagen and loss of elastin [259], however it could not be demonstrated that AAA stiffness was predictive of rupture [260]. It was thought that the assumed physical model (isolated uniform elastic ring) was too simple.

The failure of MRI to estimate WSS and of a simple model of AAA behaviour to predict rupture led to the idea that a combination of 3D imaging and computational modelling could be used to estimate WSS and tissue stress, as potential quantities for use in prediction of plaque and AAA rupture. This field was originally referred to as ‘image guided modelling’ [261] and later became known as ‘patient specific modelling’ (PSM). In Edinburgh, work on the development of protocols for PSM was undertaken in AAA using CT [262] and in carotid arteries using 3D ultrasound [263]. Studies on AAA WSS and rupture using PSM were undertaken later [264, 265].

C. Musculo-skeletal biomechanics and orthopaedic engineering

The rise in life expectancy has led to a significant increase in orthopaedic issues, as ageing populations experience a natural decline in bone health. Cumulative wear and tear on the musculoskeletal system, combined with age-related bone density loss, increases the risk of fractures, joint degeneration, and mobility issues. Court-Brown and Caesar [266] analysed the changing epidemiology of adult fractures by reviewing around six thousand fracture cases treated at the ERI and found that approximately 30% of fractures in men, 66% of fractures in women were potentially osteoporotic and predicted a significant rise in these. Their analysis also showed that osteoporotic fractures being primarily limited to thoracolumbar spine, proximal femur, proximal humerus and distal radius, was no longer correct; they identified 14 different anatomical locations where osteoporotic fractures were found to occur. In collaboration with Engineering the age-dependent mechanical response of bone to load was determined. A large sample of cadaveric bone specimens were subjected to mechanical tests to evaluate stiffness and strength – cortical (or compact) bone in tension [267] and trabecular (or spongy) bone in compression [268]. Mechanical tests were followed by examination of porosity, mineralisation and microstructure. The studies showed that mechanical properties deteriorated markedly with age.

Rising life expectancy also increases the need to undertake revision of previously replaced joints. Prosthetic components inevitably suffer wear over time, which also results in the degradation of the bone. Skeletal structures, which were adequate at the time of primary implantation, deteriorate severely and the bone stock left is diminished. A successful technique for hip revision surgery involves use of morselised allograft bone, which is compacted into the bone defects and new prosthetic components are then cemented into the grafted bed. If initial stability of the new components is ensured, the grafted bone is then slowly re-incorporated and remodelled, reconstituting the host skeleton. Ensuring stability requires that the bone graft can sustain shear forces. It was common practice to use relatively large bone particles, often called croutons, for grafting. Pioneering work at Edinburgh, using basic geotechnical engineering concepts, showed that graded graft particle mix (i.e., mix of particles of different sizes) and washing the graft enabled better compaction and strength [269, 270]. Lab experiments showed that the graft behaviour was strongly dependent on the compaction blows applied during surgery [271]. These also demonstrated that graft was a time dependent material (deformation was not instantaneous on load application) and led to the development of the first ever computational model that included post-elastic response [272]. Computer simulation was used to evaluate and optimise short term stability of revision hip replacements which included bone graft [273, 274]. These studies showed that simulation could replicate clinically observed migration (i.e., the movement) of the cup in the acetabulum. One of the most biofidelic numerical models of the human pelvis [275], which, for the first time included muscular and ligamentous supports,

was developed in Edinburgh (Pankaj's group) and showed that stresses in the pelvis were far more uniformly distributed than previously estimated. After 2010 Edinburgh established itself as a major centre for computational biomechanics research in orthopaedics.

X. BIOENGINEERING

The term 'Bioengineering' was coined in 1954 by Heinz Wolff, and the last 25 years have seen the very considerable rise of this area internationally. 'Bioengineering' refers to work that integrates engineering and biology, whereas 'biomedical engineering' refers to work aimed at providing solutions in the medical arena, but the 2 terms are often used interchangeably. An embryo Bioengineering Unit was set up in the School of Engineering in Edinburgh University in 2006. This became an Institute in 2014 headed by Alistair Elfick. The biomechanics work described in section IX was an early example of biomedical engineering in Edinburgh. A few of the other themes of work in bioengineering to 2010 are briefly described below.

A. Raman spectroscopy and related techniques

A number of optical spectroscopic techniques were developed for applications in live cell imaging and characterisation of samples of biological material. Raman spectroscopy involves induction of scattered light which contains information specific to the scattering tissues. Modifications to basic Raman spectroscopy are coherent anti-Stokes Raman scattering (CARS) and tip enhanced Raman scattering (TERS). In CARS a coherent light source is used to increase Raman scattering resulting in improved sensitivity. In TERS a small tip is positioned close to the tissue or material of interest. The tip enhances the scattering by a huge factor, and scanning of the tip allows 2D images of the surface of a material to be acquired. Developments of both TERS and CARS have been undertaken [276-281] with potential applications in many cells types [282, 283].

B. Implantable devices

An implantable device is one which is inside the patient with no wired connection to the outside. Alan Murray and colleagues developed a miniature RF transmitter which generated signals which could be picked up outside the body [284]. As part of a multi-centre collaboration an electronic pill was developed whose intention was to be swallowed and pass through the gastrointestinal system providing real time data on temperature, pH, conductivity, and dissolved oxygen [285]. In practice the pill was 1.6cm in diameter and 5.5cm long making swallowing difficult. A device for drug delivery was developed for the skin [286] and the eye [287]. The idea was that the device is implanted under the skin or eye. The drug is housed in cells whose seal could be broken by remote RF activation allowing controlled delivery over an extended period of time.

XI. POST 2010

Up to 2010, the vast majority of work involving the application of physics and engineering to medicine arose from the original DMPME or its offshoots, continuing Greening's legacy. Post 2010 is a rather different story. Research in Radiotherapy Physics is ongoing, led by Prof. Nailon. Bioengineering has established groups at both Edinburgh University and at Heriot Watt University. Large groupings of physicists, engineers and computer scientists are based in clinical and preclinical centres supporting work in MRI, PET, CT, ultrasound and retinal imaging, all under the umbrella of 'Edinburgh Imaging'. There are also activities in informatics, artificial intelligence, computational medicine and other areas. Thus, whilst no longer under one administrative umbrella, applications of physics and engineering in medicine continue strongly into the future in Edinburgh.

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Contact author:
Peter Hoskins, email: p.hoskins@ed.ac.uk