MEDICAL PHYSICS: FROM BLUE SKIES TO BEDSIDE. TURNING TODAY’S CUTTING-EDGE SCIENCE INTO TOMORROW’S HEALTHCARE TECHNOLOGY

Meeting of the Parliamentary and Scientific Committee on Tuesday 1st February 2011

MEDICAL PHYSICS

Yet this is the every-day world of medical physics, applying the fruits of basic physics research to clinical problems in a way that combines applied science, translational research and highly developed problem-solving skills.

Physics has been applied to the understanding of human physiology and disease for at least a thousand years. Over the centuries it has provided the basis of many medical techniques and devices that we take for granted, from the iconic stethoscope to a simple pair of glasses. Of course, physicists themselves do not need to be involved every time a stethoscope is used or glasses are prescribed: as is the case in many areas of technology, physics provides the tools and then slips quietly into the background. However, a new situation arose in the early years of the twentieth century, when increasing use of radiation and radioactive materials in medicine created a need for physicists to become engaged directly in clinical work.1 These early medical physicists used their knowledge, for example, to help standardise radiotherapy techniques and prescriptions and ensure the safety of both patients and staff working with radiation. Once medical physics had been established as a profession in this way, it was able to grow and diversify as new physics-based imaging and clinical measurement techniques were introduced.

Medical physics today is a diverse field, concerned with the application of a wide range of physics-based principles, techniques and technologies in medical diagnosis, treatment and research. This application takes place in several overlapping contexts.

- Support for clinical services where safety and quality depend on an advanced knowledge of physics, eg interaction of radiation with the human body in radiotherapy and x-ray imaging.
- Development and implementation of new techniques that require an understanding of complex physics, eg advanced MRI techniques.
- Research into new physics-based methods of diagnosis and therapy, eg optical imaging and measurement.

There are currently around 2,000 medical physicists working in the NHS as part of the clinical scientist workforce. New recruits need good degrees in physics or a closely-related area and undergo a four-year vocational training, combined with study for an MSc, to achieve registration with the Health Professions Council (HPC). Trainees study specialist areas of applied physics, and also relevant areas of medical science and clinical practice that will allow them to function effectively as members of multidisciplinary teams of healthcare professionals. Entry is highly competitive: some recruits have acquired PhDs before beginning their training, and many more aspire to do so in post. It is also possible for scientists who have pursued careers in academia to move into the profession if they can show that they have fulfilled the training requirements in other ways. This ensures that the NHS is able to access scientists with cutting-edge experience in emerging areas of science that are ripe for translation into the clinic.

Clinical technologists work alongside medical physicists in a variety of roles, including patient-facing work in areas such as nuclear medicine and radiotherapy, as well as less visible but nevertheless essential roles such as medical equipment management. They have traditionally come from a wide range of technical backgrounds, but graduate entry is increasingly common and vocational degree programmes are under development.

Modified training arrangements are currently being introduced by the Department of Health as part of the Modernising Scientific Careers (MSC) project.2 This involves the development of new training programmes for the entire NHS healthcare science workforce (some 50,000 staff), including a shortened three-year programme for medical physicists and, for the first time, standardised training arrangements for technologists. The first trainees who will undertake these new programmes are currently being recruited. It is important to

When parliamentarians glance across the river at St Thomas’ Hospital, how many of them are aware that the basement of the hospital houses what is in effect an applied particle physics facility: a place where particle accelerators, smaller siblings of the Large Hadron Collider at CERN, provide world-class diagnosis and treatment for cancer patients?

Dr Stephen Keevil
Department of Medical Physics, Guy’s and St Thomas’ NHS Foundation Trust and Department of Biomedical Engineering, King’s College London
Vice President for External Affairs, Institute of Physics and Engineering in Medicine

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ensure that academic strength and flexible recruitment are maintained as the new arrangements are implemented.

The origins of medical physics lie in the medical applications of ionizing radiation, and this remains at the core of the profession. It is here that the particle accelerators mentioned earlier come into play. Linear accelerators (or 'linacs') form the mainstay of radiotherapy treatment, while cyclotrons are used to produce the short-lived radioisotopes needed for positron emission tomography (PET), an advanced form of positron emission tomography (PET), which is based on the NMR phenomenon and would not have been possible without the earlier blue-skies work. It is important to bear in mind the serendipitous and frequently long-term nature of these basic science spin offs in the debate about using anticipated impact to inform research funding decisions.

The medical physics profession is approaching its first centenary, and the future looks bright. There is no sign of an end to innovations in established areas such as radiotherapy and MRI. At the same time, entirely new areas are opening up, such as optical imaging, which promises to have an important role in post-genome personalised diagnosis and treatment. These areas are explored in more detail in accompanying articles. The role of medical physics staff remains crucial in ensuring that new physics-based technology is developed and deployed effectively to provide the high quality and cost effective outcomes that our patients need and deserve.

There is also thriving medical physics activity in UK universities. In 2008 the Wakeham Review identified medical applications of physics as an important area for growth, but reported a 30% reduction in the number of medical physics academics since 2001. However, the review was concerned only with academics based in mainstream physics departments, those whose work was submitted to the physics unit of assessment in the Research Assessment Exercise (RAE). Elsewhere, the report acknowledged that 48.3% of academic physicists are not located in physics departments. We believe that this figure includes a significant number of medical physics researchers who were submitted to medical units of assessment. For example, the staff of the Division of Imaging Sciences and Biomedical Engineering at King’s College London, where I am based academically, includes four physics professors, and there are plans to recruit several more. Rather than declining, it may well be that medical physics research is simply moving into a more multidisciplinary translational research environment.

Whilst this move towards translational research is to be welcomed, it is important to recognise that crucial developments in medical physics are often serendipitous and entirely unpredictable spin-offs from basic science research. When Wilhelm Röntgen discovered x-rays in 1895 he was working in a basic physics laboratory investigating electrical discharge through vacuum tubes, with possible medical applications presumably far from his mind. But once the discovery had been made the implications were obvious, and within three months it had been translated into a diagnostic tool of unprecedented importance. Translation into clinical practice is rarely so obvious or so immediate: Edward Purcell and Felix Bloch discovered nuclear magnetic resonance (NMR) in 1946, again in the context of fundamental physics research, but it was the early 1970s before Paul Lauterbur and Peter Mansfield developed MRI, which is based on the NMR phenomenon and would not have been possible without the earlier blue-skies work.

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3. Available at http://www.rcuk.ac.uk/documents/reviews/physics/review.pdf [accessed 2nd March 2011]
HARNESSING THE POWER OF LIGHT TO PROVIDE REAL-TIME NON-INVASIVE MOLECULAR DIAGNOSTICS

This short article has been written as a brief overview of the field of Biophotonics, with a focus on cancer detection. The objective is to highlight the potential of a rapidly advancing field, likely to have a significant impact on the way clinical diagnostics of the future are performed. The UK has a major role to play in this development and the impacts on the NHS and patient care are likely to be considerable.

WHAT IS BIOPHOTONICS?

Biophotonics is the term for all techniques that deal with the interaction of biological material and light. This refers to emission, detection, absorption, reflection, modification, and creation of radiation from living organisms and organic material. Here we discuss the prospects of utilising light as a diagnostic tool to provide a way of testing individuals for the presence of early cancerous cells.

There are a number of competing or complementary techniques currently being investigated. These include fluorescence, Raman and infrared spectroscopies, elastic scattering and diffuse reflectance spectroscopy. They each have their pros and cons and depending on the application some may be selected above others.

THE CLINICAL NEED FOR EARLY OBJECTIVE CANCER DIAGNOSIS

The primary requirement for successful treatment of any malignancy is early detection. Although the pathogenesis of most malignancies is not fully understood, some cancers are known to develop through a pre-malignant state. Current methods of detecting early malignancies rely upon surveillance of at-risk populations or diagnostic investigations following presentation with suspicious symptoms. By the time symptoms are present tumours are usually of a significant size, and it is often too late to facilitate a full cure.

Biochemical changes within cells and tissues may either initiate disease or occur as the result of the disease process. The qualitative analysis of such changes provides important clues in the search for a specific diagnosis and the quantitative analysis of biochemical abnormalities is important in measuring the extent of the disease process, designing therapy and evaluating the efficacy of treatment. The conventional method for detection of malignancy using histopathological examination of biopsy samples relies upon the subjective assessment of tissue architecture, which is likely to demonstrate abnormal changes at a later stage than would analysis of biochemistry. Furthermore, histopathological analysis requires tissue to be removed with possibly undesirable consequences. Evidently, the development of a rapid, non-invasive, qualitative histochemical analysis technique, enabling objective biochemical analysis of tissue, would be of great value. This may be possible with a variety of optical techniques.

Over the past few years a number of groups have been working towards real-time, non-invasive techniques that utilise light to study abnormalities in tissue. Recent technological developments have made it possible to obtain significant amounts of biochemical or architectural data from extremely complex biological tissue in very short time scales (milliseconds to seconds). Optical diagnosis...
relies upon measurement of the interaction of light photons with the constituents of biological tissue. The resultant data can provide an evaluation of histochemistry or morphology. This information can aid with the deduction of the pathological state of the tissue, and hence lead to a diagnosis. Light can interact with tissue in a number of ways, including elastic and inelastic scattering; reflection off boundary layers; and absorption, leading to fluorescence and phosphorescence. All of these can be utilised in some way to measure abnormal changes in tissue. Many authors have used the term ‘Optical Biopsy’ when describing these techniques. Optical biopsy is a misnomer because no tissue is removed in the analysis, however it does help to convey to the lay-person the general principle of using light to detect cancerous transformations in tissue.

Early forms of optical biopsy systems, utilising tissue fluorescence, have been used as an adjunct to current investigative techniques, mainly to improve targeting of blind biopsy. Some such as that shown in Figure 1 utilise agents to provide an enhanced disease specific signal. Future prospects utilising molecular-specific techniques may lead to the possibility of complete replacement of biopsy with objective optical detection providing a real-time, highly sensitive and specific measurement of the tissue pathological state. However until its efficacy is proven it is most likely that optical detection will be used as a complementary technique to improve targeting of biopsy selection.

The clinical requirements for an objective, non-invasive real time probe for the accurate and repeatable measurement of tissue pathological states are overwhelming. There is a clinical need for optical diagnosis in a number of important areas:

1. Situations where sampling errors severely restrict the effectiveness of excisional biopsy, such as the high failure rates associated with blind biopsies, whereby the clinician has to randomly select sites for sample collection. This method is used to screen for pre-malignant conditions such as ulcerative colitis and Barrett’s oesophagus.

2. Where conventional excisional biopsy is potentially hazardous, examples of vulnerable regions include the central nervous system, vascular system and articular cartilage.

3. An immediate diagnosis during an investigative procedure would eliminate the need for many secondary procedures by enabling treatment to take place directly following diagnosis. This is especially useful with the development of treatments utilising light energy, such as photodynamic therapy and laser ablation. This is likely to improve patient outcomes and decrease waiting times by reducing the number of costly procedures required.

4. Tumour margins could be identified during surgical resection, thus enabling a more accurately targeted resection to be performed.

5. A surgeon with any doubt over a diagnosis could cross-validate a previous diagnosis prior to excision of an organ or lesion using a non-invasive optical probe.

Techniques such as Raman spectroscopy (RS) and Fourier-Transform Infra-red absorption spectroscopy (FTIR) have recently provided evidence of discrimination between multiple pathology groups within each organ.1 Raman spectroscopy, which can be performed endoscopically at any excitation wavelength, is most likely to provide in vivo diagnosis.2 FTIR currently shows the greatest promise for rapid in vitro diagnosis and spectral imaging, where water content of tissues does not prove problematic.

Other techniques such as optical coherence tomography and optoacoustic imaging are similar in vivo imaging techniques are always eye-catching, it should be noted that these techniques still provide information only about structure and cellular morphology. To provide real information about early molecular changes and disease prognosis those techniques that provide extra-value information on tissue biochemistry associated with disease will be the way forward. In the longer term the use of contrast agents able to provide significant signal enhancement of low concentration molecules of interest, for diagnosis and monitoring, may enable signals to be probed from outside the body.3

**SUMMARY**

There are significant benefits for UK patients and the NHS in improving diagnosis of disease at an early stage. While conventional medicine of the 20th century treated the effects of disease, molecular medicine in the 21st century will treat its causes. This leads to the requirement for personalised medical treatment selection and monitoring – with clinical decisions based on patients’ own tumour expression, enabling the selection of effective treatments for the individual and hence minimising unnecessary procedures.

The impact of technology for patient care can be immense, but so can the cost to resources. This must be carefully managed and health economic arguments regarding benefits versus opportunity costs are vital. Novel diagnostic technologies, such as those found in the Biophotonics arena can provide UK plc with significant income if we can exploit these disruptive technologies in International healthcare markets.

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**Figure 1:** An image taken during fluorescence bladder cystoscopy following administration of a drug which is differentially accumulated in abnormal tissues. Illumination of the tissue with blue light produces a strong red fluorescence from these regions of accumulation. This can enhance the performance of biopsy selection and tumour margin removal.
Approximately 1 in 3 people will develop some form of cancer during their lifetime and around 1 in 4 people die from cancer. Cancer is a disease of the genome where damage accumulates over time. With the ageing population profile in the UK it is expected that by 2025 there will be an additional 100,000 cases of cancer diagnosed each year. Although the incidence of cancer has steadily increased over the past 30 years, the positive news is that survival rates from cancer have improved year on year.

There are three pillars of cancer treatment; namely surgery, radiotherapy and chemotherapy. The management of cancer involves using a combination of treatment options such as surgery followed by radiotherapy. It is 100 years since Marie Curie won her second Nobel prize for the isolation of radium. The discovery of radium led to the first treatments of cancer with radiotherapy. 100 years on and approximately two in every five patients cured of their cancer will have received radiotherapy as part of their treatment. Radiotherapy is also cost effective, 13 times more cost effective than chemotherapy (http://www.bbc.co.uk/news/health-12299533). Although the main principles for treatment with radiotherapy have been established for some time the technology and application of radiotherapy continues to evolve to improve survival and reduce side effects of treatment.

For a number of reasons there has, for many years, been a national under-provision of radiotherapy in the UK compared to international standards. It is estimated from international best practice that 52% of all cancer patients should receive radiotherapy, but in the UK approximately 40% of cancer patients are given radiotherapy. This means that 30,000 patients a year are not receiving the best cancer care. (https://www.sor.org/news/files/images/FAQs_about_the_campaign.pdf) To achieve comparable rates of survival from cancer to those in leading western countries it is likely that the gap in the provision of radiotherapy will need to be closed.

Medical physicists are crucial to radiotherapy services. The role of the medical physicist is threefold; they are central to patient safety, they develop new radiotherapy treatments, and they are involved in research and development of radiotherapy equipment and techniques. Medical physicists ensure that the radiotherapy machines are working optimally, and that the correct amount of radiation is given as precisely as possible to the cancer. This is crucial to the success of radiotherapy treatment and the high levels of safety are maintained by approximately 800 medical physicists working in UK hospitals. Medical physicists are also involved in the development of a radiotherapy plan where sophisticated computer programs are used to determine how to give radiation to the tumour whilst protecting normal
healthy tissue from harm. For many years, UK based medical physicists have been involved in the development of new treatment techniques for radiotherapy aimed at improving the effectiveness of treatment as well as reducing the potential side effects. A recent example is the development of Volumetric Modulated Arc Therapy by Elekta, an internationally leading manufacturer of linear accelerators used in radiotherapy treatments. Elekta worked closely with medical physicists at the Royal Marsden Hospital in Sutton to develop the radiotherapy technique and the hospital treated the first patient in the world with this technique in February 2008.

The UK has a long history of scientists contributing to the field of medical physics and to radiotherapy. Sir Godfrey Hounsfield received a Nobel prize for Medicine in 1979 for the invention of the CT-scanner, whilst Sir Peter Mansfield received the same prize in 2003 for the invention of the MR scanner. Both CT and MR scans are now routinely used to define the size and location of a patient’s tumour and normal healthy tissue prior to designing radiotherapy treatments. Professor Steve Webb, at The Institute of Cancer Research, was an early pioneer in the development of intensity modulated radiotherapy, a modern form of radiotherapy that is better able to spare healthy tissue, leading to fewer side effects from treatment. In 2008, Medicare in the US spent $1 billion on intensity modulated radiotherapy treatments (The Wall Street Journal – A Device to Kill Cancer, Lift Revenue, 7th December 2010).

Where are the next advances in radiotherapy treatment in the UK? Proton radiotherapy is a clear example of blue skies research leading to patient treatments. Proton radiotherapy was first proposed in 1946 as a way to treat cancer (Wilson, Radiology (1946)). Early treatments with protons were performed by pioneering physicists in particle accelerator laboratories in the US and Sweden in the mid 1950s. Despite the early promise of this treatment technique it took until 1990 for the first hospital-based proton radiotherapy centre to be opened at Loma Linda in California. By the end of 2010 there were 29 proton radiotherapy centres worldwide. Why are protons expected to improve the radiotherapy treatment for cancer patients? Figure 1 shows the way radiation dose is deposited as energy in human tissue by a proton radiotherapy beam and a traditional photon radiotherapy beam (10MV x-rays – dashed line). The tumour is shown at some depth within a patient and it is clear that the proton beam gives up most of its energy where the tumour is located, and delivers less radiation on the way to the tumour. In comparison the traditional radiotherapy beam is less suited to treating the tumour with a single beam as more radiation is deposited prior to reaching the tumour. Therefore a number of radiation beams are required from different angles to create a cross-fire effect at the tumour. The better characteristics of the proton radiotherapy beam make it much more suitable for reducing the amount of radiation the healthy tissue receives.

The survival of childhood cancers has improved over the past 30 years and continues to do so. However, as the tissue and bones of children are still developing they are more sensitive to radiation than adults. Childhood cancer survivors also live with any potential side effects of treatment for much longer. Oeffinger et al (NEJM (2006)) found that a childhood cancer survivor is three times more likely to have multiple health conditions than a sibling that did not have childhood cancer. Proton radiotherapy is highly likely to reduce the side effects of treatment for childhood cancers and therefore reduce the burden of life-long health conditions for these patients.

Proton radiotherapy is currently available to UK patients via a specialised commissioning service of the NHS for a limited number of clinical indications. An expert reference panel receives patient referrals for treatment abroad at one of three centres: the Paul Scherrer Institute, Villigen, Switzerland, the Centre-Protontherapie, Orsay, France, or the University of Florida Proton Therapy Institute, Jacksonville, USA. This national service has been available since April 2008 and has resulted in more than 70 UK patients being treated abroad to date. Although providing a necessary and important clinical service, treatment abroad for several weeks can provide significant challenges for patients and their carers. The treatment of patients abroad provides a service only for those who will benefit most from this form of treatment. However, in its current form the number of patients receiving this form of radiotherapy is unlikely to meet fully the UK demand. An early estimate of the number of patients that could benefit from proton radiotherapy in England alone is in excess of 1700 cases per annum (Improving Outcomes: A strategy for cancer. Department of Health (2011)). Treating this number of patients at facilities abroad would be a significant logistical challenge associated with substantial costs. It is therefore highly likely that UK based proton radiotherapy facilities will be required in the next five years. Medical physicists will be essential for the safe and effective development of proton radiotherapy services within the UK. Technical developments and innovations made by these scientists, in collaboration with clinical colleagues and industry, will enable further improvements in the treatment of cancer with proton radiotherapy, enhancing treatments for future cancer patients.

![Figure 1: Reprinted with permission from ‘Technology Insight: proton beam radiotherapy for treatment in pediatric brain tumors’ Torunn I Yock and Nancy J Tarbell, Nature Clinical Practice Oncology (2004) 1, 97-103](image-url)
THE DEVELOPMENT OF MAGNETIC RESONANCE IMAGING

The UK played a pivotal role in the development of magnetic resonance imaging, in particular led by physicists from Nottingham, Aberdeen and London. Professor Sir Peter Mansfield won a Nobel prize in 2003 for his contribution to this work. The technique builds on the analytical chemistry technique of nuclear magnetic resonance which produces spectra representing the chemical constituents of small samples, but gives no spatial information. The basic phenomenon of nuclear magnetic resonance imaging involves a patient lying in a large powerful magnet while harmless pulses of radio waves are transmitted into the body. The MRI scanner then records the weak radio waves which are subsequently emitted by the body and uses these to create detailed images of the body. The technique relies on a property of some nuclei termed spin and the fact that these nuclei take one of two energy states – a low or high energy state – when placed in a magnetic field. By transmitting radio waves at a specific frequency it is possible to excite nuclei from the low energy state to the high energy state. After some time these nuclei then drop back from the high energy state to the low energy state, emitting bursts of radiofrequency energy which are detected by carefully designed radiofrequency coils surrounding the anatomy of interest.

In order to create an image of the human body we need to be able to spatially localise the weak nuclear magnetic resonance waves emitted by the body. This is done by applying a magnetic field gradient created by applying electrical currents through carefully designed coils of wire known as gradient coils. By spatially varying the magnetic field this changes the resonant frequency or Larmor frequency of the protons.

CLINICAL MAGNETIC RESONANCE IMAGING

Some of the first clinical magnetic resonance imaging systems were installed in UK hospitals with early applications to the brain and body. The area of MRI has been a remarkably exciting field to work in with almost every year bringing an expansion of both magnetic resonance techniques and applications. Indeed there are now more than 40 million MRI scans acquired every year.

The strength of magnetic resonance imaging flows from...
two characteristics – the impressive soft tissue contrast and the flexibility with which images demonstrating different image contrast can be displayed. As an example Figure 2 shows how areas of tissue damaged by vascular dementia can be chosen to appear as bright compared to the surrounding intact brain tissue and dark cerebrospinal fluid which surrounds and cushions the brain.

Figure 2 – One of the strengths of MRI is excellent soft tissue contrast. The image above shows bright areas of vascular damage surrounding the dark ventricles filled with cerebrospinal fluid.

Brain and spine imaging are the most frequent use of MRI, but improvements in basic physics and engineering have meant that MRI is now used widely in musculoskeletal imaging, abdominal imaging, cardiac imaging and beyond.

The basic technique of magnetic resonance imaging has been expanded and augmented by a series of methodological improvements driven by physicists and engineers. These include magnetic resonance angiography (MRA) which demonstrates the movement of flowing blood in vessels throughout the human body, diffusion tensor imaging which studies the random movement of water molecules which are changed by diseases such as stroke, and magnetic resonance spectroscopy which studies metabolites in the brain and body. Magnetisation transfer imaging and perfusion MR imaging further expand the range of techniques available for medical imaging, all driven by the enquiring minds of physicists and engineers.

THE ROLE OF THE MEDICAL PHYSICIST IN MAGNETIC RESONANCE IMAGING

The role of a medical physicist in magnetic resonance imaging is both varied and exciting. Typically they will have a leading role to play in the safe use of magnetic resonance imaging. The powerful magnet that the patient lies in is strong enough to pull any ferromagnetic item out of a careless user’s hands or pockets, and some medical implants mean that not all patients can be scanned. As with any piece of medical equipment it is important that magnetic resonance imaging systems are regularly tested as part of a planned programme of quality control work which the medical physicist will normally lead on.

A mainstay of a medical physicist’s working life is the development of new techniques for clinical use and magnetic resonance imaging is no exception. Programming the highly complicated MRI scanners to perform new techniques requires years of training and a substantial degree of skill and we are fortunate that the NHS has so many talented medical physicists who are eager to rise to this particular challenge. As well as programming the scanners the medical physicist also has a leading role to play in designing tools for the analysis of images using either the manufacturer’s analysis computers, or other computer workstations.

Finally the NHS has a key role to play in medical research, particularly via the National Institute for Health Research (NIHR) which aims to improve translational, organisational and health service research.

A POWERFUL TOOL FOR MEDICAL RESEARCH

While magnetic resonance imaging is an excellent clinical imaging technique, it has a parallel role to play in basic and translational research with applications in oncology, cardiology, psychology, psychiatry, obesity and musculoskeletal research.

My own role bridges the area between research and clinical, aiming to use MRI to answer new research questions in the area of psychiatry, neurology, psychology and neuroscience and to translate new research techniques into clinical practice as the neuroimaging coordinator for the NIHR funded Biomedical Research Centre for Mental Health.

Two examples of this include new techniques to minimise the impact of patient motion on the quality of images and developing tools to aid clinicians in diagnosing Alzheimer’s disease, a priority for the nation and the government. Figure 3 shows the key areas at the base of the brain where patients first lose grey matter as the cortex thins. I was delighted when the Department of Health chose to use some of my work to publicise the launch of the latest NIHR funding round in early March.

Figure 3 – Image illustrating the loss of grey matter in the human brain in Alzheimer’s disease. The areas in white demonstrate thinning of the cortex towards the base of the brain, particularly in the temporal lobe.

SUMMARY

Medical physicists have played a key role in the development of magnetic resonance imaging and now that the technique is established continue to do so through both clinical and research work.