Physics and Medicine 2

Diagnostic imaging

Peter Morris, Alan Perkins

Physical techniques have always had a key role in medicine, and the second half of the 20th century in particular saw a revolution in medical diagnostic techniques with the development of key imaging instruments: x-ray imaging and emission tomography (nuclear imaging and PET), MRI, and ultrasound. These techniques use the full width of the electromagnetic spectrum, from gamma rays to radio waves, and sound. In most cases, the development of a medical imaging device was opportunistic; many scientists in physics laboratories were experimenting with simple x-ray images within the first year of the discovery of such rays, the development of the cyclotron and later nuclear reactors created the opportunity for nuclear medicine, and one of the co-inventors of MRI was initially attempting to develop an alternative to x-ray diffraction for the analysis of crystal structures. What all these techniques have in common is the brilliant insight of a few pioneering physical scientists and engineers who had the tenacity to develop their inventions, followed by a series of technical innovations that enabled the full diagnostic potential of these instruments to be realised. In this report, we focus on the key part played by these scientists and engineers and the new imaging instruments and diagnostic procedures that they developed. By bringing the key developments and applications together we hope to show the true legacy of physics and engineering in diagnostic medicine.

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Introduction

Physical techniques have always had an important role in medical diagnosis, from the simplest measurements of body temperature and pulse rate, to the sophisticated microscopic analysis of biopsy samples. In a report examining "milestones in medicine", Wells[1] noted that ten Nobel Prizes have been awarded for physics and engineering in medicine. To these should probably be added Robert R Ernst who was awarded the Nobel Prize for Chemistry in 1991 for his development of multi-dimensional nuclear magnetic resonance (NMR) techniques, including Fourier imaging, and Paul Lauterbur and Sir Peter Mansfield who were jointly awarded the Nobel Prize for Physiology or Medicine in 2003 for their development of MRI. An editorial in the *New England Journal of Medicine*[2] identified the development of body imaging as one of the 11 most important advances in medicine during the past millennium. These scientific advances, particularly in non-invasive medical imaging, have revolutionised clinical practice and laid the foundations for modern day personalised treatment and preventive medicine. Imaging techniques use the entire breadth of the electromagnetic spectrum, and magnetism and sound. The Wellcome *Witnesses to 20th Century Medicine* series[3] provides insight into the early history of the main developments in this discipline. In this report, we focus on the imaging techniques that have had or are expected to have important effects on medical diagnosis, and the key part played by physical scientists in their development.

X-ray imaging

The first medical radiographs rapidly followed the discovery of x-rays by Wilhelm Röntgen at the end of the 19th century.[4] These were simple projections through tissue showing dense structures such as bone or foreign objects.[5] They were greatly enhanced by William Coolidge's development of the hot cathode tube, which brought stability and enabled higher x-ray photon energies to be achieved than were previously possible.[6] However, soft tissue contrast was poor until Sir Godfrey Hounsfield, working at the Electrical and Music Industries laboratories (Middlesex, UK), developed the electromagnetic interference (EMI, now CT) scanner. This scanner took x-ray projections at different angles and combined the results to generate image slices in fine detail.[7] Hounsfield used a so-called translate rotate geometry in which an x-ray tube and detector moved in parallel across a gantry recording a projection, and the gantry then rotated to record the next projection. Even though the basic mathematical principle for deriving the image from projections had been worked

Key messages

- X-ray imaging was discovered at the end of the 19th century, but the development of x-ray CT in the second half of the 20th century enabled this instrument to distinguish the contrast between different soft tissues.
- The development of the cyclotron in the 1930s, and later the nuclear reactor, provided artificially produced radionuclides in sufficient quantities for the widespread development of nuclear imaging and emission tomography.
- MRI was developed from nuclear magnetic resonance, a non-imaging technique used for chemical analysis, and is based on the application of magnetic field gradients to enable the spatial localisation required for cross-sectional imaging.
- Ultrasound imaging has become a major diagnostic imaging technique for the visualisation of soft tissues and has revolutionised obstetric care.
- Magnetoencephalography and electroencephalography offer new insights into neural networks and brain function, and will have an increasingly important role in medical diagnosis and treatment.
- Imaging techniques are being combined to produce hybrid imaging systems and will have a fundamental role in the direction of chemotherapeutic and surgical treatment, and in real time guidance of radiation therapy.

Search strategy and selection criteria

The scope of our report was those techniques that have contributed most substantially to diagnostic imaging. We searched PubMed with the terms "computed tomography", "cyclotron", "doppler", "electroencephalography", "electromagnetic interference scanner", "nuclear magnetic resonance", "magnetic resonance imaging", "magnetic resonance spectroscopy", "magnetoencephalography", "nuclear medicine", "positron emission tomography", "radionuclide imaging", "single photon emission tomography", and "ultrasound" for reviews describing the physical basis and historical development of each instrument, and the most important clinical applications. This information, supplemented by expert opinion, was used in more refined searches to trace step changes in clinical practice back to their physical origins. Identification of developments that are most likely to make important contributions to diagnostic medicine in the future, was in part guided by citation profile, but was inevitably more subjective according to our experience and expertise. Searches were not restricted by date. The date of the last search was December, 2011.

out years previously,[8] image reconstruction still presented a substantial challenge. Allan Cormack shared the 1979 Nobel Prize with Hounsfield for his contribution to the technique.[9,10]

The early results from the EMI scanner[11] had immediate effect and changed forever the expectations of radiological imaging. The first systems were head scanners that enabled intracranial tumours and infarcts to be seen as regions of hypointensity, and calcification and haemorrhage as regions of hyperintensity. This distinction paved the way for differentiation between haemorrhagic and non-haemorrhagic stroke and enabled the safe treatment of non-haemorrhagic stroke by thrombolysis. Whole body scanners soon followed, extending the range of clinical applications, which now include dynamic cardiac imaging.[12] New generation scanners, using fan beam and other geometries, have greatly increased the speed of data acquisition; with current generation helical scanners sub-second imaging is possible and full three dimensional (3D) examinations can be completed in a few seconds[13] (appendix p 1).

See Online for appendix

Developments in the past 10 years include multisource, multidetector scanners and dual-energy CT and photon-counting spectral techniques for the determination of material composition. New detector technologies and iterative reconstruction processes will further enhance image quality.[14] More than 30% of CT scans are now of the chest where high resolution spiral CT is used to show chronic interstitial processes in the lung and to enable a bolus of contrast medium to be tracked in a technique known as CT pulmonary angiography. In the cardiovascular system, this process shows obstructions such as pulmonary embolism or atheroma in coronary arteries (figure 1). Although the mainstay of CT imaging remains in tumour diagnosis, it also retains a traditional role in bone investigations where 3D visualisation and superb spatial resolution (0·2 mm) are helpful in complex cases. The widespread use of CT imaging does raise some issues of radiation exposure. Manufacturers are now introducing dose reduction techniques to protect patients. Eisenberg[15] provides an overview of CT applications and compares this technique to PET and MRI.

Nuclear imaging and PET

The founder of the use of radioactive tracers is George de Hevesy[16] who, shortly after the first proven production of an artificial radionuclide (^{30}P) by Frédéric Joliot and Irène Curie in 1934, reported the dynamics of ^{32}P phosphate incorporation in bone.[17] Initial progress was slow because of the limited neutron flux available from the radium-beryllium sources that were used for radionuclide production. This situation changed with the development of the cyclotron by Ernest Lawrence at Berkeley in the 1930s and more strikingly with the demonstration by Enrico Fermi in 1942 of a self-sustained nuclear chain reaction, leading to the development of nuclear reactors. The mainstay of nuclear imaging for the next two decades was the rectilinear scanner, developed by Benedict Cassen and Lawrence Curtis.[18] Imaging of large organs with mechanical scanners was very slow, and the need for a large stationary detector was clear. In 1957, Hal Anger constructed the first prototype of the modern gamma camera.[19]

^{131}I was the most important radionuclide in the early development of nuclear imaging. Not only was it used to study the thyroid, where it accumulates naturally, but it was also used for therapy and as a radiotracer to label different radiopharmaceuticals. However, the development that made nuclear imaging available to most regional hospitals was the ^{99m}Tc generator,[20] originally known as the moly cow. ^{99m}Tc (half life 6 h) is the daughter of ^{99}Mo (half life 66 h) from which it can be extracted on a daily basis with a simple elution procedure. It is still used in more than 80% of nuclear medicine studies, but global disruption of supplies in the past 5 years has been cause for much concern because of the small number of ageing research reactors.[21] The gamma camera provides useful functional images, but they are of low spatial resolution. However, during the 1960s, beginning with the work of David Kuhl and Roy Edwards[22] and continuing with contributions by Stig Larsson,[23] tomographic reconstruction was developed into a technique that came to be known as single photon emission computed tomography (SPECT). This procedure is widely used in the measurement of blood flow and perfusion. Regional cerebral blood flow measurements were introduced by Charles Ingvar and Niels Lassen[24] who used ^{133}Xe to do the first functional brain imaging studies in people.The selective uptake of potassium and rubidium into the myocardium was shown in 1954.[25] This development led to measurement of regional myocardial blood flow with ^{201}Tl-thallous chloride[26] and, in the past 20 years, ^{99m}Tc-labelled tracers. Other important applications include lung perfusion and ventilation and hepatobilliary and kidney function, but the most common procedure nowadays is bone scintigraphy with ^{99m}Tc-polyphosphates or similar bone-seeking agents to show bone metastases.[27]

With the development of cyclotrons in the 1930s, the possibility of using positron emitters for biochemical research arose. The first use in people, by Cornelius Tobias, showed the labelling of red blood cells with ^{11}C carbon monoxide;[28] the first attempts at clinical application—the localisation of brain tumours—were in 1951 by Gordon Brownell, William Sweet and colleagues at Massachusetts General Hospital (MA, USA)[29] and by Frank R Wrenn and colleagues at Duke University (NC, USA).[30] The first cyclotron installed in a medical centre was at the Hammersmith Hospital (London, UK) in 1955. Several abortive attempts to produce a PET scanner for human beings were made before Mike Phelps and Ed Hoffman and their team at Washington State University were successful in 1974. The first PET images of blood flow, oxygen and glucose metabolism, and bone scans were achieved with this instrument.[31,32]

Positron emitting radionuclides including ^{11}C (half life 20 min), ^{13}N (10 min), ^{15}O (2 min), and ^{18}F (110 min) have fewer neutrons (lower mass number) than their stable isotopes and tend to be elements of low atomic number. They are more easily incorporated into the biomolecules of interest than are the heavier radionuclides used in SPECT. PET is therefore an excellent instrument for molecular imaging. Unfortunately, the short physical half lives of these PET radionuclides necessitate, with the exception of ^{18}F, an on-site cyclotron and rapid radiolabelling facilities. For many years this requirement restricted PET imaging to research applications and a few tertiary clinical centres. Nowadays, regional cyclotrons and extensive delivery networks ease the more widespread clinical use of ^{18}F tracers. PET relies on the simultaneous detection of the pair of 511 keV gamma rays produced as the positron emitted by the radionuclide injected into the body annihilates with an electron. This permits the origin of the annihilation event to be determined without need for physical collimation, resulting in greatly increased sensitivity compared with single photon techniques.[33] The detectors are arranged in a ring or series of rings for 3D applications. Coincidence detection identifies the line on which the radionuclide is located and reconstruction algorithms similar to those applied in x-ray CT are used to generate 2D or 3D images. The development of more efficient detectors with rapid response times (600 ps or less) enable time-of-flight PET in which the small differences in arrival times of the photons assist in the location of the annihilation event along the line connecting the detectors. Despite improvements in overall system sensitivity, the small amount of administered radioactivity used (limited by radiation dose) means that the images appear noisy. Substantial effort has been expended in development of effective image reconstruction algorithms, especially iterative methods based on maximum likelihood estimation.

After the first demonstration by Ingvar and Lassen[24] in 1961 that it was possible to study brain activity on the basis of changes in regional blood flow required to meet increased energy need, PET rapidly became the method of choice for functional neuroimaging and during the ensuing decades began to elucidate the workings of the brain (eg, Toga and Mazziotta[34]). Initially, this work was based, like predecessor studies, on blood flow (with ^{15}O as radiotracer), but metabolic approaches were soon developed. Foremost among these, and crucial for later clinical exploitation, was ^{18}F-fluorodeoxyglucose (^{18}F-FDG), a glucose analogue that is transported into cells and phosphorylated by the enzyme hexokinase, trapping it inside the cells. ^{18}FDG-PET thus measures glucose transport and is a good indicator of metabolic rate, which increases to meet energy demand during brain activity. Researchers appreciated early on that PET had sufficient sensitivity for mapping membrane receptors and transporters, and radiolabelled ligands were developed to target specific systems including dopamine D2 and D3 receptors (^{11}C-raclopride) and serotonin transporters (^{11}C-DASB, figure 2). This approach has been especially useful to the pharmaceutical industry, enabling in vivo binding studies of new pharmaceutical agents, either by radiolabelling the agents themselves, or in competitive binding studies with established radioligands.

PET has important clinical applications in neurology and cardiology, but at least 90% of the clinical workload is in oncology.[35] ^{18}F-FDG-PET is used to identify regions of hypermetabolism associated with malignant tumours and is especially important in location of metastases. Hypermetabolism is not necessarily restricted to the tumour itself (appendix p 2). The development of low cost cyclotrons and the availability of FDG from third party suppliers have been key in increasing clinical uptake.[36] Clinical PET has been especially successful in

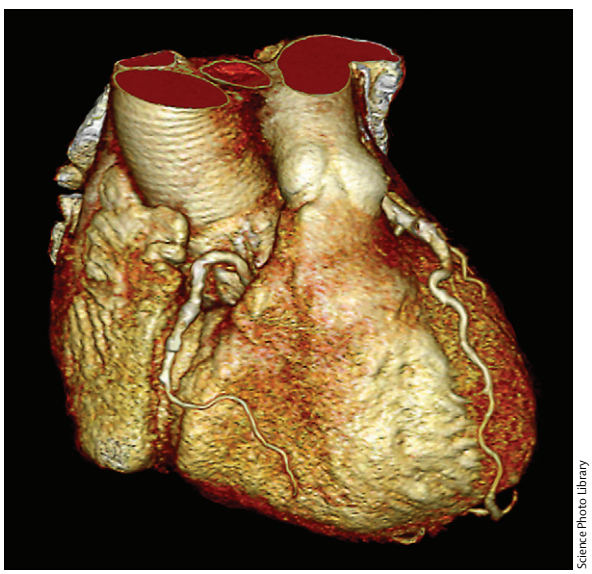

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Figure 1: **3D CT image of the heart**
Anterior view of the right-hand side of the heart, showing the coronary arteries.

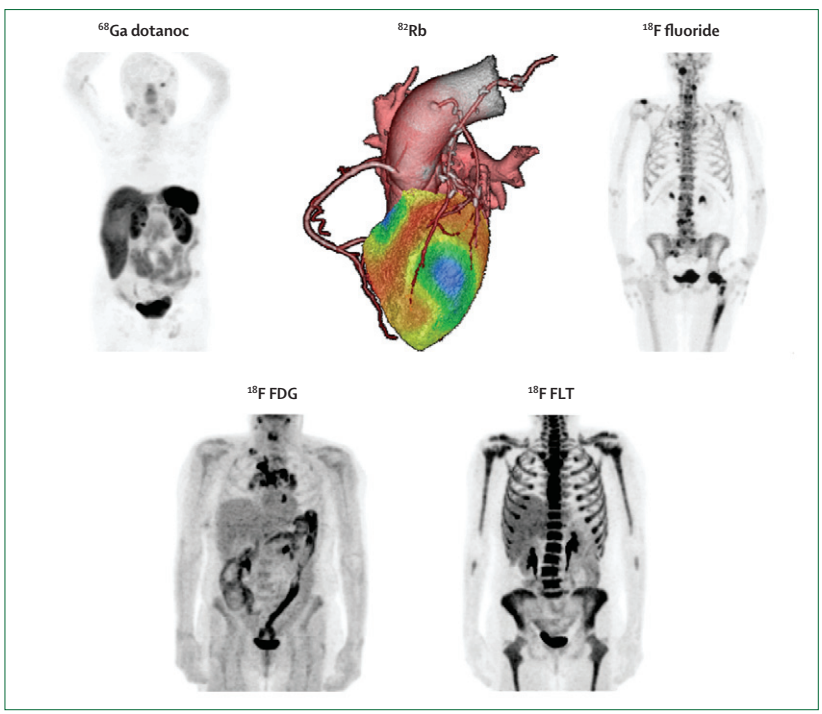

Figure 2: **PET ligands and their uses**
^{68}Ga-Dotanoc: somatostatin receptors. ^{82}Rb: myocardial perfusion (in this example, the PET image is overlaid onto a CT angiography study). ^{18}F-Sodium fluoride: bone imaging. ^{18}F-fluorodeoxyglucose (FDG): glucose metabolism. ^{18}F-fluoro-L-thymidine (FLT): cellular proliferation. Image courtesy of Peter Ell, Institute of Nuclear Medicine, UCL/UCLH NHS Trust, UK.

lung tumours, colorectal cancer, and lymphomas, and has substantially changed the management of these diseases.[37,38] In neurology, ^{18}FDG-PET has been useful in locating epileptogenic foci as regions of hypometabolism in interictal scans. Hypometabolism associated with diffuse brain disease, particularly Alzheimer's disease and other forms of dementia, is also readily identified with ^{18}FDG-PET, and is useful in differential diagnosis. In the past 10 years alternative radiolabelled peptides have been introduced that localise to amyloid brain deposits. In particular, the development of Pittsburgh Compound B and other similar compounds that localise to amyloid plaques promise many clinical applications, helping achieve early diagnosis and the potential for therapy monitoring of Alzheimer's disease.[39] Heavy positron emitting radionuclides are increasingly being used as radiolabels and a wide range are now available. In cardiology, for example, ^{82}Rb is used to measure myocardial blood flow and coronary flow reserve before planning coronary artery surgery to restore myocardial blood flow (figure 2).

Clinical PET is now always used in combination with x-ray CT to provide an anatomical context for the tumour uptake and to enable fast, low-noise attenuation correction. Commercially available hybrid PET-magnetic resonance is being actively developed for much the same reasons. Emission tomography, especially PET, despite limitations in resolution and sensitivity, provides unique ability to measure picomolar concentrations of radioactively labelled tracers. It continues to have great potential for investigating molecular processes in vivo, and complements the diagnostic information available from alternative higher resolution techniques.

MRI and magnetic resonance spectroscopy

MRI depends on the magnetic properties of some nuclei, most notably the protons in the hydrogen atoms of water, and was developed from its parent technique NMR spectroscopy, which is widely used in chemical analysis.[40,41] It relies on the use of magnetic field gradients to provide spatial information, and these field gradients can be manipulated electronically, giving the technique great versatility. The move from test tube analysis to whole body diagnosis was striking: in 1977 the first image was published showing live human anatomy[42] and, within a year, crude whole body images were being generated.[43,44]

At practically realisable magnetic field strengths, the MRI frequency is in the radiofrequency part of the electromagnetic spectrum; this brings safety (the photons have insufficient energy to break chemical bonds) and is one of the few so-called transparent windows into the human body. The exquisite soft tissue contrast (figure 3 shows an example of what can be achieved at ultra-high-field, ie, 7 T) has revolutionised medical diagnosis, and MRI is well established as the method of choice especially for neurological applications such as the diagnosis of multiple sclerosis.[45] Soft tissue contrast originates mainly in differences in the relaxation properties of the nuclei in different tissues, rather than in the smaller (about 15%) differences in water content. Initially, spin lattice (T_1) relaxation—the process through which nuclear magnetisation is restored to its equilibrium value after perturbation—was the basis for diagnostic procedures. This was driven by the knowledge that cancerous tissue could be differentiated on this basis,[46] and quickly led to applications in multiple sclerosis[47] and in stroke at the Hammersmith Hospital and in cancer in Aberdeen University (Aberdeen, UK).[48] Researchers soon appreciated that spin spin (T_2) relaxation—the process describing the decay of the proton signal—was an equally useful contrast mechanism. Other forms of relaxation process have also proved useful and magnetic resonance pulse sequences have been developed to exploit each of these contrast mechanisms, or indeed combinations of them (an example of the clinical use of T_2* contrast can be found in the appendix p 3[49]).

Standard MRI sequences typically take a few minutes to cover a region of interest, and while acceptable for structural studies, dynamic information is lost. In the case of cardiac MRI, this loss can be addressed by gating the acquisition to the electrocardiography (ECG) signal, so that images at different phases of the cardiac cycle are built up during many acquisitions and can be shown as a cardiac movie. Aperiodic motion requires faster imaging

to freeze the movement and Peter Mansfield[50] showed early on how to generate images in a few tens of milliseconds with rapidly switched magnetic field gradients in a technique known as echo-planar imaging. Fast imaging enabled dynamic contrast-enhanced MRI in which a contrast agent (usually a chelate of the gadolinium ion, Gd^{3+}) changes the relaxation time of water—eg, in brain tumours where breakdown of the blood–brain barrier enables the agent to accumulate at a rate determined by tumour type and grade. This approach has been successfully adopted in breast cancer diagnosis.[51] Availability and cost are limiting factors in screening the general population, but for individuals with a high risk factor MRI is cost effective and preferable to conventional mammography with its radiation exposure about which concern is growing. In addition to relaxation based contrast, the magnetic resonance signal can be sensitised to many other physiological variables, including blood flow, perfusion, and diffusion, and several of these have proven to be clinically useful. For example, changes in apparent diffusion coefficient are an early indicator of stroke and a perfusion to diffusion mismatch can identify brain tissue (the ischaemic penumbra) that is viable but at risk of damage after stroke.[52]

During the past two decades, functional MRI (fMRI) based on the different relaxation properties of oxyhaemoglobin and deoxyhaemoglobin, in combination with echo-planar imaging, has largely supplanted PET as the functional imaging method of choice.[53] It has enabled the centres of the human brain engaged in a wide range of sensory, cognitive, and emotional tasks to be located with high precision—eg, the ocular dominance columns in the visual cortex.[54] Attention is increasingly being focused on the way in which these brain centres interact, and so far about a dozen networks have been identified on the basis of correlations between the fMRI signals of the network nodes. This functional connectivity can be related to anatomical connectivity with diffusion tensor imaging. In this technique, the faster diffusion of water molecules along rather than across fibres is used to follow the fibres connecting one region to another.[55] These techniques have revolutionised neuroscience, as evidenced by the exponential growth in fMRI studies, but their effect on medical practice has so far been limited. One notable exception is the use of fMRI and fibre tracking in guiding neurosurgery to ensure that eloquent cortex and critical connections remain intact, and in some centres this practice has become routine. However, as methods for network analysis improve, identification of the functional disconnectivity associated with schizophrenia and other psychiatric disorders might be possible and could have a substantial effect on the diagnosis and treatment of these seriously disabling disorders.

Magnetic resonance spectroscopy (MRS) looks back to the analytical role of NMR, but adds spatial localisation, enabling biochemical analysis to be done in vivo. ^{1}H-MRS (appendix p 4 shows an example spectrum) can be used to assess neuronal loss (with the neuronal marker N-acetyl aspartate) and thus the progress of neurodegenerative diseases and their response to therapy can be examined. Most tumours also have characteristic metabolic signatures, enabling them to be studied with MRS. Almost all MRS studies are proton based, mainly because they do not require additional hardware to standard MRI, but also because the proton is the most sensitive of the NMR accessible nuclei. Multinuclear spectroscopy (MNS) has many potential clinical applications, if sensitivity issues can be addressed. One possible solution is the development of hyperpolarisation techniques, such as dynamic nuclear polarisation, which have the potential to increase the magnetic resonance signal by 5–6 orders of magnitude.[56] The first clinical trials of hyperpolarised pyruvate for the diagnosis of prostate cancer began in 2010 (NCT 01229618). Hyperpolarised noble gases (^{3}He and ^{129}Xe) have also extended the application of MRI to studies of lung function and promise to have an important role in characterisation of respiratory disease.[57]

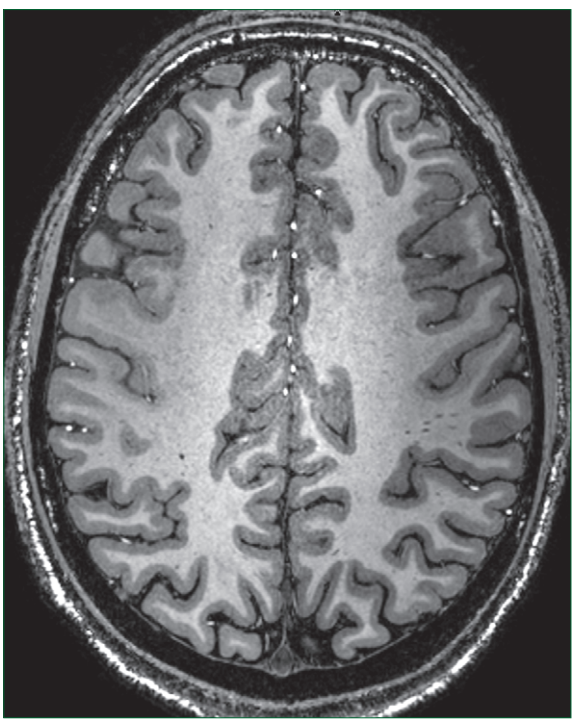

Figure 3: **High resolution (0·5 mm isotropic) image of the human head**
Acquired at 7 T with a magnetisation prepared rapid gradient echo sequence, showing excellent soft tissue (white matter or grey matter) contrast. Image courtesy of Sir Peter Mansfield Magnetic Resonance Centre, Nottingham, UK.

Throughout the development of MRI, a detailed understanding of the dynamics of the nuclear spin system, and how it can be manipulated, has produced a constant flow of new applications that shows no signs of saturation. Coupled with advances in engineering, including the development of ever higher magnetic fields and parallel transmission, together with targeted contrast agents that highlight specific tissues and enable tracking of stem

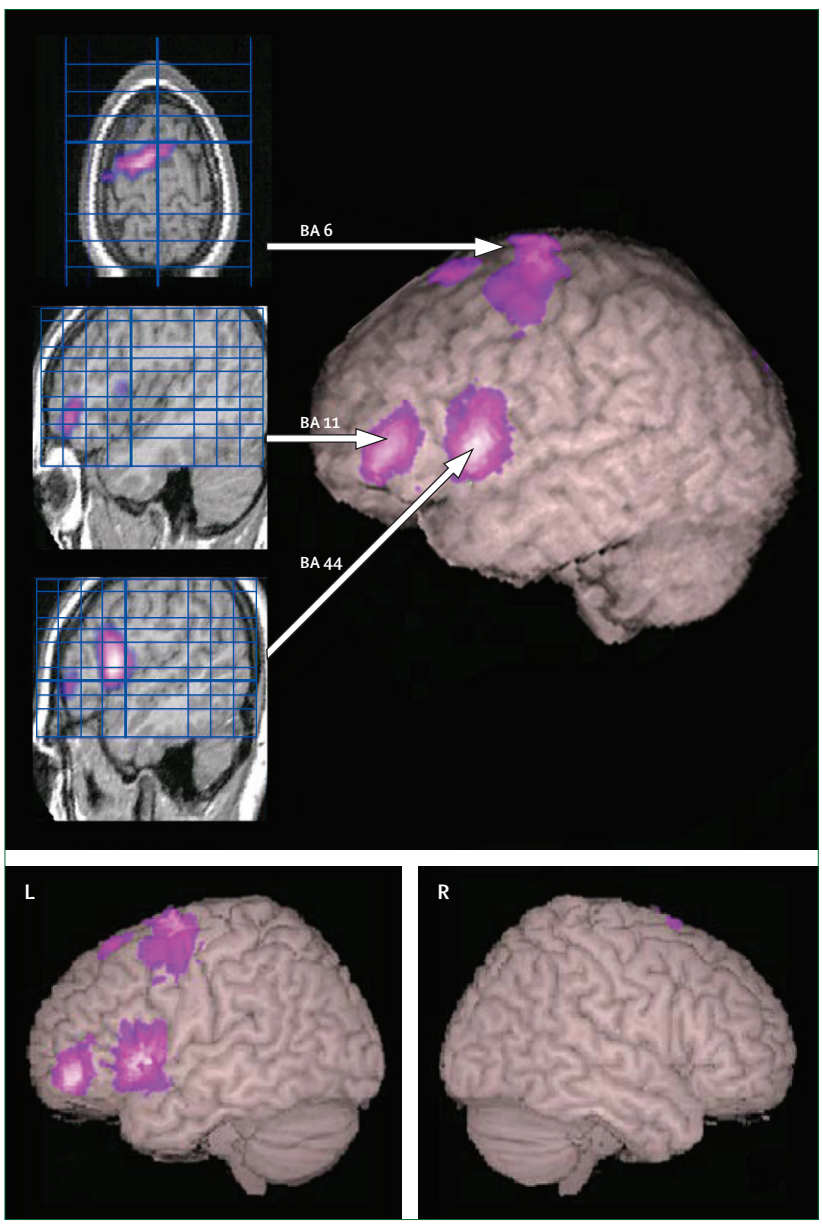

Figure 4: **Lateralisation of language areas with magnetoencephalography source imaging in a verb generation task**
The colour overlays show those regions with significant task-related decreases in beta band oscillatory power and correspond to Brodmann areas (BA) engaged in language processing.[63] Image courtesy of Paul Furlong, University of Aston.

cells, the range of clinical applications of MRI and MRS is set to continue to grow in the decades ahead.

Electroencephalography and magnetoencephalography

The body generates several inherent electromagnetic signals that are useful in medical diagnosis. Best known and most widely applied is ECG, which is available from most family doctors, and an excellent means of screening for heart problems. Electromyography and electrooculography allow monitoring of skeletal muscle function and ocular muscle function, respectively. The brain itself generates electrical signals, which can be monitored with depth or cortical electrodes at surgery, or by electroencephalography (EEG) in which electrodes are fixed to the scalp and evoked potentials or neural oscillations recorded, as originally shown by Hans Berger in 1929.[58] Such EEG methods are useful in, for example, establishing the presence of a neural response to an auditory stimulus and thereby identifying suitable candidates for cochlear implantation, a highly successful, if controversial, method to restore hearing.

Distortions of the electric potential caused by the poorly conducting skull make localisation of the neural origin of the surface signals difficult. However, the magnetic field, also produced by neural activity, is not distorted by the skull, and so magnetoencephalography (MEG) is an attractive alternative.[59] The magnetic fields are small (of the order of 100 fT), and modern MEG relies heavily on the superconducting quantum interference device used to measure them.[60] Typically, several hundred sensor coils linked to such devices are incorporated in a helmet surrounding the head. Many external sources of magnetic fields would swamp the signal from the brain, so noise reduction techniques are essential; the pick-up coils are often configured as gradiometers rather than magnetometers, and the whole MEG system is contained within an electrically and magnetically screened room. Reconstruction of an image of the brain region giving rise to the externally detected fields is challenging because no unique solution exists (the well known inverse problem). Many methods have been developed to constrain possible solutions, including beamformer approaches.[61] These have been used to show that changes in brain rhythms (neural oscillations) are highly focal and consistent with fMRI measures based on haemodynamic response (appendix p 5[62]).

The use of MEG in neuroscience is growing rapidly, but this technique has not been widely used for medical applications so far. A notable exception is in epilepsy: resection of the epileptogenic cortex is a useful treatment option in drug resistant epilepsy, but eloquent cortex must be indentified and spared. For example, the standard way to lateralise language function (usually, but not always, present in the left hemisphere) is the Wada procedure in which sodium amobarbital is injected into the carotid artery supplying each hemisphere in turn and the disruption of speech and language processing noted. Figure 4 shows an MEG based alternative in which a verb generation task has been used to identify the Brodmann areas associated with language processing, which in this individual are clearly left-sided.[63] The electromagnetic signals produced by neural activity suggest potential for the development of a brain–computer interface. Such approaches already show great promise in restoring control to people who are paralysed.

Ultrasound

By comparison with most other medical imaging techniques, the equipment required for diagnostic ultrasound is relatively inexpensive and portable, enabling it to be used at the bedside[64] or in the primary care setting. It relies on the reflection of sound waves at frequencies of between 1–100 MHz, well above the limit of hearing (anything above the 20 kHz threshold being termed ultrasound). The reflections arise from boundaries between structures with different acoustic impedance. The first studies with ultrasound in people were done in the late 1940s and the first clinical findings were reported in 1958.[65] Ultrasound is generated by electrically excited piezoelectric crystals within a hand held probe. The depth of the structure is inferred from the timing of the reflected pulse in a technique analogous to echo sounding for location of fish shoals or mapping of the sea bed.

Transducer arrays enable 2D images to be acquired almost instantaneously (real time), making the technique highly suited to dynamic investigations. The higher the frequency of the ultrasound, the better the spatial resolution, but the poorer the tissue penetration. Thus, for specialist applications in the eye, frequencies up to 10 MHz are used, whereas for studies of liver or kidney, frequencies in the range 1–6 MHz are preferred. The most widespread use of diagnostic ultrasound is in obstetrics, for the assessment of infertility, fetal development, and gynaecological masses (appendix p 6). However, although ultrasound is generally deemed safe, in the USA, Food and Drug Administration regulations allow such scanning for medical purposes only and state that 3D assessment of fetal development should be kept to a minimum.[66,67] The clear definition of boundaries, for example between blood and the cardiac wall, also makes ultrasound very useful in the assessment of cardiac function, including patency of valves, and in the detection of cardiomyopathy. In both applications, the ability to image dynamic processes in real time is especially useful. However, the technique does have some serious limitations. Ultrasound is strongly reflected at interfaces with bone (or gas in lungs or bowel), so appropriate soft tissue windows have to be found. Imaging of the adult brain is not feasible, but good images of the brain can be obtained in children.

Blood velocity can be measured in accessible arteries with the doppler shift—the well known frequency shift for a source moving towards or away from the detector, familiar as the change in pitch of an emergency vehicle's siren as it passes the observer. Sophisticated colour flow and power doppler displays have proved especially useful in assessment of blood flow—eg, in the carotid arteries to identify people who are at risk of transient ischaemic attack or stroke, and are thus potential candidates for endarterectomy. Figure 5 shows a 3D doppler ultrasound of blood flow in a developing ovary.

Modern scanning electronics are highly complex and image quality has been greatly improved with electronic phased array systems with broadband operation,

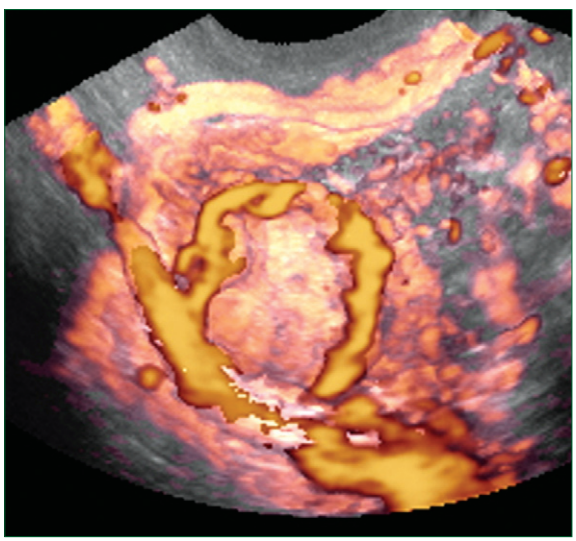

Figure 5: **3D doppler ultrasound**
High resolution 3D doppler ultrasound image of the corpus luteum developing within the ovary, showing the classic ring of fire pattern of blood flow. Image courtesy of Nick Raine-Fenning, University of Nottingham, UK.

compound scanning, and post-processing techniques. One helpful development has been the use of harmonic imaging. This technique depends on the different propagation velocities of ultrasound in compressed versus relaxed tissue and leads to the generation of harmonics either in the tissue itself or in contrast agents, such as microbubbles, in which it was first reported.[68] Harmonic mode images have less noise and clutter, leading to reduced artifacts in liquid cavities thus enabling hypoechoic masses to be distinguished from cystic lesions in the kidney, ovaries, and liver, improved depiction of fetal anatomy, and visualisation of stones in the gall bladder and tumours in the pancreas, liver, and other organs (appendix p 7).[69] Much activity has taken place in the development of ultrasound contrast agents, principally microbubbles[70,71] which highlight the vasculature and have their major clinical application in delineation of focal lesions of the liver. Other developments have led to the use of high intensity focused ultrasound for therapy—eg, in the ablation of fibroids and treatment of prostate carcinoma.[72–74]

Conclusions and future perspectives

In this report, we have inevitably been selective, focusing on the major imaging techniques and on the advances that have enabled the development of new diagnostic procedures. Other instruments that have not been covered, such as optical fluorescence, infrared, and UV are also useful, especially when combined with endoscopic procedures.[75] Medical imaging is increasingly being used not only for diagnosis but for medical screening and as an integral part of treatment planning. In surgery, ultrasound, x-ray, and nuclear imaging are used intraoperatively to position a device—eg, a balloon catheter for angioplasty—

or for image guided surgical excision, such as in sentinel node biopsy. Some operating theatres have been designed so that x-ray and MRI can be brought into theatre and images obtained within several tens of seconds.

Imaging has become an integrated part of radiotherapy planning, such that real time 4D tracking can be used to track tissue movement thereby reducing the radiation dose to normal tissues. Thus in the x-ray treatment of tumours a portal imaging device can be used to assess the efficacy of treatment. The image quality obtained from non-optimal imaging devices working at the MeV rather then keV energies is not high; however, quality is expected to improve substantially in future.[76–78] Successful attempts have been made to combine linear accelerators with MRI systems—a great challenge since the magnetic field of the MRI system has the potential to deflect the electron beam used to generate the x-rays, and to focus electrons released in the target tissue. One therapy and imaging combination that is proving useful is high-intensity focused ultrasound with MRI. In this case, MRI is used not only to position the device and plan treatment, but also to monitor the effective dose. The target tissue—eg, a fibroid—is ablated by raising the tissue temperature above 70°C, at which point proteins coagulate. The temperature can be checked according to the temperature dependence of the proton water signal to ensure that it reaches the required level at the target, and equally importantly, that it is not raised beyond safe limits in surrounding healthy tissue. MRI-compatible robotic surgery is being developed (appendix p 8).[79] We remain far from an automated process of diagnosis and treatment, but this is one direction in which the discipline will move during the next decade or so.

Conflicts of interest

We declare that we have no conflicts of interest

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