

Science + health

Advancing prevention, diagnosis and treatment



*Report of a seminar organised jointly by the Institute of Physics,
the Royal Society of Chemistry and the Institute of Biology*

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New technological developments derived from interdisciplinary research in the physical, molecular and biological sciences are revolutionising healthcare. Remarkable physical techniques have been developed which allow clinicians to image inside the body non-invasively, as well as providing new therapeutic methodologies that minimise surgical intervention. Advances in materials science, particularly at the nano-level, are now being applied to living systems with the ultimate aim of engineering new body parts and implants, designing advanced biosensors and diagnostic chip technology, and improving drug delivery. The mapping of the human genome has opened up a whole new field whereby drug-based therapies can potentially be tailored to a patient's genetic make-up. Many of these novel therapeutic approaches present significant socio-economic challenges in terms of how we implement them, their cost to the health system, how we use them as patients, and how they affect the choices we make about our quality of life.

The Institute of Physics, the Royal Society of Chemistry and the Institute of Biology held a seminar at the Royal Society in March 2006 to explore some of the emerging medical technologies and the issues they raise.

Professor Penny Gowland, Professor of Physics in the Sir Peter Mansfield Magnetic Resonance Centre at the University of Nottingham¹, discussed the many advances in the powerful technique of magnetic resonance imaging (MRI) - not only in terms of its growing importance in clinical diagnosis but also as an analytical tool in physiological and biochemical research. **Dr Molly Stevens**,

Reader in Regenerative Medicine and Nanotechnology at Imperial College London², described nanotechnological approaches to engineering tissues with the ordered structures needed to function correctly when implanted. She also surveyed nano-scale approaches to targeted drug delivery.

Professor Paul Elliott, of the Department of Epidemiology and Public Health at Imperial College London³ explored the emerging field of pharmacogenetics, whereby small genetic differences between people affect their susceptibility to disease and their response to particular drugs. He considered the implications for drug development and

personalised medicine. Finally, **Professor James Raftery**, a health economist at the Wessex Institute for Health Research and Development, University of Southampton⁴ reviewed the range of emerging high-tech health developments, considering their cost-effectiveness and how they are likely to affect future funding and provision of healthcare.

Magnetic resonance imaging

Magnetic resonance imaging is a prime example of how a fundamental physical phenomenon has been harnessed for a practical benefit. MRI developed from nuclear magnetic resonance (NMR), which was discovered in the 1940s. In this technique, nuclei possessing a magnetic moment (such as hydrogen nuclei) are made to align in a powerful magnetic field; when a radio-frequency field is applied, they absorb and emit energy in a way that is characteristically dependent on their environment. The first

application of NMR was in the 1960s - to analyse chemical compounds; then in the 1970s, researchers realised that the technique could be used to image living tissue non-destructively. By detecting NMR signals from the hydrogen in water molecules across different tissues, structural details could be mapped to produce an anatomical image. The first images took many hours to produce; however, in the 1980s Sir Peter Mansfield at the University of Nottingham developed an ingenious method for collecting the signals in less than a second using applied gradient magnetic fields⁵. This approach revolutionised MRI, as it now called. Today, most large hospitals use MRI scanners routinely as a complementary and sometimes safer alternative to X-rays; every year, 1 to 2 per cent of the UK population have an MRI scan.

MRI continues to develop and be used in remarkable ways. Professor Gowland described some of the advances made possible with the high magnetic-field scanners now available. As the magnetic field strength is increased, so does the resolution of the images. The Nottingham MRI Centre now has a 7-tesla scanner (140,000 times the strength of the Earth's magnetic field), which allows researchers to look at changes in brain activity in response to stimuli in real time - in effect to watch people learning. "We speculate that these kinds of images could be used to study conditions such as autism, dystonia and Alzheimer's disease," said Professor Gowland.

Another area that is rapidly advancing is the use of MRI to guide and monitor surgical procedures (instead of X-rays). Interventional MRI is particularly helpful in treating children with heart conditions and also in neurosurgery - so reducing the number of operations and shortening hospital stays.

As well as imaging the structure of organs, magnetic resonance-based spectroscopical analysis can be employed to study the body's biochemistry *in vivo*. By injecting glucose labelled with carbon-13 (to produce an NMR signal), changes in metabolism - particularly in the brain - can be followed and compared in normal and diabetic patients. Even lungs, which have a low water content, can be

imaged by breathing in hyperpolarised helium to increase the 'contrast' between structures. Other contrast agents are used to monitor blood flow and oxygenation, and to follow particular biochemical processes in the cell such as gene expression.

MRI is regarded as much safer than diagnostic techniques relying on ionising radiation, and there are still huge developments required to enable it to fulfil its potential. Nevertheless, Professor Gowland fears that an EU Directive limiting workers' exposure to electromagnetic fields - which are based on speculative, unproven claims of adverse health effects - could jeopardise further development of the field, in particular halting the use of interventional MRI completely, before it has even had a chance to start to show its full range of applications⁶. The impact of the Directive in limiting the use of MRI would be disproportionate to the scale of potential benefits. "The problem is that no attempt has been made to quantify the level of risk, as is required when a precautionary approach is being adopted. This has been compounded by a worrying level of ignorance of science amongst some officials who claim to talk authoritatively on the subject," she commented.

Tissue engineering, nanotechnology and medicine

Another fast-moving field with enormous potential is the application of the techniques of nanotechnology to healthcare. Molly Stevens' research group⁷ has been creating bioactive interfaces between tissues and artificial materials by mimicking the cell's natural environment at the nano-level (at a scale of a billionth of metre). Such techniques not only improve the efficacy of artificial replacements but also offer an effective methodology for growing new tissue for grafting.

Dr Stevens pointed out that 5000 people a year in the UK die from liver failure because of a shortage of livers available for transplantation. Similarly, there are a million bone defects a year that require bone grafts to repair. However, there may not always be enough bone available from another part of the body, and the grafting process

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can be extremely painful. So, strategies for regenerating new tissue are urgently needed.

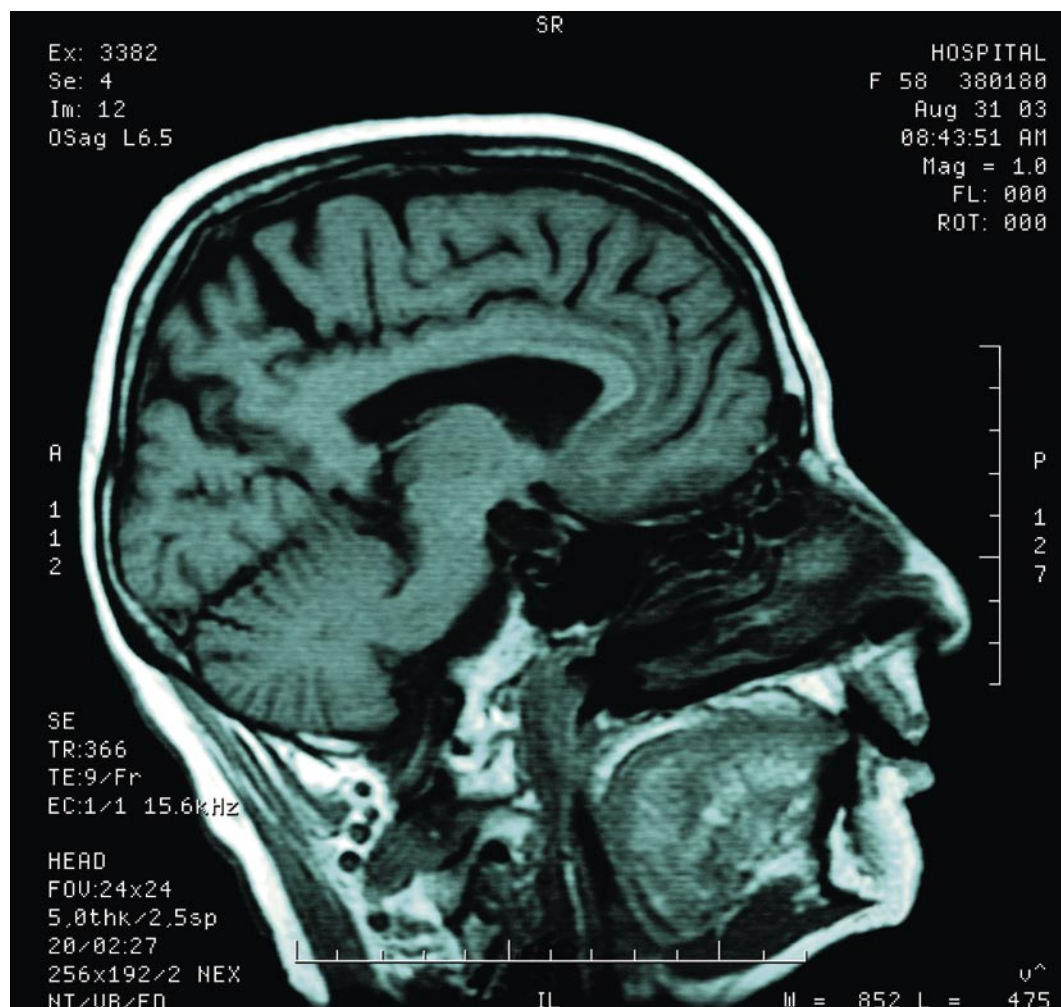
The standard approach is to take cells from the patient and culture them in the laboratory on an artificial scaffold (for example, a polymer) so that they proliferate to form new tissue. This can then be implanted to repair the damaged site. However, most tissues have a complex hierarchical organisation at all scales from the nano to the macroscopic level. For example, bone consists of cylindrical structures called osteons through which blood vessels pass. Each osteon is built of concentric layers of nano-sized collagen-hydroxyapatite fibres. Bone cells sit within the layers and are covered with a forest of receptors which control gene expression and cell-signalling by recognising specific ligands (chemical groups) on the surrounding fibres. It is this interaction with the intracellular medium that controls cell growth to produce

new tissue with the correct mechanical and biochemical properties.

Understanding the cells' complex micro-environment is a vitally important factor in tissue engineering. Researchers are already considering strategies for tailoring interfaces between living tissue and artificial implants such as hips or teeth, and for implanted biosensors. Correctly patterning the surface of the implant at the micro and nano-level can guide cell growth so as to improve the implant's adhesion and long-term integration.

Dr Stevens' group is developing nanofibre scaffolds that can encase each cell. In this way, they provide the correct environment to stimulate cell receptors and encourage formation of the tissue required. Nature makes these fibres by the process of self-assembly, and this approach has been emulated in the laboratory. An American

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research group working on nerve regeneration has designed large peptide structures with hydrophobic and hydrophilic regions that assemble into a network of nanofibres. When bioactive ligands are added, the fibres encourage stem cells to become neurons. "The technology, though elegant, remains very expensive," said Dr Stevens, "we have developed a way of making nano-scale fibre scaffolds that is much cheaper." A high voltage is applied to a polymer jet, which is drawn out until the fibre is a nanometre-thin. These nanofibres can be designed with bioactive regions that encourage cells to adhere, and differentiate and proliferate in a guided manner - as they would in the body.

Materials designed at the nano-level are also candidates for targeted drug delivery. These include hollow nanocapsules which, for example, release an anticancer drug only when they pass through the leaky blood vessels typically found in tumours. There are many mechanisms being looked at: for example, gold nano-shells hosting drug molecules can be made to liberate their contents by employing harmless infrared radiation once they have reached the tumour site. Dendrimers, which are large tree-like polymeric structures, can also be attached to drugs and designed so that they recognise receptors only on cells affected by disease.⁸

Pharmacogenetics and personalised medicines

Drug design is also being tailored in another way. The development of DNA profiling is allowing scientists to investigate how people's genetic makeup affects their response to drugs - pharmacogenetics.⁹ Small differences in a gene sequence at the single nucleotide level (called single nucleotide polymorphisms, or SNPs) can determine someone's susceptibility to disease and their reactions to drugs. If SNPs are correlated with a particular pharmacological response, then tests can be developed that can detect whether a patient would benefit from a drug, or conversely suffer an adverse reaction. Paul Elliott described an example of the antihypertensive drug Debrisoquine (no longer used clinically); 7 per cent of the population lack the enzyme (a cytochrome p450 enzyme) to metabolise it, so they

suffered severe side-effects.

Not surprisingly, the pharmaceutical industry is putting a great deal of effort into studying how pharmacogenetics can help in the costly and time-consuming process of drug discovery. If people who most benefit from the drug could be identified from their genetic profiles, while those for whom it is ineffective or hyper-effective (so causing side-effects) could be screened out, then drug trials could be directed at selected groups. This would save money, and provide useful information such as the correct dose for patients with a particular genetic makeup. Furthermore, more drugs would reach the market if they could be indicated for a targeted genetic group.

So why are not genetically-indicated drugs and tests more routinely available? "At the moment, there is no decisive evidence to suggest that prescribing drugs based on genetic tests should become routine clinical practice," said Professor Elliott. He posed a series of issues that have to be addressed.

For the clinician and patient

- Prescribing a drug with a pharmacogenetic test may not offer an obvious benefit.
- Clinicians already carry out their own susceptibility tests by starting the drug treatment in small doses and then monitoring the response.
- The cost of the test, and length of time waiting for the test results, may be an obstacle.
- There is also the question of whether the patient or health provider takes responsibility for the test.
- If the test reveals that the patient may not benefit or is likely to experience side-effects, it may raise therapeutic, economic and legal issues if an alternative, less-effective drug is prescribed.

For the health services and society

- The health service will also have to consider cost versus benefits, and how genetic tests should be licensed and regulated.
- Acceptance of a genetically-based drug would depend on whether the adverse responses are common, mild or severe.
- It may not be worth testing millions of people for a common condition if side-

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effects are rare.

- Responses may be not clear-cut since they may be affected by other factors such as drinking alcohol or the presence of other diseases.
- Much more information is needed about the genetic variability in susceptibility to complex diseases such as heart disease, diabetes and cancers, and how this is reflected in the response to drugs.
- Inevitably, pharmaceutical companies are most likely to offer genetically tailored drugs for which there is the largest market and for which they can obtain patents. This may mean that some diseases get neglected.

Testing would also generate huge amounts of data, and there are issues on how they would be stored and retrieved. Nevertheless, the data could be a valuable resource to be used to assess side effects in a real-world situation. This data-sharing in itself also presents ethical concerns. Patients - and possibly family members with similar genetic profiles - would have to give their consent; or robust safeguards would need to be in place to enable analyses of such data whilst protecting the confidentiality of individuals. There is the question of access by insurance companies and employers. If sections of society are classified according to their

genetic susceptibilities, it could create a genetic underclass.

Professor Elliott believes that we need to know more about the costs and benefits of pharmacogenetics, and how it will be implemented in clinical practice. There also needs to be public dialogue in order to gain acceptability and maintain public confidence. “Despite a lot of interest, this new technology is unlikely to become available for a few years yet,” he concluded.

New health technologies: costs benefits and impact

James Raftery continued the theme, exploring how technological developments impact healthcare in terms of cost and efficacy. He described work done at the National Horizon Scanning Centre,¹⁰ University of Birmingham, which identifies new technologies for the Department of Health, and summarised 11 developments identified by the US Institute for the Future:¹¹

- Rational drug design based on genetics and molecular modelling
- Imaging techniques for diagnosis
- Bioengineered and artificial organs, and joint and implanted sensors
- Minimally invasive surgery, robotics and



Small differences in a gene sequence can determine someone’s susceptibility towards disease and their reactions to drugs. Can we use this information to produce treatments tailored for individuals?

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image-guided surgery

- New vaccines for non-infectious diseases
- Blood substitutes
- Genetic testing, therapy and pharmacogenetics
- Stem cell therapies
- Implants of tissues and organs from animals
- Diagnostic and therapeutic devices based on nanotechnology
- Information technology

The study also focused on four particular applications from a recent study by the Australian Productivity Commission¹²

- Insulin-sensitisation drugs for preventing type 2 diabetes
- Implanted atrial defibrillators to prevent strokes
- Robotic-assisted surgery for prostate cancer
- A vaccine for Alzheimer's disease

The studies showed that, despite individual instances of saving money, new technologies tended to expand the patient base dramatically by redefining what can be treated and identifying new risk factors for disease. They also raise the issue of how various types of healthcare should be classified in terms of value (as inferior, normal or as a luxury good). As countries become richer they tend to spend more on healthcare. The scale of benefits and therefore the cost-effectiveness is much less clear, however.

What does this all mean for the health services? "There will be a multiplicity of ways of delivering health services in the future, with patients increasingly taking responsibility for monitoring and managing their own treatment," commented Professor Raftery. Individuals will inevitably deal with their health in diverse ways, some adopting passive and traditional approaches, while others will opt for a variety of self-medication strategies including complementary therapies. Health services will have to monitor how patients use costly treatments such as enzyme replacement therapy. Some general hospitals are likely to have to become centres for specialist treatments.

With higher unit costs, the role of the NHS comes into question. Increasingly, it is acting more as a funder than as a provider.

In this role, the NHS clearly cannot fund every treatment available. Based on recent analyses of cost-effectiveness, the National Institute for Health and Clinical Excellence,¹³ which provides national guidance on health treatment, is now laying down limits for cost-effectiveness.

Finally, as emphasised earlier, how medical data are stored is a significant issue in a diverse system of health provision. Patients are increasingly likely to carry their own records in electronic format, and will thus have to take responsibility for disclosure of information and for their own health management. GPs may find themselves in a different role more as advisers rather than providers. "It's a very uncertain future but an exciting one," said Professor Raftery.

Further information

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