FEATURES ABOUT

- Children's mental health
- The human heart
- Digestion
- Access to care

A PICTURE OF HEALTH

A Selection of Irish Health Research 2007

Improving people's health through research and information

HRB
Health Research Board

A PICTURE OF HEALTH

A Selection of Irish Health Research 2007

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INTRODUCTION

The Health Research Board (HRB) is the lead agency in Ireland supporting and funding health research. Our aim is to improve people's health, build health research capacity, and make a significant contribution to Ireland's knowledge economy.

The HRB provides research funding for universities, hospitals, and charities, maintains health information systems, conducts research linked to national health priorities, and plays a major role in communicating the benefits of health research. The HRB has an annual budget in excess of €50 million and a research investment portfolio of approximately €160 million.

At the HRB, we are strongly committed to increasing awareness of the value and benefits of health research among the general public, healthcare policy makers and health practitioners. One of the ways we do this is through *A Picture of Health*.

A Picture of Health – A selection of Irish Health Research 2007, is the fifth publication in the series and brings together, in layman's terms, the findings of a selection of HRB-funded research projects that came to an end in 2006.

The book presents research from a total of 48 researchers from five third level institutions and eight hospitals throughout the island of Ireland. The research spans a broad range of research areas including Health Services Research, Public Health, Cardiac Disease, Molecular Biology and Nursing.

While it showcases the most recent breakthroughs in Irish health research arising from these HRB-funded projects, it also gives us a taste of some ongoing research programmes that will feature in next year's *Picture of Health*.

We hope you enjoy reading A Picture of Health 2007!

IMPROVING CHILDREN'S MENTAL HEALTH Autism and ADHD in the scientific spotlight

Irish research is advancing our understanding of the genetics of autism and ADHD

The mental health of children and young people in Ireland is high up the HRB's research agenda. For instance, attention deficit hyperactivity disorder (ADHD) disrupts a child's family life and education and often persists into later life, sometimes with accompanying behavioural, social and psychological problems. Dr Michael Gill, of Trinity College Dublin (TCD), has been investigating genetic influences in ADHD and more recently, examining how these relate in response to the drug methylphenidate which is commonly used to treat the disorder.

Meanwhile, autism remains a complex, hard-to-treat mental disorder which has a profound and ongoing impact upon a young person's development. Between 25 and 40 per cent of children with autism suffer from gastrointestinal disturbances, such as diarrhoea, abdominal pain and food intolerances, especially to wheat and cow's milk. It's long been assumed that these problems arise from the behavioural disturbances that are the hallmark of autism – and they have also attracted a great deal of 'unscientific' comment and analysis in the media.

Professor John O'Leary of Coombe Women's Hospital has established the existence of a new variant inflammatory bowel disease among autistic patients. His research into the genetics and pathology of this aspect of autism has put the link between the gut and the brain at the centre of our understanding of this complex disorder.

Which children respond to methylphenidate?

Current treatment for ADHD includes advice about diet, behavioural management, educational support and medication – the latter often being recommended in moderate to severe cases. Methylphenidate (Ritalin) is a stimulant drug which is one of the most common medications for ADHD. It has been in use for many years, with clinical trials suggesting that around 70 per cent of children benefit from methylphenidate, but parents and teachers are, understandably perhaps, still anxious about its use.

Research and ADHD

Attention Deficit Hyperactivity Disorder (ADHD) is a condition in which a child has difficulty controlling some aspects of his or her behaviour leading to three major symptoms: inattention, hyperactivity, and impulsivity. It is not a new condition, but diagnosis is being made more frequently than in the past, and is receiving increasing attention in the medical press and in the popular media.

The prevalence of ADHD in Ireland is not known but it has been shown to occur in 4-5 per cent of children in the United States and Canada and is 3 to 4 times more common in boys than in girls. Seventy per cent of children with ADHD still have difficulty during adolescence, and 35 per cent still have difficulty in adult life. However, as children mature the symptoms change somewhat. Whereas the primary complaint in a child might be hyperactivity, in an adult this becomes restlessness, disorganisation, and impatience.

Research suggests that a child is born with an inherited tendency to develop ADHD. Why some children develop ADHD and some don't, depends on other factors.

For more information see the website of The Children's Clinic (www.thechildrensclinic.ie)

It may be possible to reassure them by identifying which children have most to gain from methylphenidate. Dr Michael Gill has been looking at genetic and other factors which influence how a child might respond to the drug. In a previous study, he focused upon the involvement of genes related to the brain's dopamine system in ADHD. Dopamine is a chemical messenger which plays a role in many brain functions, from movement to the experience of pleasure. There is evidence that dysfunctional dopamine pathways are found in many disorders including Parkinson's disease, schizophrenia, depression, drug addiction - and ADHD. 'Our hypothesis was that DNA variants in dopamine system genes and in particular, the dopamine transporter gene, might contribute to the occurrence of ADHD.

We thought that DNA variation at the dopamine transporter gene might be involved in the response of children with ADHD to methylphenidate,' Gill says, explaining that methylphenidate acts by blocking the dopamine transporter protein. Previously, Gill's group had identified DNA variation at the dopamine transport gene that was contributing to the risk of developing ADHD. This DNA variation appeared to cause the dopamine transporter protein to be overactive. He therefore suspected that children whose DNA revealed an overactive dopamine transporter might respond better to methylphenidate than those whose dopamine transporter was normal.

This earlier study was both retrospective and subjective – that is, parents were asked to rate how well they

thought their child had responded to the medication in the past. The findings seemed to confirm Gill's theory and led to the current HRB-funded prospective study with children who had not previously been on methylphenidate.

The study began with 132 families of children with ADHD, of whom 94 ended up going on the medication and providing a full set of data – DNA samples, neuropsychological test results, behavioural analysis, and parent and teacher feedback. 'This was a much more accurate way of looking at the problem than the previous study,' says Gill. 'We are very confident in the quality of data we have from this sample.'

"Healthy children pay subtly more attention to the left side of visual space. Children with ADHD show no bias or even tend to pay more attention to the right side."

Approximately 50 per cent of the children in the study showed significant improvement on methylphenidate. Detailed neuropsychological tests done in this study measured several aspects of attention where, clearly, children with ADHD have problems. 'We were particularly interested in spatial attention because this involves the right fronto-parietal lobe of the brain where abnormalities have been found in ADHD,' he says.

Healthy children pay subtly more attention to the left side of visual space. Children with ADHD show no bias or even tend to pay more attention to the right side. Interestingly, right spatial bias is also seen in individuals with damage to the right parietal lobe of their brains. When the spatial attention test findings were matched to dopamine transporter gene data, those ADHD children with the 'high risk' gene variant (the overactive dopamine transporter described above) were more likely to pay more attention to the right side – to show right spatial bias. Those with a 'low risk' gene variant (normal dopamine transporter) had a left sided bias similar to that seen in normal controls. 'Having a right-sided bias in spatial attention also predicted response to methylphenidate,' says Gill. 'Therefore, instead of having to have a DNA test, children can have a simple pencil and paper test lasting five minutes, which is much easier from a practical point of view.'

These findings on spatial attention and the 'high risk' dopamine transporter confirm what was found in the earlier study – but are stronger because of the prospective nature of the current study. Gill would now like to introduce the spatial attention test into the clinical arena, helping doctors and parents make more informed treatment decisions.

"Instead of having to have a DNA test, children can have a simple pencil and paper test lasting five minutes."

Gill's team has also been looking at sustained attention, which is very abnormal in children with ADHD. Generally, they will have a very short attention span. Without medication, they will either respond too quickly to stimuli, or not at all. Methylphenidate was found to improve specific aspects of sustained attention. They also found that children who scored high on a scale measuring autism-like symptoms, such as communication and social difficulties, responded poorly to methylphenidate. This finding had been suspected in the clinical arena for some time and has now been confirmed. These children often have neurodevelopmental abnormalities that lead to problems in addition to ADHD and may be regarded as a 'severe' sub-group of ADHD. The research suggests that they may require other forms of treatment in addition to, or even instead of, medication. Therefore, these studies suggest that the probability of a child with ADHD responding to methylphenidate can be weighted by looking at their score on an autism scale, their genetics, and neuropsychological testing. 'These will show if they are more likely, or less likely, to respond,' says Gill. 'It would be easier to make an informed choice on treatment and could lead to additional interventions.'

The study further revealed that having traits of Asperger's syndrome, eneuresis (bed-wetting) and attachment problems also made response to methylphenidate less likely, but that age, IQ and social class did not – perhaps contrary to expectation – affect response to medication at all.

Gill is extending these studies to other genes that may be involved in ADHD. There is now the possibility of genome-wide analysis which will uncover new genes involved in ADHD which, in turn, will lead to new prospects for therapy. He is also working with colleagues in neuroscience on imaging, with functional magnetic resonance, to see if some of the functional abnormalities in ADHD can actually be visualized in brain function as children get involved in attention tasks while having the scan. Finally, along with colleagues in the Trinity College Institute of Neuroscience, he would like to understand how these systems work in the normal brain. These studies, overall, are at a 'very exciting stage.'

A new angle on autism

Several years ago, Professor John O'Leary, and others, identified a new form of inflammatory bowel disorder (IBD) associated with autism. 'We have always known that children with autism tend to suffer from various gastrointestinal problems, such as food fads, bloating and abdominal pain. But this has been a very 'soft' aspect of autism, which has been difficult to assess objectively,' he says.

O'Leary's HRB-funded work is dedicated towards gaining a detailed understanding of new variant IBD (also known as autistic enterocolitis) in terms of its pathology and genetics. The hope is that his findings will lead to new approaches to treating and managing this difficult disease.

The study involved the analysis of gut mucosal and blood samples from a group of children and young people with regressive autism, compared to normal controls. The first clear finding to emerge is that new variant IBD changes over time – it is more severe among young children, milder in young adults, giving some hope that over time, it could 'burn out'. Study of the tissue samples from the gut showed that younger patients were more likely to have an inflammatory condition called lymphonodular hyperplasia (LNH) in the terminal ileum part of the bowel, while older patients had a low grade colitis.

An important part of this work has been to create a 'map' of the immunology of the gut mucosa in new variant IBD to see how this differs from that found in the normal gut and in other inflammatory bowel diseases. An immune response is characterised by populations of white blood cells called T cells and molecules called cytokines which either promote, or

dampen down the inflammatory process. Using analysis of gene expression, the researchers found dysregulation in levels of three pro-inflammatory cytokines, known as IL (interleukin)-1, IL-6, and tumour necrosis factor-alpha (TNF-α), and in IL-10, which is anti-inflammatory, in younger patients In older patients, there was dysregulation of a gene called HLA class II, which is important in immune system balance. Meanwhile, certain populations of T cells known as CD4 and CD8 were also out of balance in the autistic children, compared to those in healthy controls. The way the immune map tends to change with age parallels the way the symptoms of new variant IBD tend to decrease in severity. 'This is the start of understanding this new form of inflammatory bowel disease in terms of the local immune response,' O'Leary explains.

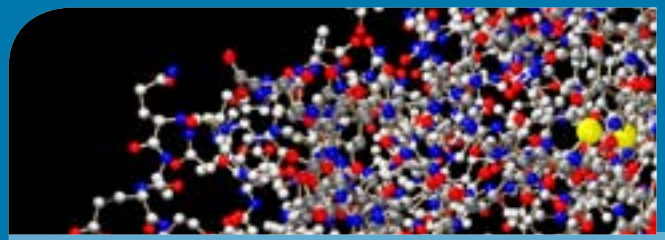
"There is clinical evidence that the gut and the brain interact, and that if you treat gastro-intestinal symptoms, behaviour can improve."

To further distinguish new variant IBD, O'Leary carried out genetic analyses on his participants, looking for variants in a gene called NOD-2 (more recently re-named as CARD15), which has been found in nearly half of patients with Crohn's disease. No significant NOD-2 abnormalities were found, suggesting that new variant IBD is not an unusual or precursor form of Crohn's disease, even though it shares some features with this and with ulcerative colitis in younger patients. However, there are four or five other genes that may play a role in new variant IBD. One is a serotonin receptor found in the gut. Serotonin is perhaps better known as a brain chemical that plays a part in mood; many antidepressants work on serotonin pathways in the brain.

O'Leary's team is also using microarray technology to compare gene expression in the gut among patients with new variant IBD, ulcerative colitis, Crohn's disease, LNH (not linked to autism) and healthy controls. Microarray technology is an approach that allows the analysis of the expression of many different genes in one experiment – useful because it gives a bigger picture of the pattern of gene activity in a particular disease.

However, it is still too soon to know how autism and new variant IBD are related; the evidence does not point to a 'cause and effect' mechanism, nor is there a 'gene for autism'. O'Leary suggests that maybe some antigen challenge (exposure to specific proteins in foodstuffs) or changes in the gut flora may precipitate adverse changes in behaviour in some children, especially those who already have a genetic susceptibility to autism. Certainly it appears that the interaction between the digestive system and the brain (the gut-brain axis) is important. For instance, IBD is associated with a 'leaky' gut and this might allow toxins to pass from the gut through the blood-brain barrier, causing changes in behaviour. While O'Leary's team have not yet been able to demonstrate the leakiness of the gut in autistic patients who have new variant IBD (these experiments are very hard to perform), it has been shown previously by American researchers.

What does all this mean in terms of treatment for autism? 'There is clinical evidence that the gut and the brain interact, and that if you treat gastro-intestinal symptoms, behaviour can improve,' comments O'Leary. He hopes to extend the study of new variant IBD to older patients to see if the disease continues to evolve and whether it does eventually burn itself out.



UNDERSTANDING A PAINFUL PROBLEM New hope in rheumatoid arthritis

Researchers at St Vincent's University Hospital are looking for improvements in the understanding and treatment of rheumatoid arthritis

Rheumatoid arthritis (RA) is an autoimmune disease – one in which the immune system mounts an attack on the body's own tissues without an obvious external cause. It is characterised by a progressive inflammatory destruction of cartilage and bone in the joints. One to two per cent of the Irish population is affected by RA and the disease is marked by pain, disability and complications, with a high social and economic cost. In recent years, research has focused upon gaining a better understanding of the inflammatory process underlying RA and other autoimmune diseases. The role played by signalling molecules known as cytokines in triggering the inflammation has been better clarified, for example. A major advance for patients has been the introduction of biologic therapies which can block tumour necrosis factor α (TNFα), a cytokine which plays a major role in the inflammatory process. Infliximab (Remicade) and etanercept (Enbrel), unlike traditional therapies such as steroids, can actually modify the disease process, because they block the underlying process rather than just addressing the symptoms.

The molecular approach to the study of inflammatory diseases such as RA involves looking at the role of specific protein molecules and how these interact in pathways that lead to clinical signs and symptoms. HRB-funded researchers at the Department of Rheumatology at St Vincent's University Hospital are combining laboratory and clinical studies to improve their understanding of RA to offer new hope to patients suffering from this painful condition.

Improving treatment

Treatments for rheumatoid arthritis which target TNF-α have been used in Ireland since 1999 in patients who have failed to respond to one other disease-modifying drug. They are still not used as first-line therapy because of the cost, although they are being introduced earlier in the disease, because they do modify its progress. Infliximab is a monoclonal antibody, which binds to TNF and neutralises its action, and is given by a three hour infusion that requires a day admission to hospital every few weeks.

"Some patients are too disabled or frail to give themselves injections, so they must rely on the hospital-based treatment."

The other drug, etanercept, is a TNF receptor fusion protein which also blocks TNF-α and is given by injection at home. While this is preferable to many, there are some patients who are too disabled or frail to give themselves injections, so they must rely on the hospital-based treatment.

Dr Ceara Walsh of the Department of Rheumatology at St Vincent's University Hospital carried out an audit of the first 300 patients to receive anti-TNF therapy and found that 20 to 30 per cent experienced complete remission of the disease. The rest fell into one of two groups: either they responded but continued to have some low-grade disease activity, or they failed to respond at all or relapsed after an initial response. Walsh wondered if the group in remission would continue their improvement if they were taken off anti-TNF therapy with conventional therapy substituting it. She was also interested in whether a 'flare-up' of RA in these patients could be predicted by some 'marker' which could be measured in a blood test, thereby allowing a closer and more controlled monitoring of their condition. There was a very good reason for this approach. 'While the anti-TNF therapies are fantastic as a revolutionary treatment option, they are expensive, hard to administer for the patient and their long-term effects are not known,' Walsh explains.

"If a patient can go without anti-TNF therapy while maintaining their remission, there would be several benefits."

So if a patient can go without anti-TNF therapy while maintaining their remission, there would be several benefits.

A new protocol had to be developed for the study, because it is already known that if the anti-TNF therapy is stopped altogether, the disease will come back. Out of a group of 21 patients, eleven had their therapy withdrawn and the rest continued with it. The former were followed up for six months and beyond and all but one stayed off their treatment. Two of these patients have now been followed up for two years. Three of the patients had 'flare-ups' and received a short course of steroids to deal with this.

In lab work, the researchers looked at marker proteins on the surface of their T lymphocytes, a type of white blood cell active in inflammation, comparing samples from patients in remission with those from both patients with active disease and from healthy controls. The patients in remission had more T cells with a specific receptor protein which has not previously been studied in RA. 'We have noticed that this cell expansion seems to be lost in patients who have a 'flare-up' and now we want to see if this happens before the relapse occurs,' Walsh says. Monitoring the T cells in this way might allow doctors to tailor the dosing schedule of therapy to counter a potential relapse.

'The study also tells us we need to understand more about the T cell biology and pathways in this disease,' she comments. She hopes this research will lead to smarter prescription of anti-TNF therapies with fewer problems for patients with travel and issues such as childcare costs.

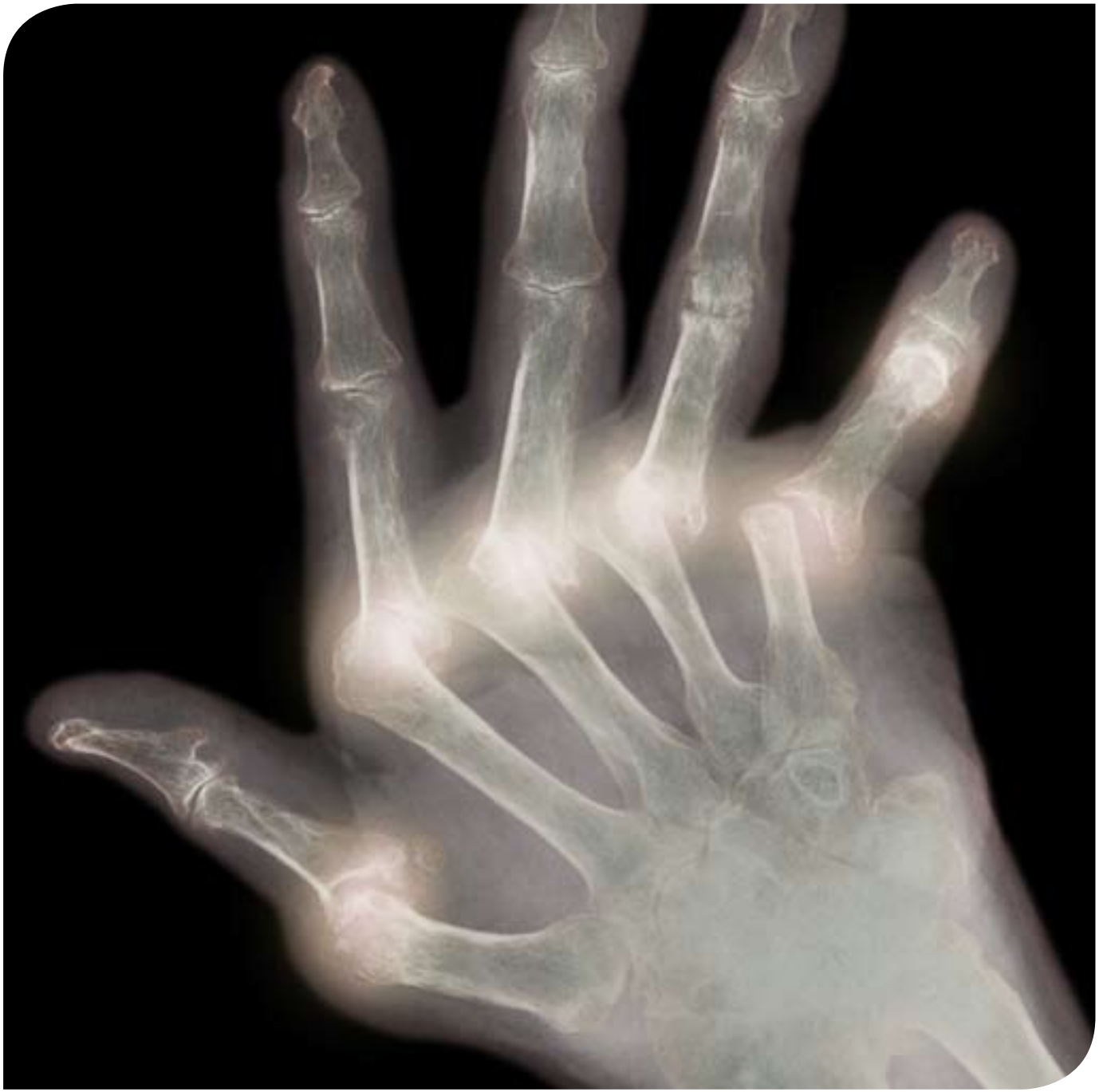
In another part of the study, they have been looking at switching patients who had responded to one anti-TNF therapy but had ongoing disease activity to another

agent in order to assess the economic impact; this showed a positive impact in terms of improvement of disease activity and reduction in both healthcare and patient-related costs. And finally, patients who had failed to respond to anti-TNF therapy were switched to a new therapy called rituximab (Rituxan), a monoclonal antibody which targets B cells. The participants underwent arthroscopic biopsy of the tissue lining their knee joint before and after treatment with rituximab. This showed a reduction in the number of inflammatory B cells after treatment which matched the improvement in their symptoms.

An inflammatory protein

The molecular profile of inflamed tissue often differs from that of healthy tissue by the presence of a range of specific 'biomarker' proteins. These might be present only during inflammation or they might be present in normal tissue as well, only at a lower level. Some of these could be used in testing or screening for the disease, where the relationship between their presence and the disease pathology is well enough understood. Understanding the role that each 'biomarker' protein plays in inflammation, and how they interact with one another, is important for getting a better understanding of this complex process.

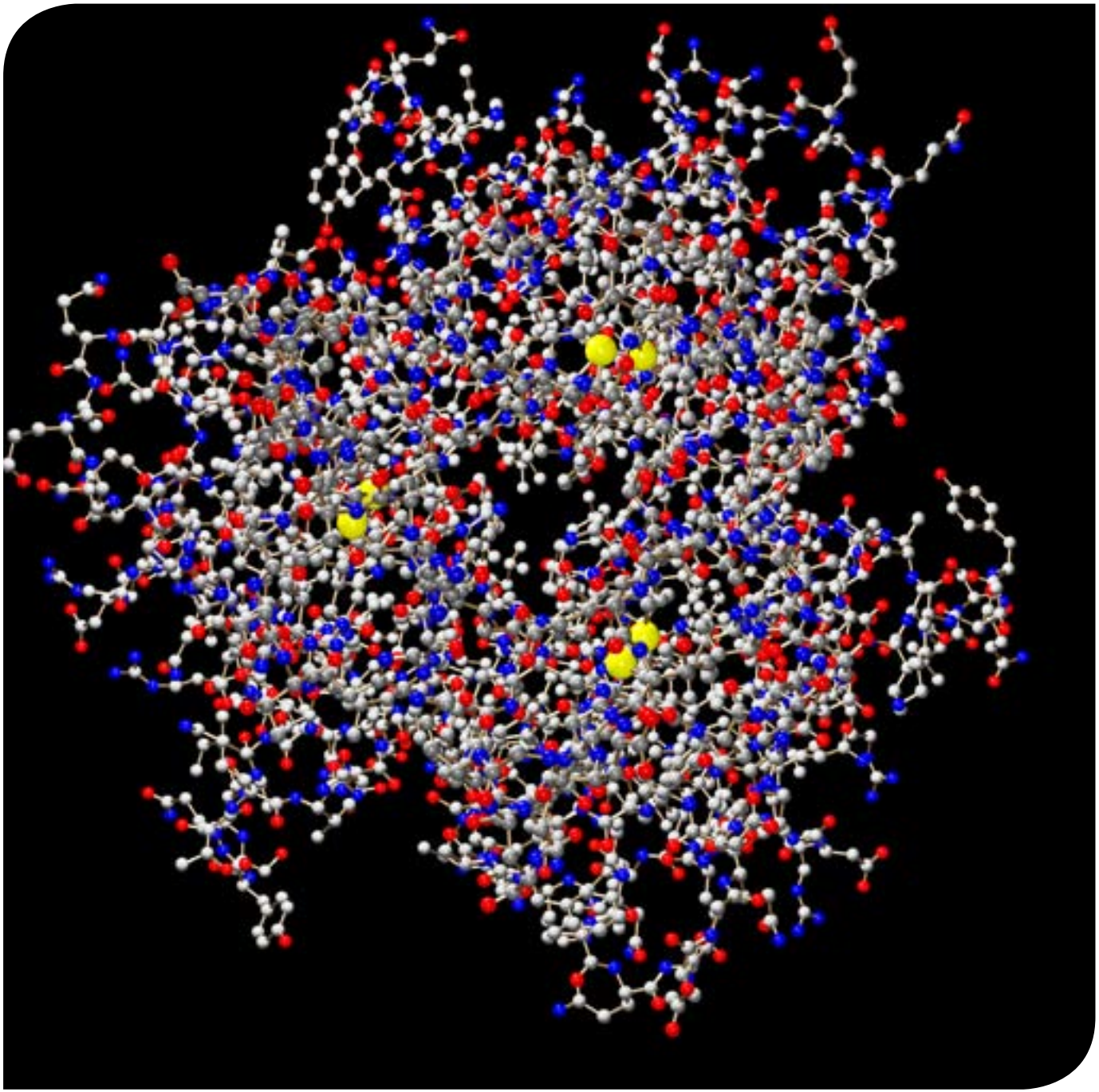
Dr Ronan Mullan, also of the Department of Rheumatology at St Vincent's University Hospital, has been looking at one such marker, called serum amyloid A(A-SAA). One of a group known as acute phase proteins, A-SAA is detectable in blood serum at low levels but increases dramatically – as much as 1000-fold – within hours of an inflammatory stimulus. Although A-SAA is not specific to RA, high levels have previously been demonstrated in the serum and inflamed joints of arthritis. Mullan learned that the presence of A-SAA leads to production of enzymes called matrix metalloproteinases (MMPs), which destroy articular cartilage and bone.



Mullan's current HRB-funded work goes deeper into the role of A-SAA in rheumatoid arthritis. Active rheumatoid inflammation is an extremely complex process, characterised by swelling, the formation of new blood vessels (a process called angiogenesis), the recruitment of leucocytes (white blood cells) into joint tissue, and joint destruction through the proliferation of fibroblast cells. 'Serum amyloid A induces all these pathological changes in the joint by upregulating pro-inflammatory events,' he explains.

His experiments looked at how A-SAA acts as a molecular signal in the inflamed joint, altering the expression of certain specific genes so that either more, or less, of the proteins they code for (known technically as upregulation or downregulation of the genes) are produced. They also looked at whether A-SAA was chemotactic to certain cell types – that is, could it stimulate changes in chemical concentrations within the tissue that would attract the cells into the joint?

Using an *in vitro* model of angiogenesis, Mullan showed for the first time how A-SAA is chemotactic to vascular endothelial cells and induces endothelial cell tube formation. These tube-shaped structures are an *in vitro* equivalent of new blood vessel formation *in vivo*. 'We also discovered that serum amyloid A upregulates the expression of leucocyte adhesion molecules on the surfaces of the vascular endothelium,' he adds. This means that the vascular endothelium becomes more 'sticky' and preferentially binds to circulating inflammatory white blood cells. Moreover, A-SAA is also chemotactic to leucocytes, which adhere to the surface of the vascular endothelial cells. It also stimulates the proliferation of fibroblast cells, which are known to invade the joint in rheumatoid arthritis.



Finally, the researchers showed that A-SAA upregulates Nuclear kappa Beta (NF—κβ) – a major intracellular signalling molecule that is known to be of critical importance in driving inflammation.

The researchers were also able to identify a new receptor for A-SAA in the joint called CLA-1. Blocking this receptor led to a fall-off in A-SAA mediated events. This suggests that A-SAA does work, at least in part, through this receptor. Moreover, the receptor is already known to be involved in the transport of cholesterol – and this could shed light on another aspect of RA.

"The strong links between the lab and clinical studies seen in this research project do suggest that A-SAA is a very significant player in rheumatoid arthritis, and may be a valuable target for new therapies in the future."

Clinical follow up studies have shown that having RA is associated with an approximately doubled risk of developing cardiovascular disease. It is well established that cholesterol transport and metabolism is a factor in cardiovascular disease – with higher levels of low density lipoprotein (LDL) or 'bad' cholesterol being a potent risk factor. It may be that A-SAA plays a role in linking RA and cardiovascular disease through the CLA-1 receptor – but the exact mechanism of this remains to be clarified. This careful dissection of the multifaceted role of A-SAA gives us a much clearer, more detailed picture of inflammation in RA at a molecular level.

This lab work has been translated to the clinic, where levels of A-SAA were measured in a group of 62 patients with inflammatory RA before and after receiving anti-TNFα therapy. Elevated levels were associated with higher levels of known collagen cleavage biomarkers, previously shown to be surrogate (indirect) markers of joint destruction. There was also a link between high A-SAA levels and joint destruction measured one year into the trial by joint damage visible in radiographic analysis. Furthermore, changes in two collagen cleavage biomarkers C2C, and C1,2C, and a synthesis marker for type II collagen CPII, one month into the trial, predicted radiographic progression of disease at one year. Mullan adds that those who did not respond to anti-TNFα therapy tended to have higher A-SAA levels. 'Therefore, A-SAA may be driving the disease in patients who are resistant to anti-TNFα therapy,' he says. The strong links between the lab and clinical studies seen in this research project do suggest that A-SAA is a very significant player in rheumatoid arthritis, and may be a valuable target for new therapies in the future.

THE PERFECT PRESCRIPTION Better access to medicines

New research across Ireland shows how prescribing medicines can be made more effective and equitable

The prescription of a medicine is the most common form of treatment for patients in primary care. Most people have received a prescription drug at some time in their lives, and 95 per cent of older people are on long term medication for a chronic condition such as heart disease or arthritis – indeed, many of them will be taking five or more different drugs. Patients want a high standard of prescribing from their doctor but, with over 5,000 different drugs on the market today – and new ones being introduced all the time – this can be challenging.

Good prescribing involves assessing the risks and benefits of a particular drug for the individual patient. It also means not over-treating or under-treating with medication. Some drugs, such as benzodiazepine tranquillisers and antibiotics, are used too much, while therapies that could help protect against heart disease through controlling high blood pressure and high cholesterol, are under-prescribed. Added to this, the Irish national drug bill now exceeds €1.8 billion and there is, understandably, increasing pressure to prescribe only those drugs which provide good value for money. HRB-funded researchers affiliated to the Department of Phamacology and Therapeutics, Trinity College, and St James's Hospital, Dublin, have been looking at some of these issues, and have put forward many new ideas for improving the art of prescribing.

Value for money

Total spending on healthcare in Ireland was €12.6 billion in 2006 and approximately 15 per cent of this expenditure was on medication. 'There has been a year on year increase in spending on drugs over the past six years,' comments Dr Michael Barry of the Department of Pharmacoeconomics at St James's Hospital. His key question is – are we getting value for money?

The National Health Strategy of 2001 introduced the idea of Health Technology Assessments (HTAs) where treatments, including medication, could be investigated for their cost-effectiveness. Nine per cent of the national drug budget is spent on statins – a figure amounting to €105 million in 2005 – with the Number 1 seller being atorvastatin (Lipitor).

Prescribing costs in Ireland

Medicines account for just over 10 per cent of total public expenditure on health. The total payment to pharmacies by the state for the year 2004 was €1,092.7 million, a 15.8 per cent increase as compared with a payment of €943.21 million in 2003. The National Centre for Pharmacoeconomics identifies the drug groups which account for the greatest expenditure to the GMS payments board and uses the GMS database to analyse drug utilisation and expenditure trends. Increasing the cost-effectiveness of Irish healthcare technologies may or may not reduce health service expenditures, but it should result in greater health impact per unit of expenditure.

For more information on economic evaluation of pharmaceutical products and the development of cost effective prescribing, see the website of the National Centre for Pharmacoeconomics (NCPE) in Ireland (www.ncpe.ie)

"If someone has a history of heart disease, treating them with a statin will protect them from a recurrence, such as another heart attack – and it is economically worthwhile to do so."

Statins lower cholesterol levels and large clinical trials have shown that they can prevent heart disease and stroke.

'We had already established that statins are highly cost-effective in the secondary prevention of heart disease,' says Dr Barry. That is, if someone has a history of heart disease, treating them with a statin will protect them from a recurrence, such as another heart attack – and it is economically worthwhile to do so.

Secondary prevention involves protecting those who have a previous history of cardiovascular disease, while primary prevention is aimed at those who have no history, but may be at risk. Dr Barry's recent HRB-funded study focused upon whether statins are also cost effective for primary prevention of CHD. We all have a varying risk of developing CHD, depending on factors such as cholesterol levels, blood pressure, weight, age, smoking, and gender. Research on populations with CHD has enabled doctors to calculate an individual's risk – and this is generally quoted as a percentage risk of developing CHD over the next ten years.

'We used an economic model to establish the risk level at which statins become cost effective,' explains Dr Barry. The model used data that compared rates of heart disease among people who were, and were not, prescribed statins. The findings showed that statins become cost effective at a threshold of a 15 per cent risk of CHD over ten years. That is, there is now a clear economic justification for prescribing these drugs to those whose risk is 15 per cent or more.

In money terms, the study shows that the incremental cost effectiveness of statin therapy in high risk individuals ranges from €17,900 per life year gained (LYG) to €33,800/LYG under the General Medical Services (GMS) scheme, (also known as the Medical Card scheme). The incremental cost effectiveness was €24,500/LYG to €48,500/LYG under the Drug Payments scheme. Incremental cost effectiveness refers to the additional cost associated with the additional improved outcome associated with a particular health technology – in this case, statin therapy. All of the statins were cost-effective, but atorvastatin (Lipitor) was the most so.

These findings provide very useful guidance for both patients and GPs, since a person's heart disease risk can easily be determined during a single visit to the surgery. The study is also, says Dr Barry, part of a bigger picture as it will help develop the capacity and infrastructure needed to carry out other Health Technology Assessments, which can then be used as a rational basis for prescribing decisions.

"Prescription medications ought to be available to all who can benefit from them – regardless of where they live, how much money they have or their age."

Inequities in prescribing

Prescription medications ought to be available to all who can benefit from them – regardless of where they live, how much money they have or their age. But Dr Kathleen Bennett and Dr Cara Usher of the Department of Pharmacology and Therapeutics, Trinity Centre, St James's Hospital, have found that marked prescribing inequalities do exist in Ireland.

They used the GMS scheme and Long Term Illness scheme databases, both of which include information on all prescriptions dispensed, together with details of the patient's age, gender and which *health board they live in. The study built on earlier work that showed that the elderly and women are disadvantaged when it comes to the prescription of heart medication.

One focus of the work was to investigate regional variations in prescription of secondary preventative therapies for people with diabetes. These medications include statins and fibrates (to control cholesterol), various drugs for high blood pressure, and aspirin, which has a proven record in preventing heart disease.

Heart disease is a major complication in both type 1 (insulin-dependent) and type 2 (non-insulin dependent) diabetes and, indeed, accounts for around 70 per cent of all deaths in this group. People with diabetes have a two to five times higher risk of dying from heart disease than those without diabetes. Accordingly, The Irish Cardiovascular Health Strategy recommends that patients with diabetes should be treated as those who have pre-existing heart disease (people who have had a heart attack, for instance) and should virtually all be on secondary preventative therapy.

The study reveals that this goal is far from being reached, and that there are wide variations in prescribing between the different *Health Board regions. For instance, high rates of prescribing of secondary preventative therapies were found in the *Midland Health Board region. Meanwhile, aspirin prescribing was high in the *Eastern Region and statin and ACE inhibitor (a blood pressure drug) prescribing was consistently high in the *South East (after the Midland and Eastern Regions). However, low prescribing rates were found in the *Western regions. Highest variations were seen for statin and AT2 antagonist (another blood pressure drug) prescribing.

Commenting on these variations, Dr Bennett says that much remains unexplained although the shared care approach to diabetes in the Midlands could account for high prescribing rates there. Other factors at work may include variations in demographics, lifestyle, medical practice and proximity to teaching hospitals. 'There ought to be fair and equitable access to treatments across the country,' she says. 'This was laid down in the National Health Strategy in 2001.'

* This research was conducted using data, prior to 2005, before the new Local Health Areas of the HSE were indentified therefore it refers to the old Health Board Structure.

The study also found that those over 75 were less likely to receive statins and fibrates than younger patients, and men were more likely to receive aspirin, ACE inhibitors or fibrates than women, which confirms what has been found in previous research. Older people are often not included in clinical trials so there is less of an evidence base for prescribing them statins. Also, doctors are sometimes reluctant to prescribe a further drug to an elderly person who may already be taking several other medications.

The study highlights the need for an ongoing assessment of prescribing practice in Ireland, says Dr Bennett, in order to reduce these inequalities. In another HRB-funded study, she and her colleagues have contacted GPs in various regions, 'feeding back' to them their prescribing practice and giving them an opportunity to discuss this. Regular reviews of a patient's prescriptions, particularly for the elderly, could provide a good opportunity to drop inappropriate medications (such as long-term benzodiazepines) and add in those that might be beneficial, like statins.

We can also learn something from the UK, where the National Service Frameworks include prescribing targets and accompanying incentives for GPs. Better patient education can also play a role in optimising prescription practice; the informed patient will know about their medications and will have the confidence to ask questions and maybe request a review of their prescriptions. 'The improvements need to come from both GP education and patient empowerment,' says Dr Bennett.

Improving prescribing practice

GPs can work together to develop higher prescribing standards. Professor John Feely of the Department of Pharmacology and Therapeutics, St James's Hospital, has led a study which put forward a new set of guidelines called 'quality prescribing indicators'. 'We evaluated the best evidence from around the world in this field, and also the views of experienced practitioners in order to devise a set of indicators which would be applicable for the use of medicines in Ireland,' he explains. 'For patients, there is a reassurance in knowing that their doctors are working to the highest standards and that their prescribing is being reviewed by other specialists to ensure that these standards are both achieved and maintained.' While it is not reasonable to expect all doctors to have knowledge of all the medicines that their patients might need, the aim is that prescribers will be very familiar with a range of regularly used drugs and then have access to backup information on less commonly used ones.

In one part of the study, a group of 105 GPs assessed the prescribing indicators, giving a high ranking to those based on evidence and a lower one to those based on cost alone. The researchers then showed them how their own prescribing compared with the standards they had set – an exercise which led to some interesting changes. Three months on, the team found that there were improvements in prescribing standards for asthma and diabetes, and a greater use of paracetamol. 'We have been encouraged by the co-operation of GPs in this matter,' says Feely.

He goes on to describe the development of a new prescribing indicator called the 'missed opportunity'.

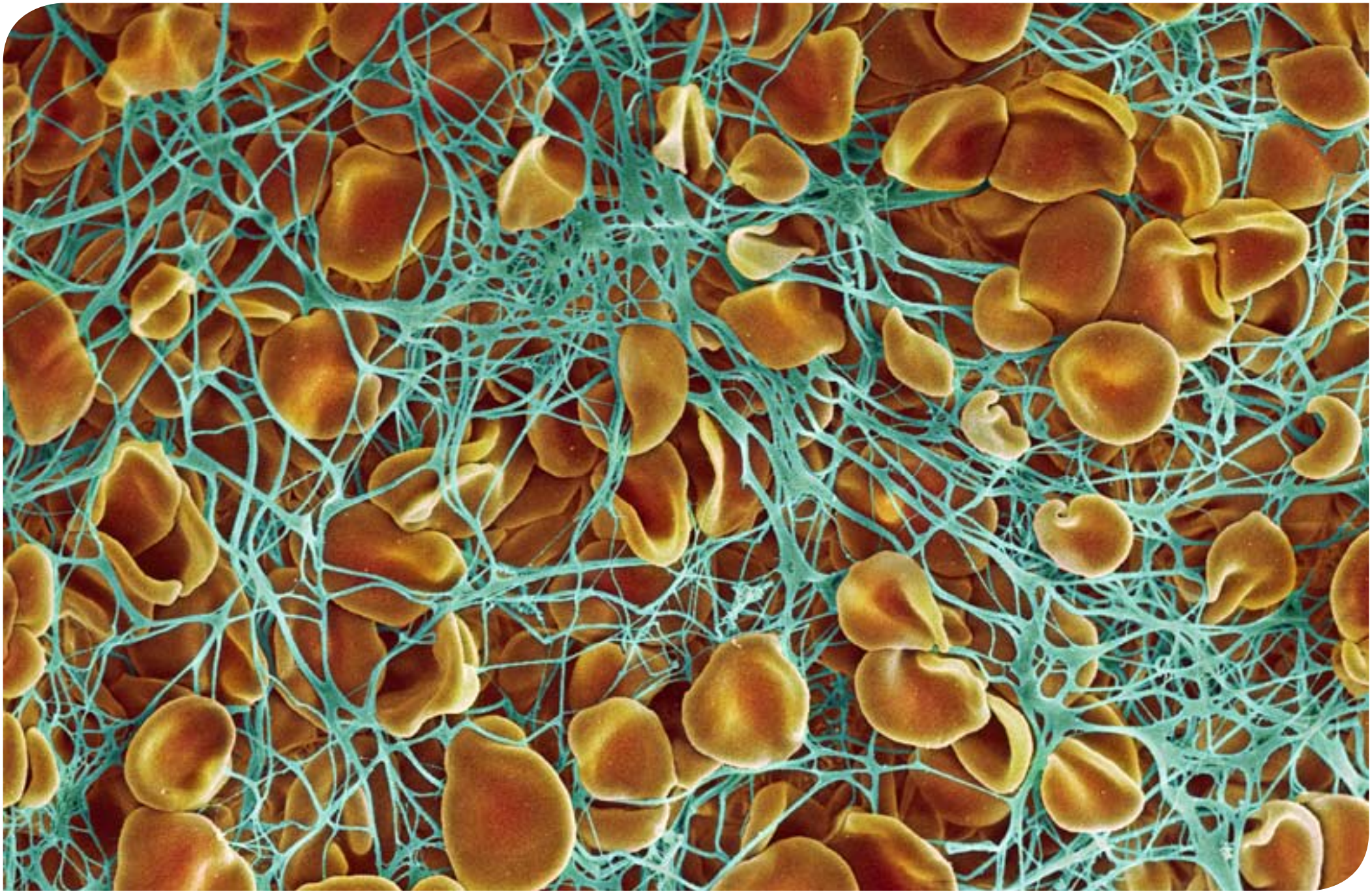
One example concerns the failure to prescribe drugs to thin the blood or antiplatelet drugs, such as aspirin, to older people at risk of stroke through a heart rhythm abnormality called atrial fibrillation. Through raising awareness of the 'missed opportunity', Feely believes GPs in Ireland are now more likely to prescribe such medications.

In the future, he would like to see a computerised application of the new quality prescribing indicators in everyday medical practice. 'Sometimes medicines are prescribed by more than one prescriber, with neither fully aware of the totality of the patient's medicines,' he says. 'This, of course, would be detected on a computerised database.'

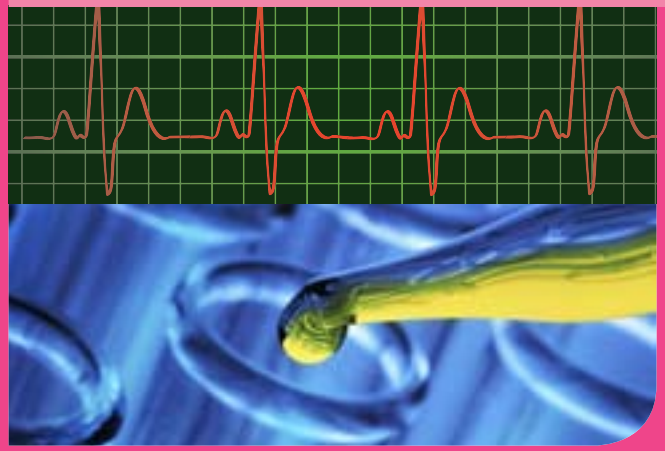
Moreover, a system in which prescribing could be linked to possible side effects, admissions to hospital, or serious illness would greatly enhance doctors' ability to trace the outcome of good and bad prescribing. Such systems are already in operation in parts of Scotland and France. 'We, by getting together such information, and knowing the frequency with which medicines are used, can develop a true picture of how drugs are performing in practice,' Feely says. 'I also hope that where we can identify less than optimal prescribing, there would be a means of feeding this information back to the prescriber, giving them the opportunity to update their skills or medical knowledge.'

Finally, Feely would also like the database approach applied to the 'missed opportunity' patients. Many thousands of patients are at risk of heart disease through untreated high blood pressure or high cholesterol – conditions which are relatively easy to manage with medication. People in Ireland could be screened for blood pressure and cholesterol – as they are elsewhere. 'We would like to be able to use electronic databases that contained the results of such screening to see whether patients at risk are being offered appropriate therapy. Ideally, we'd like to see linkage between diagnosis and treatment that would allow a group of peers to comment on quality issues. Also, by linking all prescribing, both hospital and general practice, we could warn prescribers with regard to potential interactions between different medicines.'

"GPs can work together to develop higher prescribing standards."



UNDERSTANDING THE HUMAN HEART A molecular approach to heart disease



Irish researchers seek to understand the genetic and molecular basis of heart problems, as well as improving treatment

Cardiovascular disease, including heart attacks and strokes, is the leading cause of death among the Irish population, accounting for 40 per cent of all deaths in 2005. A heart attack occurs when a blood clot forms within the coronary artery, blocking the supply of oxygen to the heart muscle. The majority of strokes occur when a clot forms within the arteries that serve the brain. Generally, the formation of such clots is triggered by the rupture of fatty deposits called atherosclerotic plaque which narrow, and even block, the arteries serving the heart and brain.

But blood clotting is an essential survival process that protects the body from blood loss following injury. It involves the switching on of blood cells called platelets, which then stick together within a protein mesh to form a clot, sealing the site of injury from further blood loss. Dr Sarah O'Neill of the Royal College of Surgeons in Ireland (RCSI) has been looking at the molecular mechanisms underlying switching on of platelets, which could help towards a better understanding of why blood clotting sometimes happens and when it does not. One reason for this inappropriate blood clotting may be that some people carry genetic variants in genes involved in platelet function, according to new research from Professor Denis Shields, University College Dublin (UCD). Understanding how such genetic factors interact with environmental risk factors is important in prevention of heart disease. For those with diagnosed heart problems, there is also a need to improve on current treatments. Dr Alan Keenan, also of UCD, has been adapting the standard stent – a device that keeps blocked arteries open – so it can release drugs that could stop the vessel from re-narrowing, thereby protecting the patient from a further heart attack.

Say NO to blood clots

Most of the time, platelets circulate around the body in blood in a quiescent state. But when they are needed for clotting, they adopt an activated state. Naturally there is a great deal of interest in how the platelet switches from the quiescent to the activated form – because if we understood this, it might lead to ways of stopping the inappropriate blood clotting that causes heart attacks and strokes.

Heart disease in Ireland

Approximately 10,000 people die each year from cardiovascular disease (CVD) – including coronary heart disease (CHD), stroke and other circulatory diseases. CVD is the most common cause of death in Ireland, accounting for 36 per cent of all deaths. The largest number of these deaths relate to CHD – mainly heart attack – at 5,000. Twenty-two per cent of premature deaths (under age 65) are from CVD.

To have a healthier heart it is recommended to
- Get active
- Eat well, lose weight
- Stop smoking
- Drink less alcohol

For more information see the website of the Irish Heart Foundation (www.irishheart.ie)

It is already known that a gaseous molecule called nitric oxide (NO), which is released into the bloodstream from cells lining the blood vessels, plays a part in keeping platelets in the quiescent state. NO does this in two ways – by passing into the platelet (or being generated within it) or by interacting with proteins on its surface.

"Understanding how genetic factors interact with environmental risk factors is important in prevention of heart disease."

Dr Sarah O'Neill has been investigating this second, less well understood, way in which NO can keep platelets in the 'off' position. Researchers have discovered in recent years that NO can bind to sulphur atoms within an amino acid called cysteine in a protein sequence. So far, S-nitrosylation has been studied in only a few proteins and its role is still not well understood, although it looks as if it can have a profound effect on a protein's function and will affect signalling pathways within the cell itself.

O'Neill's approach to studying the platelet NO switch is based upon her longstanding interest in integrins, which are proteins on the surfaces of cells, and how they can change their conformation, or shape, under the influence of an enzyme activity involving cysteine residues.

The current work is focused on the S-nitrosylation of an integrin (known as $\alpha_{IIb}\beta_3$) that is found only upon the platelet surface. There are 50,000 copies of this particular integrin molecule on the surface of each platelet, so it is presumably of great significance. The integrin acts as a molecular switch, turning the platelet off or on. It is not fully understood how this happens.

However, in the quiescent platelet, the integrin molecule adopts a 'genuflecting' shape, but when the platelet is activated, it undergoes a dramatic conformational change, flying open like a switch blade. The integrin binds to an antibody with a fluorescent tag when the platelet is activated, but not if it is quiescent. Therefore, the researchers used the tag to show that NO could reverse the conformational change of the integrin from the activated form back to the quiescent form. In other words, NO does appear to act as a switch, turning the platelet from 'on' to 'off' when it binds to the integrin molecules on its surface.

Working with Dr Tia Keyes of Dublin City University, O'Neill also used a technique called Raman spectroscopy on purified platelet integrin to show that NO does indeed bind to the molecule at cysteine residues. This is the first-ever demonstration of the S-nitrosylation of an integrin. O'Neill says that her findings suggest that the surface of the platelet might be acting as an 'NO sink'. 'This has two implications. First, the platelet could donate its surface NO to a milieu that will keep other platelets quiet and stop them being recruited to clot formation. Or, the opposite, the platelet acting as a sink could remove NO from the circulation, and increase the reactivity of the blood vessels towards clotting,' she says.

The group is now looking at other platelet proteins that might be nitrosylated and how all this works in the signalling pathways of the platelet, leading, hopefully, to a better understanding of how platelets are turned on or off.

Gene variants

How readily platelets are activated might be controlled by genetic influences. We already know that there is a genetic factor in heart disease from studies comparing risk between identical and non-identical twins. But the actual genes that are involved remain to be identified. Dr Denis Shields, together with Dr Alun Evans of Queen's University Belfast (QUB), have a long-standing interest in the genetics of cardiovascular risk. In the HRB-supported study, they have carried out studies on gene variants and heart disease in population groups in Ireland (North-South) and mainland Europe.

They chose to look at genes of two types – those involved in resistance to infection and those involved in blood clotting, which, of course involves platelets. 'We know that selection for resistance to bacterial and viral infection has been one of the biggest pressures in changing gene patterns in humans,' Shields explains. Inflammation is part of the natural response to infection, and it also appears to play a role in heart disease too. Therefore, they set out to look at genetic variants in proteins that occur on cells in the blood vessels. These variants might help people resist certain infectious diseases, but an unfortunate side-effect could be increased damage to the coronary arteries - through inflammation - which predisposes to heart disease.

The researchers looked at genetic variants called SNPs (single nucleotide polymorphisms) that are known to influence resistance to infection in a group of people with established heart disease – heart attack or angina - and compared them with a group of healthy controls. No strong link between these SNPs and heart disease risk was found; for some younger people with a history of heart attack, there was just a suggestion that genetic variants in their resistance to infection might make a difference between whether a clot forms in their coronary arteries or whether they undergo a narrowing known as stenosis. The former predisposes to heart attack, the latter to stable angina. This tentative association is worthy of further exploration in a larger study; it is possible that those carrying gene variants that make them susceptible to heart attack could be protected by antimicrobial therapy.

However, Shields concludes that genetic variation in resistance to infection – at least as far as these particular genes are concerned - is not a significant driving force behind differences in heart disease risk between people. 'This provides more support for the idea that the major effect on our heart disease risk may be the shift from a 'Stone Age' lifestyle to a modern one. Those people unlucky enough to have genetic variants that increase their risk of more rapid clogging of the arteries are probably just slightly more susceptible than the rest of us.'

In a second study, Shields and his collaborators at QUB looked at genetic variants influencing platelet function. Here the team did find a significant link between two specific gene variants and heart disease risk.

"The major effect on our heart disease risk may be the shift from a 'Stone Age' lifestyle to a modern one."

"Recent advances in technology open up the possibility of the genome-wide scan, where 500,000 or so gene variants can be compared at one time."

One of these relates to a protein capable of modifying a second protein which is involved in the adhesion of blood cells to the sides of blood vessels. One can easily imagine why such a protein could be important – it might play a role in the narrowing and blocking of the coronary arteries that is found in heart disease. The second variant was in a protein that occurs in high levels within platelets themselves, and may increase the tendency of the blood to form clots, blocking the coronary arteries and causing a heart attack.

Shields comments that there is much more that can be done in the exploration of the genetic factors underlying heart disease. For a start, he will be comparing his recent results with those emerging from some big international studies. Recent advances in technology open up the possibility of the genome-wide scan, where 500,000 or so gene variants can be compared at one time – Shields' group is already involved in such studies. This will accelerate the discovery of those genes that are involved with the functioning of the heart and how they interact. Of course, people cannot do anything about their genetic make-up. But there are modifiable risk factors, such as diet, smoking and exercise, which people can act on to improve their heart health, whatever pattern of gene variants they carry.

Developing better stents

Percutaneous transluminal coronary angioplasty (PTCA) is now the major treatment for blocked and narrowed coronary arteries. It involves the insertion of a catheter tipped with a balloon into the femoral artery in the thigh and ultrasound guidance through the arteries into the coronary artery where the blockage is. Here the balloon is inflated, to compress the atherosclerotic plaque, thereby widening the walls of the artery. A wire mesh tube device called a stent may be left in place after the catheter is withdrawn to keep the walls of the artery apart. But balloons and stents can injure the walls of the artery where they are placed. 'A series of inappropriate repair mechanisms then gets underway,' explains Dr Alan Keenan. For instance, there is inflammation, which leads to the migration and proliferation of underlying and newly exposed smooth muscle cells into the inside of the vessel. The result of this so-called intimal hyperplasia - and the other ongoing repair processes - is a re-narrowing of the vessel (known as restenosis) which puts the patient at risk and may call for a repeat of the angioplasty.

One way around the problem of restenosis is to insert a drug-eluting stent (DES). The drug is released slowly into the artery and inhibits the growth of the underlying cells. But drugs do not stick readily onto the bare metallic surface of a stent. Therefore, Keenan has used his background in organic chemistry and

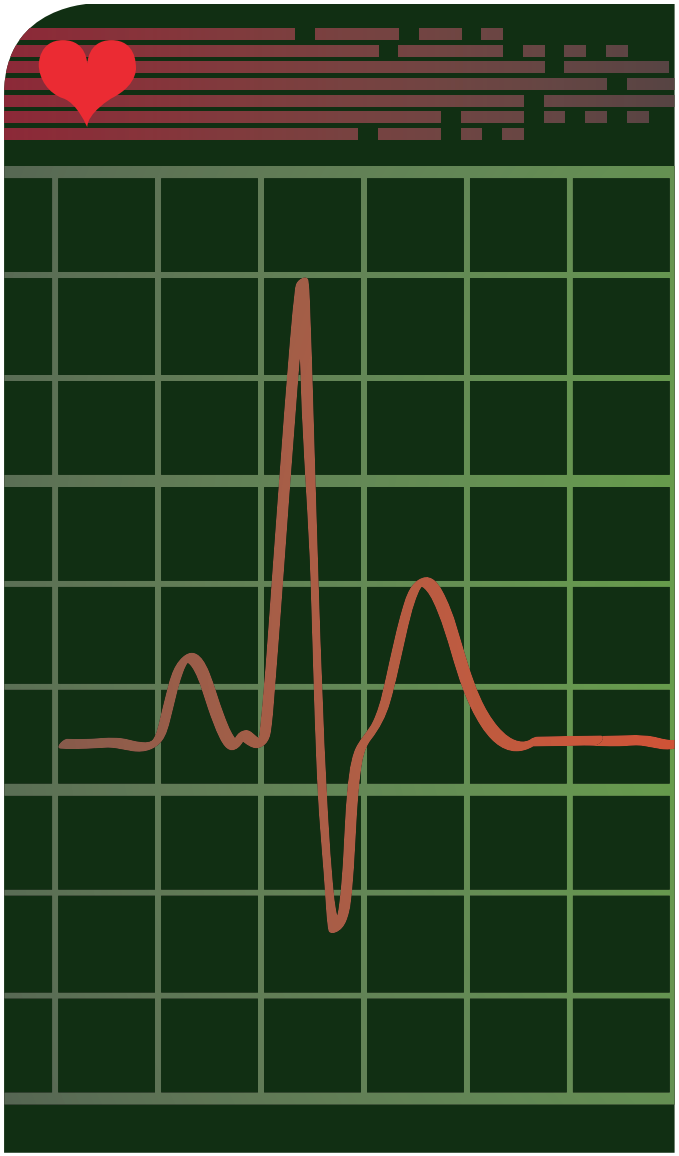
pharmacology to develop a thermoresponsive coating of an N-isopropylacrylamide derived co-polymer for stents that acts like a sponge, allowing drugs to be incorporated onto the stent's surface and then slowly released into the artery.

These co-polymers have an open mesh structure which allows drug incorporation, but undergoes a phase transition when heated so that the structure collapses, becomes water insoluble, and releases the drug into the artery by diffusion. Varying co-polymer composition allows control over the extent and rate of drug release. Keenan's team has already incorporated colchicine, which stops cell multiplication, and vascular endothelial growth factor, which promotes the growth of new blood vessels, into their coatings.

The coatings have also been developed into a microgel format within a matrix to form a 'plum pudding' type of structure which helps achieve more control over drug release. The cholesterol-lowering drug, fluvastatin, was then chosen for incorporation into the coatings in further experiments because it has anti-proliferative and anti-inflammatory properties: there is also now evidence that these drugs can stabilise atherosclerotic plaque. In these experiments, fluvastatin was released from the coating over a period of 60 days in bioactive form – this covers the time 'window' after angioplasty during which protection against restenosis is thought to be useful.

'The real strength of our system is that we can also design different populations of 'plum pudding' gels and put one drug into one population, a second into another and have it then released at different rates to combat various different aspects of restenosis,' says Keenan. The feasibility of this has already been demonstrated with different dyes – showing it can happen with different drugs is the next step.

Meanwhile, the DES also needs testing in pigs, which are a good animal model of heart disease. If such experiments prove successful, heart patients could look forward to a much better outcome from treatment with PTCA.



THE PATIENT'S VOICE Overcoming communication barriers in healthcare

Irish healthcare researchers are exploring how patients and their families communicate their needs in challenging situations

The way in which health and related services are delivered is as important to patients and their families as what is delivered in the scientific sense – but there's a danger of it being sidelined as technology advances. Irish psychology, medical sociology, and nursing experts are looking at how people cope in four challenging healthcare situations: dealing with language barriers, accepting help as they age, having a loved one in intensive care, and the transition from palliative into terminal care.

Language matters

In recent years, the arrival of refugees, asylum seekers and migrant workers has led to the establishment of new communities in Ireland where many people speak little English. While the National Health Strategy recognises the healthcare needs of these groups, communication issues make it hard for them to access and use services. Dr Anne MacFarlane, Lecturer in Primary Care General Practice at the National University of Ireland (NUI), Galway, has studied a group of Croat-Serb and Russian-speaking refugees and asylum seekers, asking what language barriers mean to them when seeking healthcare in the local community.

'What came across strongly was that these people do put enormous effort into trying to communicate with general practitioners and public health nurses,' she says. Typically, they will use multiple strategies – such as using informal interpreters from their family or their community, learning words and phrases by heart, using mime or gestures, or taking a dictionary to the consultation.

Her study uncovered a basic and serious level of dissatisfaction among participants, particularly with respect to GP consultations. 'Despite their efforts, they did not feel they were getting their message across or being listened to.'

For instance, '*K1 relied on the use of her dictionary but found that this was very limited. She tried to explain to her GP that a scar she had was the result of an erupted cyst of her ovary. Her GP couldn't understand fully and thought it was due to an operation for appendicitis. K1 was extremely worried about this misunderstanding, but had no way of addressing the problem.*'

Asylum seekers and health care services

Asylum-seekers are persons whose applications for asylum or refugee status are pending a final decision and this can take up to three years in Ireland. These individuals who have fled their country and may have suffered serious human rights abuses, may have specific physical and psychological health needs due to their previous experiences prior to arriving in Ireland.

A number of issues have been raised by asylum seekers including difficulty coping with life events such as separation or death of family members, lack of easily available and relevant information, chronic loneliness and social isolation and language and communication difficulties. Service providers have raised similar issues such as language and communication difficulties and lack of information on health care services.

A strategic plan 2006-2009 has been put in to action to ensure that essential work in the area of Refugee and Asylum protection is kept to the forefront in the public domain, with policy makers and with practitioners in the field.

For more information see the Irish Refugee Council (www.irishrefugeecouncil.ie)

She explained that, like others, she prepares for visits to the GP at home using a dictionary and memorising phrases. She also visits her friend who owns a medical dictionary/self-help book. However, she was not happy to use a friend or relative as an interpreter because she did not want her children's health discussed in the community. This was particularly the case for one child with a skin condition; she was worried that others might think that the condition was contagious.

The overall impression coming out of this study was that people didn't feel listened to and knew the language barrier was a factor. They couldn't help wondering if GPs perhaps thought they were not very intelligent because they couldn't speak English and whether they were thought less of because they did not happen to be Irish.

MacFarlane checked out GPs views of the issue in a telephone survey and in face-to-face interviews. 'They seemed to believe that, while the use of informal interpreters is not ideal, these communication issues were settling down. This is in contrast to the views of the asylum seekers and refugees themselves'.

In her view – echoed by the refugee/asylum seeker participants – formal medical interpreting services ought to be made available to GPs so the patient can be assured of getting the best of attention – even in the presence of a language barrier. Findings from the research have been presented regionally, nationally and internationally including an important written submission to the consultation phase of the HSE's first ever National Intercultural Health Strategy.

Stigma about service use

Most older people would prefer to stay in their homes, rather than moving to sheltered accommodation or a nursing home. But they may only be able to do so with support. So most developed countries – including Ireland – are expanding services, such as home help and meals on wheels, to enable their ageing populations to keep their independence.

In 2000, the first large-scale survey of health and social services for older people in Ireland revealed something unexpected. 'We found a lot of negative attitudes, including embarrassment, towards taking up services, explains Rebecca Garavan of the Department of Psychology, Royal College of Surgeons in Ireland (RCSI), Dublin, who co-ordinated the research. She has explored these attitudes in a further research project done in conjunction with the Healthy Ageing Research Programme (HARP), a large five year HRB-funded study of community-dwelling older people in both the Republic of Ireland and Northern Ireland.

A significant minority held negative attitudes towards both service users and the services themselves. Furthermore, some services such as meals on wheels, home help and personal care – those very supports that enable people to continue living independently – seemed to be much more stigmatising than assistance in the form of hearing or walking aids. For instance, 22 per cent thought that using services suggests the person has an unsupportive family, while 13 per cent agreed that service users 'rely too much on the system'.

"The stigma attached to services is decreasing over time as more people take them up."

Over a fifth of the sample felt that services were provided in a way that 'discourages older people from seeking the services' and over a quarter agreed that 'the government does not care about older people.' Fourteen per cent said others would feel sorry for them if they became service users. Among those who had the most difficulty in carrying out activities of daily living, almost half had never thought about obtaining home help, even though they had a lot to gain from such support.

'It is hard to pinpoint exactly where these negative attitudes come from,' says Garavan. 'Traditionally, these services were delivered by the Church or charities to the poor, weak, sick and alone. So maybe by signing up to them you are putting up your hand and saying *you* are poor, weak, sick or have no one who will adequately care for you – including family.'

Added to this, support services are still fairly limited in Ireland and may be seen as only for the truly desperate.

People may also be reluctant to discuss their need for services with their family for fear of upsetting them. As one participant put it, *'Not sure – they might be insulted …think they are not providing for me. But they are so busy.*'

There is also worry about the implications of handing over responsibility for daily activities. *'I think if you can do for yourself, you should. It makes you get up and do things, and if you don't, you'd sit all day and do nothing….It would make you lazy…I've been working all my life,'* said another participant.

However, the stigma attached to services is decreasing over time as more people take them up. There were notable reductions from the 2000 survey to the more recent 2004 one. Garavan says older people are now using the word 'entitlement', but she still sees a need for them to be shown that using available services is quite normal and acceptable; it is not the start of a 'slippery slope' or a loss of control, but a way of keeping people in their own homes which is what most say is what they want.

"Using available services is quite normal and acceptable; it is not the start of a 'slippery slope' or a loss of control, but a way of keeping people in their own homes."

The experience of having a loved one in intensive care

Margaret McKiernan knows from her experience as clinical nurse manager in an intensive care unit (ICU) just how stressful it is for families when a loved one is critically ill. 'The literature suggests that in intensive care, the need to stabilise critically ill patients takes priority over the assessment and care of families, particularly in the initial time after admission,' she explains.

From interviews with families of ICU patients in a university hospital, McKiernan captured four significant aspects of their experience: the need to know, being there with the patient, making sense of it all, and caring and support.

"Small acts, such as hair washing, mouth care and applying make up to their loved one were identified as being hugely important to the family."

The 'need to know' focused on the importance of being prepared and the need for information to be reinforced and above all, to be honest and clear. 'The need to know was overwhelming and expressed by all participants irrespective of the patient's diagnosis or outcome. It was interesting that participants all identified nursing staff as their key source of information' says McKiernan. However, experienced nurses were said to be better at giving information, with younger, less experienced nurses seen as more focused on the demands of the technology.

Family members also found it important to have physical contact with their relative to maintain a

connection with them. *'It helps us, if you are actually sitting there and seeing her and knowing she is alive, even with all those things she has on her,'* said one participant. All wanted to have completely open visiting (some ICUs have a 'rest time' when visiting is not permitted) to help them juggle all the other issues in their lives, especially in the first few days following admission. *'If visiting hours were too restrictive, it would be too upsetting for people…you've enough problems and worries inside you,'* commented another participant.

Meanwhile, families said it was also important to 'make sense' of their situation, by monitoring and tracking the care their relative was receiving. 'Small acts, such as hair washing, mouth care and applying make up to their loved one were identified as being hugely important to the family,' explains McKiernan. 'There was a concern for families, that amidst all the technology nurses might forget those little things which can give such a feeling of security and reassurance,' explains McKiernan.

The presence of technology raised ethical issues too. Many mentioned concerns over initiating and maintaining treatments – on a ventilator, for example – which the patient might not have wanted. They were very much aware that they were acting as the patient's advocate. This was expressed by one participant: *'He said I'm depending on you now ….we said we would look out for him and make sure the best was done for him.'*

And finally, the family needed support so they could keep themselves strong for the patient. Nurses were generally identified as being supportive in this way. Indeed, some participants preferred that the nurse would focus all their attention on the patient, rather than diverting some of it to the family.

Ms McKiernan now wants to look at tying family care into a more organised package within the ICU, with the evaluation of specific nursing interventions which assist families of patients in intensive care. It is also recommended as a result of this research that there be the development of an identified nurse role to act as a link for the family and assess their needs for social and pastoral needs. She has already shared her findings at the Royal College of Nursing Research Conference (2007) and hopes the work can be taken forward through links between Irish and UK hospitals.

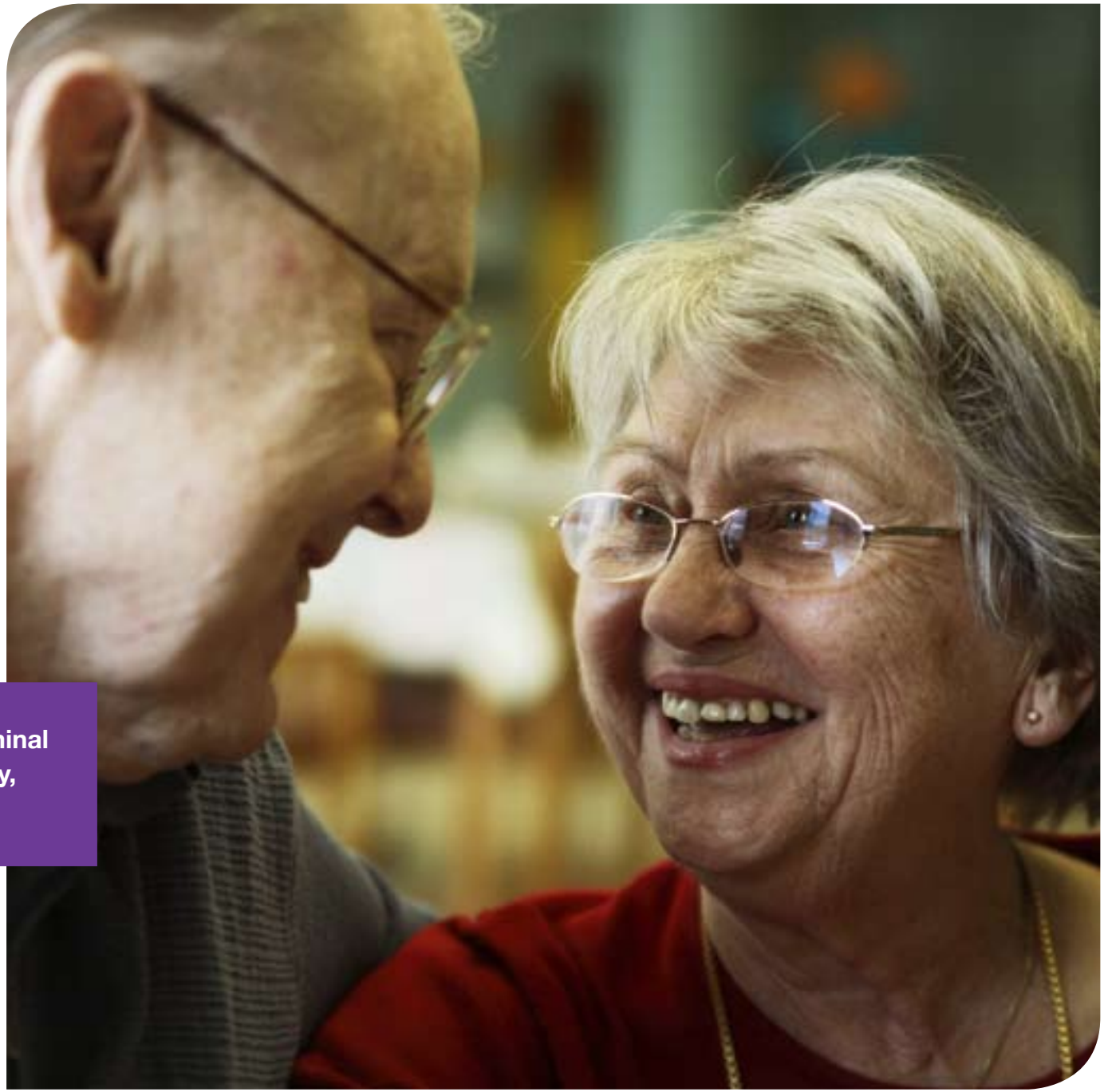
Transition

Our psychological wellbeing depends upon the successful management of life's major transitions. Philip Larkin, who lectures in Palliative Nursing Care at NUI Galway, has been looking at patients' experience of moving into the last few weeks of their lives, as they make the transition from palliative to terminal care.

Palliative care seeks to address both the medical and emotional needs of patients with progressive illness. Originally focused upon end-of-life care in cancer, palliative care began to develop as a medical discipline in the 1960s with the foundation of the hospice movement in the UK by the late Dame Cicely Saunders. Today, palliative care is being integrated, increasingly, with acute care services, and has also become a global concern, serving patients with illnesses other than cancer, especially those with HIV/AIDS. These changes have brought greater emphasis upon medical and clinical aspects with, for instance, new treatments being developed to help patients with discomforts and unpleasant symptoms.

"The transition from palliative to terminal care was often marked by uncertainty, confusion and mixed messages."

However, amidst these developments, the founding principles of palliative care mustn't be forgotten, for they focus on the experience and quality of life of the patient as that life begins to draw to a close.



"The hospice acts as a refuge that gives patients time to gather their thoughts and allows them to find peace and freedom from stressors," says Larkin. "Many said it was a place where they could finally be themselves."

With this in mind, Dr Larkin interviewed 100 patients in hospices, or in specialist palliative care units, across six European countries: UK, Ireland, Italy, Spain, The Netherlands and Switzerland. It is unusual to hear the patient's voice directly in this way – much previous research has been done with proxies, because of the challenges involved in interviewing individuals who may be very frail.

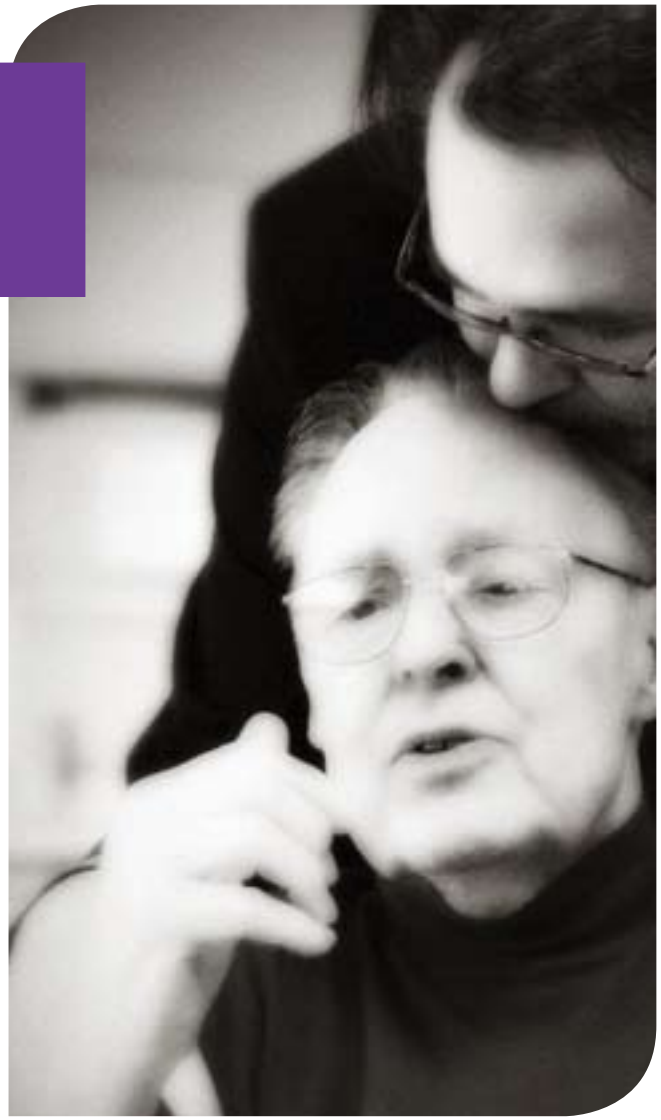
'We have found that the patients do want to be involved in research, especially in quality of life studies,' explains Dr Larkin.

He found that the transition from palliative to terminal care was often marked by uncertainty, confusion and mixed messages. Participants realised that they had a complex disease and tended to experience rapid change, rather than a slow progression of their illness. Sometimes these changes were not well handled by staff – patients are still being told 'there is nothing more we can do for you' or they are not made properly aware that they are moving towards the end of life.

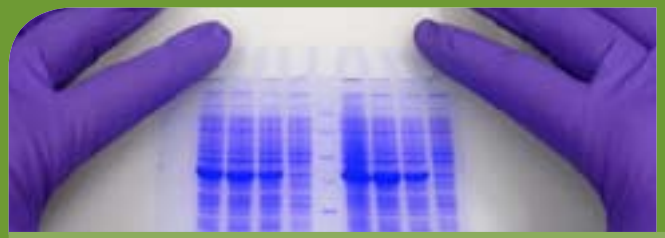
Living apart from mainstream society can be an important aspect of undergoing a life transition. The hospice or specialist palliative care unit can be seen as 'special space' of this kind, for patients in the last days of life. Not surprisingly, medical staff pride themselves on 'finding a bed' as soon as possible for those who need this.

But this very promptness can be upsetting for patients. Many felt they were not given enough time to prepare to enter terminal care, limiting their opportunities for dealing with personal life matters, legal issues and finances. A contributing factor might be that two thirds were unable to clearly identify the staff member responsible for instigating the transition, and many were unclear about the reasons for it. Maybe, Larkin suggests, the issue of the move to the hospice needs to be introduced earlier on - as soon as the patient is ready to hear it. Once settled in the hospice, patients valued the comfort and care they received there. 'The hospice acts as a refuge that gives patients time to gather their thoughts and allows them to find peace and freedom from stressors,' says Larkin. 'Many said it was a place where they could finally be themselves.'

In the hospice, patients often form very strong bonds with one another, sharing a sense that they are 'different', talking and sharing in a way in which they cannot with their relatives. 'This camaraderie was so important to them,' comments Larkin. Maybe it is time to re-think the hospice tradition of giving each occupant their own room. While some really appreciate the privacy, others want to be with others at this time, so provision of four-bedded rooms might be valuable. 'Some participants found witnessing a well-managed death was helpful to them,' he adds.



The study is now being presented internationally, with the hope that it may lead to improvements in how patients experience the transition into the last days of life.



FOR YOUR DIGESTION Insight into gastrointestinal disorders

Medical researchers at Irish centres find new approaches to a range of digestive problems

Inflammatory bowel disease (IBD), ulcers, and colorectal cancer are among the most common health problems affecting the digestive tract. HRB-funded researchers have been looking at these disorders using a range of scientific approaches. For instance, Professor David Brayden, of University College Dublin, has developed lab and animal models to look at the 'leakiness' of the gut in IBD, with a view to discovering new therapies. Meanwhile, Professor Dermot Kelleher of St James's Hospital uses proteomics to understand how the bacterium, *H.pylori,* causes duodenal ulcers.

Colorectal cancer is a major concern in both Ireland and the rest of Europe. A national screening programme could save many lives. A new non-invasive test being developed at Adelaide and Meath Hospital by Professor Colm O'Morain may lead to more accurate identification of those at risk. And Professor Cliona O'Farrelly of St Vincent's University Hospital, has discovered stem cells in the human intestine that may be applied to help patients fight a recurrence of colorectal cancer.

The science of inflammatory bowel disease

The gastrointestinal tract is lined with epithelial cells which are 'glued' together by a seal called the tight junction, creating a semi-permeable barrier that lets food and medication through. In inflammatory bowel disease (IBD), which includes both Crohn's disease and ulcerative colitis, the seal is leaky – but it is not known if this is a cause or effect of the disease. Professor David Brayden – who comes to this work with a pharmaceutical industry background in the science of drug delivery – and PhD student, Linda Feighery, have been focusing on whether compounds called myosin light chain kinase (MLCK) inhibitors can tighten up the leakiness of the tight junctions. MLCK is a protein which controls the opening and closing of the junctions, so its inhibitors could therefore have potential as a new therapy for IBD and other conditions where increased permeability may play a role.

Inflammatory Bowel Disease

Inflammatory Bowel Disease (IBD) is a condition where the bowel becomes red and inflamed. There are two main types of IBD: Crohn's disease and ulcerative colitis. Although they have many similarities they are distinctly different diseases and both can have 'flare-ups' (relapses) and periods of well-being (remissions). Both usually affect people aged 20-40 years but can sometimes occur in children and the elderly. About one in every 400 people suffers from IBD.

A key component in the treatment of IBD is a healthy diet. A balanced diet from all food groups is recommended to ensure an adequate supply of carbohydrates, proteins and fats. Most people with IBD know which foods they can tolerate and in general it is spicy, fatty and raw foods that are more difficult to digest.

Research shows that the number of people suffering from IBD is on the rise and it is especially affecting young people. For more information see the website of Irish stoma care and colorectal nurses association (www.ncnm.ie/isccna)

They attacked the problem using both *in vitro* (lab experiment) and *in vivo* (animal model) approaches. For the *in vitro* work, Feighery developed a new lab model of the gastrointestinal tract by mounting pieces of isolated mouse gut in special chambers that mimic the food and blood sides of the epithelium.

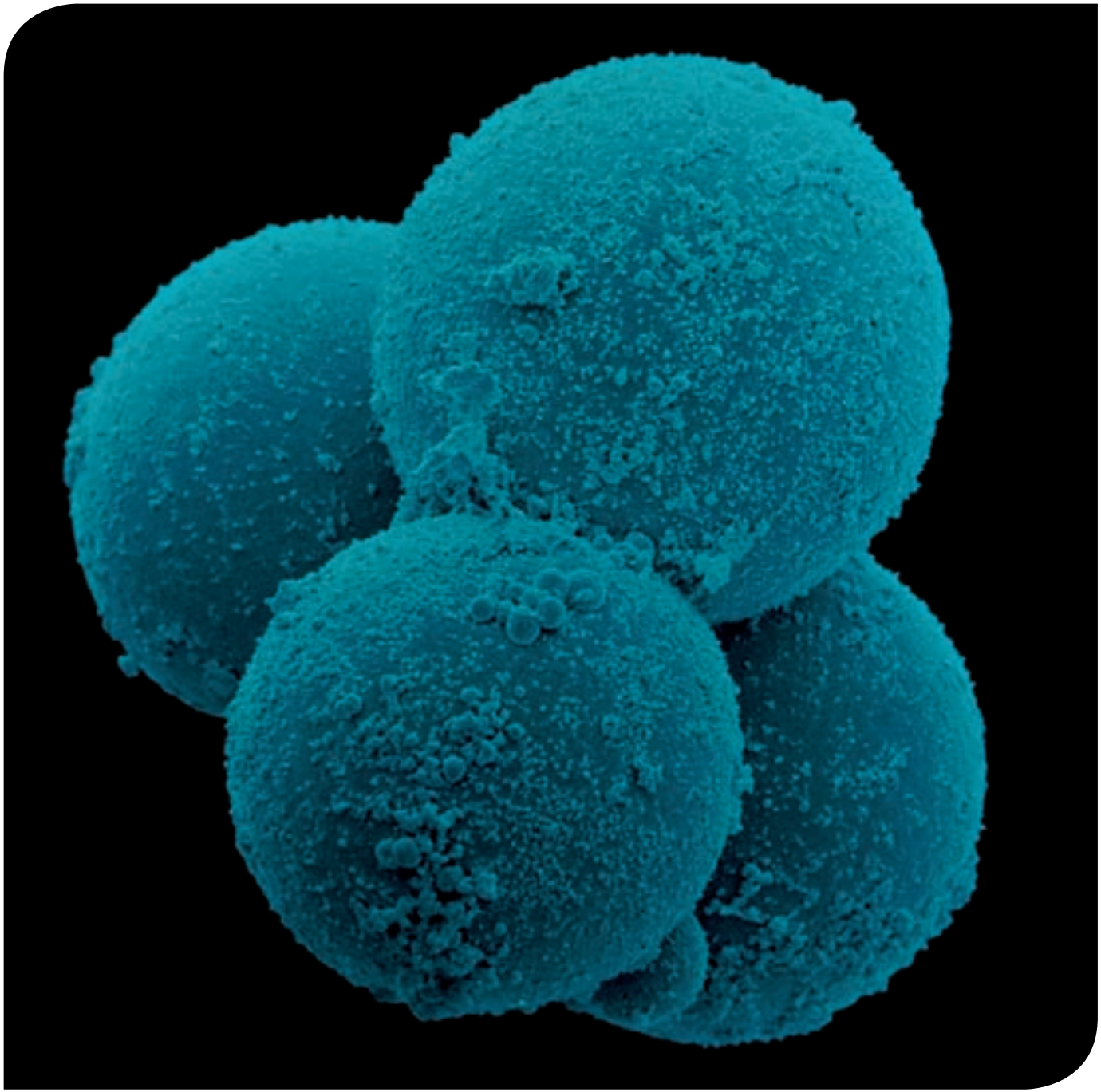
The leakiness of the epithelial barrier was assessed by measuring the electric resistance between the cells and also by monitoring the transport of sugars with a radioactive 'label' across it (these are transported poorly unless the barrier is leaky).

Feighery discovered she could open up the tight junctions with certain compounds (a fatty acid and a fungal toxin), thereby increasing the barrier's leakiness – and simulating an important aspect of IBD in the laboratory. Then she was able to show that adding MLCK inhibitors to the food side of the model could block this action. 'The compounds do inhibit myosin light chain kinase and decrease the flux of agents that go through tight junctions in this model,' says Brayden.

The work then proceeded to the *in vivo* stage where two animal models of IBD were used. One is a genetically-modified mouse called an IL-10 knock-out, the other a mouse whose bowel develops inflammation in response to ingesting dextran sugar. None of the MLCK inhibitors tested in the *in vitro* model had any effect in correcting the leaky epithelial barrier in the animal models. It is not uncommon for potential new drugs to 'fail' in this way when they move from the *in vitro* to the *in vivo* stage. Brayden suggests that the leaky gut seen in IBD is probably caused by a different mechanism than activation of MLCK – and this is why the drugs did not work in the *in vivo* disease model which is closer to the disease in man than the *in vitro* system is. It may be that these compounds could still be useful, but may need to be administered to the patient at an earlier stage.

Brayden adds that the models they developed for testing the MLCK inhibitors will be useful for testing other potential treatments for IBD. Accordingly, they have also used this approach to look at whether the probiotic *Lactobacillus salivarius* was of benefit in the two mouse models. Probiotics are preparations of 'friendly' bacteria which are said to modify the composition of the natural microbial community (known as flora) in the gut when this gets out of balance. Millions of people consume probiotic drinks in the hope that it will keep their digestive system healthy. Although some pre-clinical studies have suggested that specific probiotics might help people with IBD, Brayden and his team showed that this particular probiotic strain had no effect at all on the IBD mouse model.

"Millions of people consume probiotic drinks in the hope that it will keep their digestive system healthy."



In another part of this project, Feighery has demonstrated an interesting connection between the gut and the brain. There is evidence that victims of traumatic brain injury (TBI) from road traffic accidents sometimes experience an increased leakiness of the gut, allowing the entry of toxins and bacteria to cause septic shock and multiple organ failure. In experiments on rats being used in a study on brain disease, she discovered evidence of this gut leakiness – while other tissues looked normal. Therefore, people with TBI might benefit from being given drugs to correct any ensuing leakiness of the gut. This work will be published shortly in the Journal of Trauma. Linda Feighery received her HRB-funded PhD in 2006 on the epithelial tight junction studies.

Investigating the ulcer bacterium

Helicobacter pylori is a bacterium known to cause stomach ulcers, gastritis, gastric cancer and lymphoma. Half the world's population is infected with *H.pylori* and it has usually been present for a long time before symptoms appear. *H.pylori* is unusual in that it lives in the mucus under the stomach lining and manages to evade the immune system. 'Although we know a lot about *H.pylori* and how to get rid of it, we don't yet know how it causes ulcers,' says Professor Dermot Kelleher.

"Half the world's population is infected with *H.pylori* and it has usually been present for a long time before symptoms appear."

"When detected at an early stage, colorectal cancer is 97 per cent curable – so there is a compelling case for colorectal screening, particularly for those at high risk because of a family history of the disease."

His team has been using a high-tech proteomics approach to examine the early effects of *H.pylori* infection (within the first 24 to 48 hours) on gastric and intestinal cells, and on tissue from patients. Proteomics involves the detection, identification and analysis of proteins in cells and tissue. Proteomics technology is high-throughput, allowing researchers to work on hundreds or even thousands of proteins in parallel. It is often used to compare the patterns of protein expression in healthy and diseased tissue, thereby giving new insights into disease pathology at a molecular level.

Some bacteria, including *H.pylori*, release tiny protein-containing structures called outer membrane vesicles (OMVs) from their outer membranes. OMVs contain virulence factors (disease-causing proteins) so their analysis would be important in trying to better understand the process of infection. Kelleher's team has characterised nearly 100 proteins occurring in the *H.pylori* OMV and has selected a few of these for more detailed study. He believes the OMV proteins are disease-causing agents which hold the key to a long-standing puzzle – how *H.pylori* infects the stomach yet causes ulcers in the duodenum.

It is known that *H.pylori* causes an inflammatory immune response which is what actually makes people ill. Kelleher has found that the OMVs can trigger a similar response, independent of the intact *H.pylori* organism. They can also induce the formation of vacuole gastric epithelial cells – the cells lining the stomach – which perhaps explains how the bacterium gains access to host cells and sets the scene for further disease. Prior to this study, it was widely believed that OMVs were not a particular threat to the human host. We now know that the proteins they encapsulate are disease-causing agents in their own right. Further characterisation of these virulence factors – both inside and outside the OMV – might lead to ways of blocking or antagonising them, which could form the basis of a vaccine against *H.pylori* says Kelleher.

New screening test for colorectal cancer

Colorectal cancer is the leading cause of death from cancer in Europe. In Ireland, there are 1,800 cases of colorectal cancer each year, and around 900 deaths. Professor Colm O'Morain explains that colorectal cancer is unique in that it can be caught very early, because detectable – and treatable – pre-cancerous changes occur 10 to 20 years before the disease takes hold. When detected at an early stage, colorectal cancer is 97 per cent curable – so there is a compelling case for colorectal screening, particularly for those at high risk because of a family history of the disease. Since age is the greatest risk factor of all in colorectal cancer, there is also a strong rationale for introducing a national screening programme, as they have in the US (and is planned for the UK), for those over 55.

Colonoscopy, which involves examination of the colon and rectum for pre-cancerous changes, is the 'gold standard' for colorectal screening and has been proven to save lives. But colonoscopy is invasive and requires patient preparation, so compliance is not high. It is also a costly procedure. The alternative is the faecal occult blood test (FOBT) which detects traces of blood in the stool. Unfortunately the FOBT, while non-invasive, misses 25-50 per cent of cancers and is of less value in saving lives than colonoscopy.

O'Morain and his team have been developing a new screening test that combines the higher accuracy of colonoscopy with the non-invasive nature of FOBT. It involves measuring levels of a marker enzyme called Tumour M2-PK in stool samples. 'This enzyme is involved in the breakdown of glucose which is increased when cells turn over faster, as they do in pre-cancer and cancer,' he explains. Funding for the work has come jointly from the HRB and the manufacturers of the test.

Stool samples were taken from 162 high risk individuals; 97 of them had a normal colonoscopy, 30 had adenomas – a common type of pre-cancerous change – and 35 had colorectal cancer. Tumour M2-PK levels ranged from 0.17 to 4.2 for the first group, from 2.15 to 34 for the second, and from 3.8 to 52 for the third. In other words, there was a relationship between elevated levels of Tumour M2-PK and pre-cancer and cancer. The test was sensitive enough to detect 97 per cent of all colorectal cancers and 76 per cent of adenomas detected by colonoscopy. It also had a specificity of 98 per cent – that is, it could distinguish colorectal pre-cancer and cancer from other conditions of the colon. Therefore, the tumour M2-PK test has potential as a non-invasive colorectal cancer screening tool with high sensitivity and specificity. O'Morain envisages its use as a preliminary screen, picking out those patients who need to have a full colonoscopy examination. The next step will be to continue validating the test and find a way of automating it so it can be widely used within the Irish population.

Discovery of intestinal stem cells

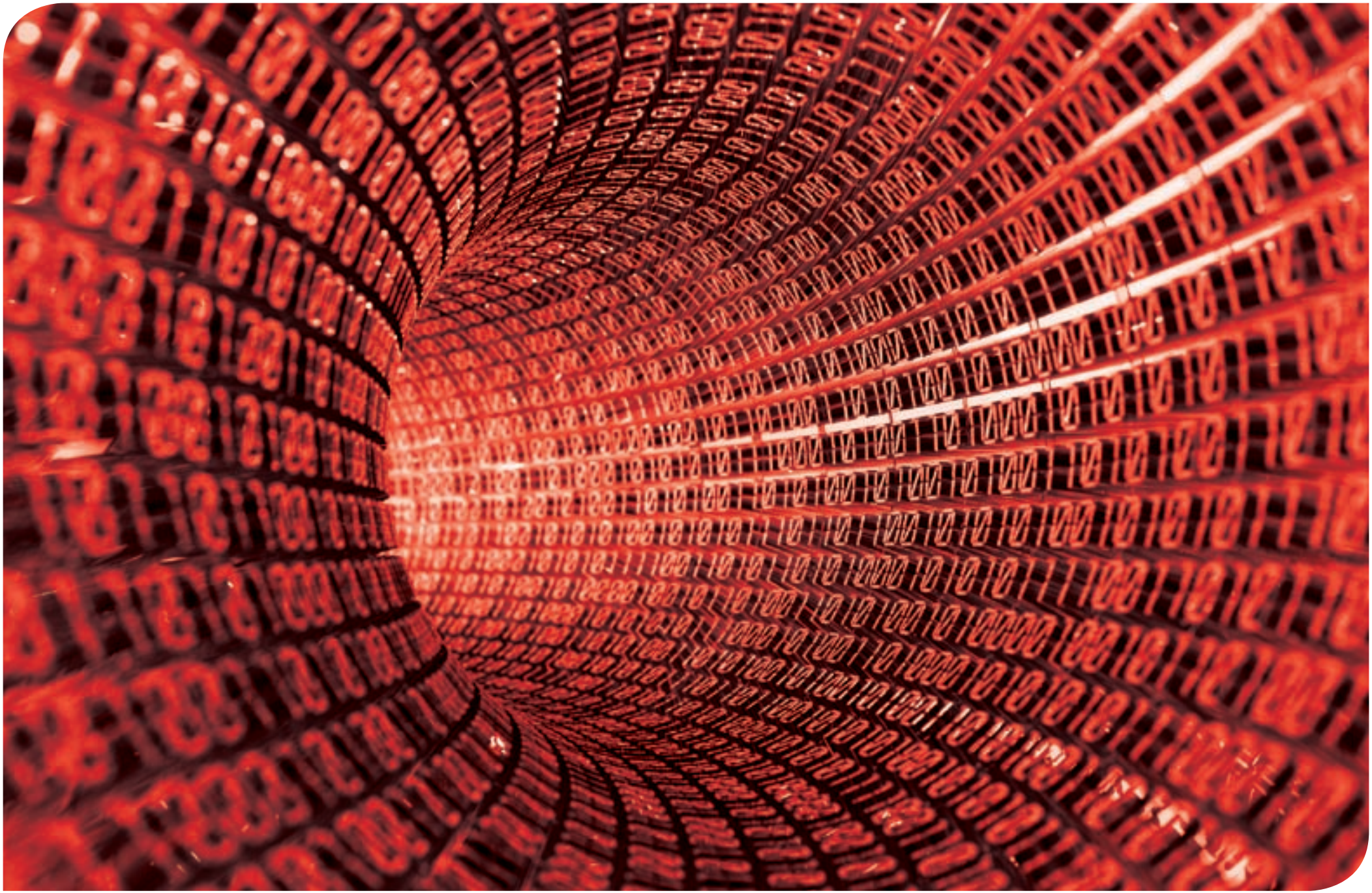
Stem cells are primitive cells which have the ability to differentiate into specific cell types, such as blood cells, skin cells and neurons. There is currently a great deal of interest in regenerative medicine, where stem cells could be used as a source of material to repair the body – in diabetes, Parkinson's disease or after a heart attack, for instance. Professor Cliona O'Farrelly has discovered a new type of stem cell in the human intestine, liver and uterus.

The immune system responds to proteins known as antigens on the surface of pathogens and other 'foreign' substances. 'The human intestine has a very complex immune system, because it needs to distinguish between food antigens and the gut flora, which are harmless, and pathogens, which are not,' explains O'Farrelly. 'We, and others, have discovered some unusual lymphoid [white blood cell] populations in the intestine which are important for this discrimination.'

The stem cells that give rise to the white blood cells that populate the immune system are known as haematopoietic stem cells (HSCs) and, mostly, they originate in the bone marrow and in the thymus. Previous work by O'Farrelly and others suggested that HSCs could also arise within the intestine itself although – as with various other reports of 'adult' stem cells - this has been seen as controversial.

Therefore the current study focused on looking for HSCs and lymphoid progenitor cells within the human intestine.

The main way of identifying stem cells involves looking for characteristic marker proteins on their surface using a technique called flow cytometry. In this case, the desired markers were known as CD34 and CD45. Five per cent of CD45 white blood cells were found to also carry the CD34 marker and so could be called HSCs. Further experiments showed how these HSCs differed from those found in the bone marrow in the other marker proteins found on their surface. They also differentiated into different types of white blood cell; in particular, they form natural killer (NK) cells, which could be important in protecting the intestine against cancer. O'Farrelly therefore sees potential application of intestinal HSCs in improving the local immune defences in the gut. 'This could be helpful in colon cancer patients, for around 50 per cent of them experience a recurrence of their tumour after surgery,' she says. She now hopes to be able to use this research to see if lymphoid cell populations are compromised in colon cancer and to see if the HSCs are capable of producing the cells that would be needed to restore the immune system in such cases.



HEALTH INFORMATICS Patient records and health data going electronic

The epilepsy patient record and Health Atlas Ireland bring the latest advances in information technology to patient care and healthcare planning

Healthcare generates massive amounts of data – prescriptions, diagnoses, scans and blood test results. This all has potential value for both patient care and research, but only if it can be organised so that useful knowledge can be extracted from it. Irish researchers are using the latest computer hardware and software to create a range of data systems to benefit patients, doctors and researchers. Two completely different projects are highlighted here – the Electronic Patient Record for patients with epilepsy, and the Health Atlas Ireland.

The epilepsy Electronic Patient Record

Epilepsy is a chronic disease whose management needs a multidisciplinary, long-term approach. The patient will typically be involved with medical, nursing, psychology, physiotherapy and administration in a variety of healthcare settings – community, primary care and specialist hospitals – during the course of their illness.

Patient records in Ireland are still largely paper-based and fragmented between different agencies, each of which has their own data. This leads to inefficiencies and unnecessary delays, which could perhaps be overcome by moving to an electronic system. Beaumont Hospital is the main specialist referral centre in Ireland for patients with epilepsy where Mary Fitzsimons, a medical physicist, and colleagues have begun to develop an epilepsy Electronic Patient Record (EPR). She explains that the arrival of a new consultant six years ago began a discussion about the management of patient data. 'We did have electronic databases on the computer but they belonged to different departments and could not 'talk' to one another. So we talked about the need to integrate what we had and this led to our interest in an electronic patient record.'

There was no system they could purchase for their requirements, so the HRB gave them a grant to develop the infrastructure necessary to create the epilepsy EPR. They bought the necessary hardware and software, and the IT department began to build the system. 'We are now in the process of introducing an electronic approach to managing patient information,' says Fitzsimons.

The web-based system is being built up on a modular basis and includes a system that can capture both generic and epilepsy-specific patient information. In its final version, it will include:-

- The main care and administrative processes in the epilepsy department for clinical, nursing, research and administration staff
- Face-to-face or remote contact with patients
- A consolidated or user-specific view of patient information
- A database for interrogation of information for clinical and research purposes

Fitzsimons lists the many potential benefits of the EPR, compared to paper:-

- Limiting access to authorized and authenticated users
- Improved quality of recorded data
- Reduction in transcription and prescription errors
- Simultaneous access by multiple users in a variety of locations
- Reduction in the number of redundant queries and diagnostic tests
- Improved availability of information at the point of care of delivery
- Easier sharing of patient information between clinicians
- A complete audit trail of all accesses to the record
- Improved security

"An EPR would mean that a patient in a rural area needing to see a specialist at Beaumont Hospital, would not have to wait for their doctor to write, because the record would automatically be shared between consultant and GP."

So, for instance, an EPR would mean that a patient in a rural area needing to see a specialist at Beaumont Hospital, would not have to wait for their doctor to write, because the record would automatically be shared between consultant and GP. Currently, they face a long path to referral because of poor communication between primary, secondary and tertiary healthcare services, maybe involving several appointments and multiple, possibly redundant, investigations. All of this wastes resources, delays diagnosis and treatment, and needlessly increases patient anxiety. Shared care, which the EPR could facilitate, would improve referral protocols, allow direct access to services, and lead to adoption of individual care plans and integrated care pathways. Moreover, epilepsy research would benefit from the EPR too, because once it is populated by patient data, investigators would find it so much easier to identify potential participants for a study.

However, the introduction of the working epilepsy EPR within the healthcare system is not without its challenges, says Fitzsimons. They are hoping to begin to implement the EPR with users at Beaumont Hospital this year and are also looking at working with neurology colleagues in Cork and Galway so that shared management of patients can gradually be introduced. 'This is a process of change,' she explains. 'We are looking at how people see the utility and

"The development of the epilepsy EPR is truly ground-breaking work."

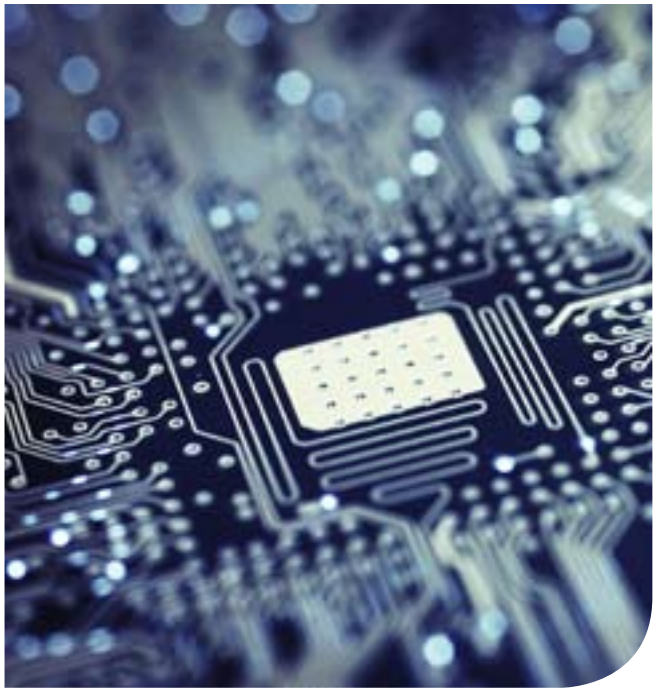
usability of the EPR, and finding out what barriers there are to implementing it in the clinical setting. Our vision is to have an EPR that can integrate patient care in Beaumont and beyond, but the implementation of this is quite detailed.'

To this end, the Beaumont team received a second HRB grant in 2006 specifically for dealing with the socio-technical aspect of their work. Entitled 'Revolutionising Chronic Disease Management with Information and Communication Technology: A socio-technical project applied to epilepsy care in Ireland', this five year R&D programme will look at the impact of the EPR on the delivery of Beaumont's out-patient and in-patient epilepsy care and research services. It will also explore what the EPR can do to improve the integration of epilepsy care services, such as community epilepsy nurses, GPs and referring physicians from regional general hospitals, as well as the patient's disease self-management. The findings of the study will be fed back to the EPR's developers so that they can put enhancements in to the system.

One big challenge for the EPR is how to integrate an e-system with paper. Currently, at Beaumont Hospital, data on medication for outpatients is very much paper-based, for instance. 'If there is some electronic data and some paper data, there is a real issue over managing both media while making a transition over to electronic,' comments Fitzsimons. 'Ultimately, what we are building must fit in with the future development of hospitals.'

And what of the patient's view? Currently, doctors at Beaumont are working with the patient advocacy group "Brainwave" to engage them with the development of a patient care pathway. This involves self-help elements such as keeping a seizure diary, which could be integrated into the EPR. Patients are certainly keen for more information to be made available to them which, again, could readily be done via the EPR.

The development of the epilepsy EPR is truly ground-breaking work. Of course, there are many healthcare databases in existence around the world. And there is a great deal of interest in the concept of the e-patient record, but projects, such as the UK's proposed Patient Identification Number in the UK are far from being fully integrated into healthcare systems. The Beaumont team has presented their work to the American Epilepsy Society and demonstrated the project to a number of experts in epilepsy care to get feedback. 'Most of them said they had nothing like this, and those who had tried something similar had run into difficulties,' comments Fitzsimons. The EPR group has also been sharing information with those involved in broadly related projects in Ireland – on haemophilia at St James's Hospital and mental health at St John of God Hospital. The hope is that the epilepsy EPR concept could be applied to other chronic diseases such as diabetes, where it also has huge potential to improve patient care and boost medical research.



Health Atlas Ireland

Data and statistics are of little use unless they are accessible and shared among those who need them. Health Atlas Ireland is a powerful tool that brings together health data from various sources, maps and statistics for the benefit of the many different stakeholders in the Irish healthcare system, including the public. The Atlas is being led by the Health Information Unit, Health Intelligence, National Population Health Directorate, Health Service Executive (HSE), and the Health Protection Surveillance Centre in partnership with University College Dublin and the National University of Ireland, Maynooth.

'We have been working on the idea for many years,' explains Howard Johnson of the Health Information Unit, Health Intelligence. 'We wanted to make useful health data locked away on our PCs available to a wider audience.' The project is multiagency, attracting support from the Department of Health and Children, the Central Statistics Office, Ordnance Survey Ireland, GeoDirectory (AnPost), the National Cancer Registry, ESRI Ireland and An Garda Síochána. 'That's to name only a few of the services and organisations that are involved,' adds Johnson. Put simply, Health Atlas Ireland integrates geographical information systems with databases and statistics.

The Atlas project won a Health Research Board grant and following the EU tendering process, development began in early 2006. It is a custom-built system using exclusively open source software (R; GRASS; PostGIS; Mapserver; Zope' PCL; Python). It is Web-enabled through a user-friendly interface. Access to the maps, data and statistics are role-based. Users do not need any special health, geographical or statistical knowledge to carry out useful work.

However, it is essential that the user understands the data and the question being addressed, and has the ability to interpret the analysis. Johnson explains. 'One session of training on Health Atlas Ireland can make you reasonably independent.' The foundations of Health Atlas Ireland have already been built and it is now being tested out in various locations and departments around the country.

Features of Health Atlas Ireland include:-

- Presentation of data as maps, tables and charts
- Zoom-in to street or house level
- Ease of use, little training required
- Support of dynamic queries at service or public level
- Scalability with ease of addition of new data
- Data protection
- Integration with An Post's GeoDirectory to show location data

"Health planning will benefit enormously, for it will be so much easier to target resources to where they are needed."

Health Atlas Ireland has many potential applications. For instance, health planning will benefit enormously, for it will be so much easier to target resources to where they are needed. Epidemiology experts will also be better able to investigate clusters of disease and outbreaks. Planning public service response to a disaster or major incident will also be aided by access to the Atlas.

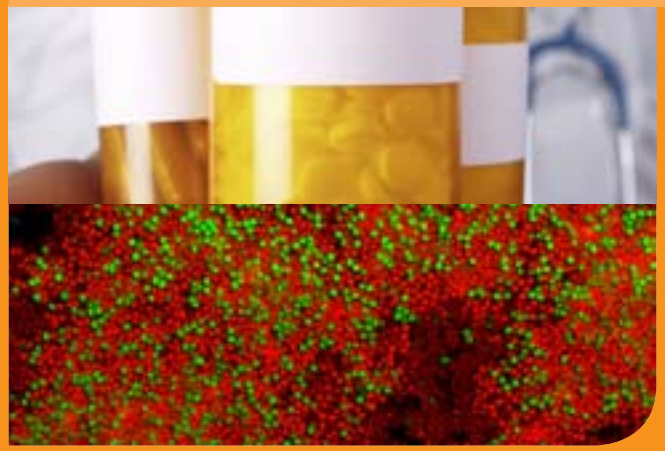
Health Atlas Ireland's wealth of data includes many different layers, such as:-

- Census datasets
- Hospital activity including diagnosis procedures
- Vaccine uptake
- Cancer statistics
- Road collision data
- Births and deaths
- Perinatal data
- Ordnance Survey Ireland data, including aerial photography
- Radiological Protection Institute Ireland maps
- Local Authority water distribution maps

The datasets in the Atlas will be updated indefinitely on an iterative basis and new applications will come on stream as the project continues to evolve.

Health Atlas Ireland is flexible and scalable in terms of data, statistics and geography. It is hoped to include an All-Island dimension, and the open source architecture will encourage its use in developing countries.

IN SHORT…



This section describes briefly, project findings from research into a variety of health-related research topics including children's dental health, safer medical devices, heart disease and cancer.

Safer medical devices

Hospital-acquired infections (HAI) often lead to complications and may even prove fatal to patients. HAI's are often associated with the formation of persistent layers of bacteria known as biofilms on the surface of medical devices, such as catheters.

In a joint all-island project, Dr Kevin McGuigan of the Department of Physiology and Medical Physics at the Royal College of Surgeons in Ireland, has been investigating how such biofilms can be removed by using a photocatalytic coating. Collaborators at the University of Ulster have developed microsensors based upon a technology called electrical impedance spectroscopy which can detect the growth of a biofilm on the surface of a medical device. They also produced inert, stable, non-toxic and biocompatible coatings of photocatalytic titanium oxide thin films. McGuigan's part has been to show, using fluorescence staining and confocal microscopy, that biofilms on such coatings are rapidly killed off by exposure to ultraviolet light.

The next step is to develop the coatings for device surfaces that are commonly used in the hospital – such as the plastic from which catheters are made. Ultimately, this research could bring a 'sense and destroy' system for the rapid detection and inactivation of biofilms on medical devices onto wards, thereby greatly improving patient safety.

Understanding cancer drug resistance

One of the main reasons why cancer treatment sometimes fails is that cancer cells become resistant to the drugs that target them. Multidrug resistance (MDR) is a particular problem, with cells that are exposed to one anti-cancer drug developing resistance to others, even if they are different in structure and mode of action.

Dr Katrina Comerford of the School of Medicine and Medical Science, University College Dublin, has been looking at the molecular pathways underlying MDR.

P-glycoprotein (P-gp) which is encoded by the MDR gene is embedded in the cell membrane and acts as a pump, transporting the drug out of the cell. When a tumour grows, it outgrows the local blood supply, creating a condition of low oxygen concentration known as hypoxia. Comerford and colleagues previously showed a link between hypoxia and the increased expression of MDR via the activation of a transcription factor – a gene that turns on another gene – called hypoxia inducible factor-1 (HIF-1). They have gone on to show a role for two other molecules, called JNK MAP kinase and c-Jun, another transcription factor, in the MDR pathway. These findings open up the possibility of developing new drugs which could inhibit hypoxia induced MDR. Such agents could be administered alongside chemotherapy to overcome resistance, thereby increasing the chances of success in cancer treatment.

The role of ADAMs in breast cancer

Some breast cancers are more aggressive than others, and there is a lot of interest in devising tests which reveal the tumours that are most likely to spread and metastasise. Professor Joe Duffy of the Department of Nuclear Medicine, St Vincent's University Hospital, has been looking at a protein called ADAM-17 which appears to be involved in breast cancer expansion, invasion, and metastasis.

Molecular biology studies show that there are two forms of ADAM-17 – a precursor and an active form. The proportion of active form to total ADAM-17 increases progressively from normal breast tissue to primary breast cancer to lymph node metastases, according to analyses done on stored breast biopsy tissue. In primary cancers, active ADAM-17 is found more frequently in node-positive compared to node-negative tumours. These findings suggest that ADAM-17 is indeed involved in breast cancer spread. Measuring levels of ADAM-17 might therefore help identify those women with an aggressive breast cancer who can benefit from more intensive treatment, while sparing those who do not need it.

Women's experience of fetal abnormality

Ultrasound examination in pregnancy is now routine and is seen by women as the first chance to 'meet their baby'. But one in 50 babies will be born with an abnormality, many of which are detected during the scan. Most women are completely unprepared for this news and healthcare professionals need some kind of structured framework within which they can help them cope with their responses.

Accordingly, Dr Joan Lalor, Lecturer in Midwifery at Trinity College Dublin, has carried out a study of women's experience of carrying a child with fetal abnormality. She interviewed 38 women in this situation, 30 of whom chose to continue with the pregnancy.

The findings led to a theory called 'Recasting Hope' which describes the adaptation process a woman goes through associated with the loss of the 'perfect child' she assumed she was carrying. As a woman tries to cope with the shock of hearing that her baby has an abnormality, she may either 'blank out' or 'seek' as much information as possible in order to face what is ahead. She then tries to make sense of what this means for the outcome of her pregnancy and, finally, will go on to try and rebuild her future with (or without) her baby. The time taken to pass through these stages cannot be predicted and nor does it depend on whether the abnormality is mild, lethal or anywhere on a continuum in between.

So now, for the first time, healthcare professionals have a theory of adaptation to fetal abnormality which they can use to plan an integrated care pathway to support these women. This is already being put into practice in at least one centre and Lalor is trying to get her findings out to as many practitioners as possible. She is also planning a follow up study to see how the women fare in the long term, paying particular attention to how their experience of fetal abnormality affects their feelings about a future pregnancy.

Understanding cancer cell immortality

Unlike healthy cells, the cancer cell tends to be resistant to apoptosis, a type of cell death (sometimes called 'cell suicide'), which can make some cancers very hard to treat. Dr Kenneth Nally of the Department of Medicine, Cork University Hospital, has been investigating an important, and poorly understood, molecular pathway related to cancer cell apoptosis.

Two key immune system molecules – the cytokines known as interferon-gamma (IFN-γ) and tumour necrosis factor-alpha (TNF-α) – can kill off cancer cells when acting together, but may have opposing effects on tumours when used separately. IFN-γ is a tumour suppressor, while TNF-α either kills cells, or promotes their survival, depending on context. TNF-α works on cells via a molecular information processing system called the IKKβ/NF-κB signalling pathway which is where Nally's research is focused. The pathway exerts a powerful influence over whether a cell lives or dies, because it can turn specific genes on or off.

In general, activation of this pathway turns on pro-inflammatory and pro-survival genes. Hence, inappropriate activation of this pathway plays a role in chronic inflammation and tumour progression, which is why inhibiting it, has been suggested as a strategy for treating both diseases. Nally has been looking at this mechanism as a way of making colon cancer cells more sensitive to apoptosis. Their findings are novel and even counter-intuitive. It turns out that the two cytokines kill through the pathway's activation of three specific and potent killer genes which are usually turned on by the tumour suppressor gene p53 (found to be inactivated in most cancers, including the colon cancers used in this research). Usually, IKKβ/NF-κB has been found to turn on survival genes, enabling cells to live. Nally's findings have important implications – if this pathway can sometimes act like a tumour suppressor, then attempting to turn it off in the treatment of inflammation and cancer, as has been proposed, may require a more cautious approach.

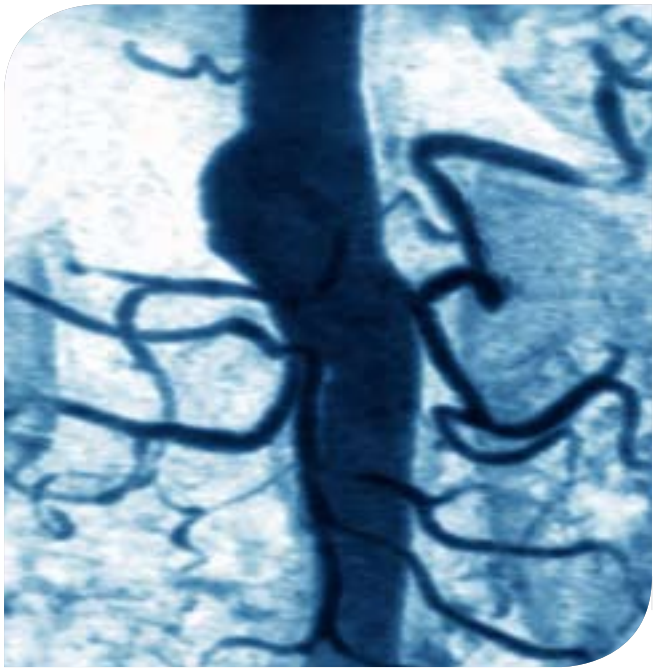
Spotlight on children's dental health

Children need more help in taking care of their teeth and gums, according to researcher Evelyn Crowley of University College Cork. In 1997, the then Mid-Western Health Board carried out dental examinations on 608 twelve-year olds and found that 37 per cent had no decay, fillings or missing permanent teeth. By 2002/3, when the survey was repeated on 173 of the original group (now aged 18 years of age), the number had fallen to 18 per cent, indicating a worsening of the children's oral health. In the interval between the two exams, around two more teeth were affected by decay, with the average 18 year old presenting with an average of four bad teeth. Children whose teeth had some decay in 1997 were more likely than children with no decay at that time to experience further decay of their teeth.

But tooth decay is preventable through restriction of sugary foods and drinks, application of protective coatings to the teeth, and the use of fluoride-containing toothpastes, water, or mouthwashes. The findings suggest that the oral health of children and young adults in Ireland would benefit if services were more focused on prevention.

Markers for chronic lymphocytic leukaemia

Chronic lymphocytic leukaemia (CLL) is the most common form of leukaemia, and it is found mainly among older people. It is a complex disease – ranging in severity from mild to life-threatening. Dr Amjad Hayat, of the Department of Molecular Medicine, St James's Hospital, has been investigating a number of clinical and molecular markers which could help identify the higher risk patient in need of more aggressive, or even experimental, therapy. Working with a group of 106 CLL patients ranging in age from 37 to 90, he focused on the occurrence of cytogenetic (chromosomal) abnormalities, mutations within the gene for the heavy chain of the immunoglobulin molecule and levels of two proteins called CD38 and ZAP-70. Their findings suggest that it would be worthwhile including measures of CD38 expression and cytogenetic abnormality during the routine assessment of patients with CLL. Meanwhile, analysis of the immunoglobulin heavy chain gene for mutations could be considered when assessing patients who are eligible for experimental therapy.



Predicting aneurysm rupture

Abdominal aortic aneurysm (AAA) is an unpredictable and potentially dangerous condition caused by a weakness in the wall of the body's main artery, causing it to balloon outwards. Commonly AAA causes no symptoms, but the aneurysm may rupture without warning, which is fatal in 90 per cent of cases.

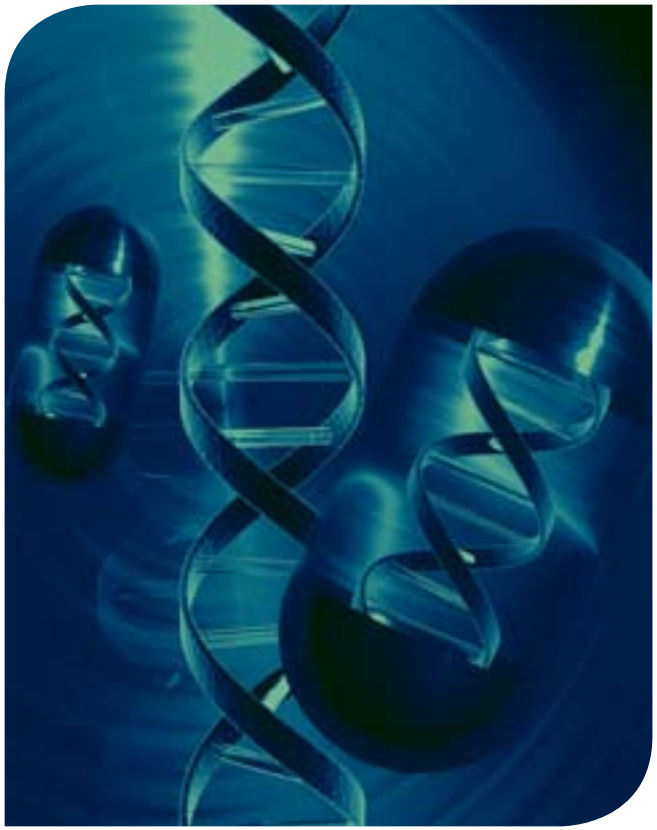
The presence of clotting, known as intraluminal thrombus (ILT), within the aneurysm is a known risk factor for AAA rupture because it further weakens the artery wall. Dr Malachy O'Rourke and PhD student James McCullough of the Department of Mechanical Engineering, University College Dublin, are exploring the relationship between blood flow in the artery and the presence and progression of ILT. He uses techniques called Flow Visualisation and Laser Doppler Velocimetry together with Computational Fluid Dynamics, which is a numerical approach, to model blood flow under physiological conditions.

Observation of the nature and movement of the vortices formed in both ideal and patient-based models of blood flow is leading to new insights into the dynamics of AAA which could help identify those patients at risk of rupture.

Gene therapy for atherosclerosis

Heart disease is characterised by a pathological process called atherosclerosis which involves the build up of fatty deposits in the arteries. Cholesterol plays an important role in atherosclerosis, with high density lipoprotein (HDL) and low density lipoprotein (LDL) having opposing effects. HDL protects by transporting excess cholesterol out of the system and preventing the oxidation of LDL, which otherwise contributes to the fatty deposits.

Professor Tim O'Brien and Dr Aideen O'Doherty of the National University of Ireland, Galway, are researching an enzyme called paroxonase 1 (PON1), an important component of HDL which is thought to have antioxidant effects. PON1 seems to stabilise HDL and enhance its protective effects. They have tried to utilise this effect by transferring the PON1 gene to a mouse model of atherosclerosis. These animals are genetically-modified to develop large atherosclerotic lesions. Analysis five weeks after gene transfer, revealed that there was an almost three fold reduction in lesion size in those mice who had received PON1, compared to those receiving control gene therapy.



The benefits were, however, short-lived; six months after the experiment there were no differences between PON1-treated and control mice. The short duration arises from the type of gene therapy vector used, and it may be that either alternative vector systems, or repeat administration, will be necessary to get a longer-lasting effect. Further gene therapy experiments will show how PON1 can best be administered to treat atherosclerosis. The findings so far are promising, though, suggesting that PON1 could be a good target for new therapies to protect against heart disease.

The nose in allergic rhinitis

Allergic rhinitis, with its sneezing, runny nose and streaming eyes, can be a misery for some. The condition is not fully understood, but stimulation of the nerves in the nose by histamine, a chemical which is released in response to allergen exposure, is thought to lead to symptoms.

Dr Richard Costello, of Beaumont Hospital, has carried out tests on patients which confirm this phenomenon, known as nerve hyper-responsiveness. His previous work, in animals and patients, showed how blood cells called eosinophils move to the site of the allergic reaction and bind to nerves in the area. This causes a problem because they release a protein called major basic protein that binds to a receptor protein, M2, on the nerve, causing it to malfunction. Usually, M2 helps maintain normal nerve function but, under these conditions, it makes the nerve hyperresponsive.

What is new about Costello's work is that he has found that this all leads to long term change in the nose. In particular, eosinophil localisation leads to a long term change in the nerves, so that the nerves are more susceptible to irritation from a variety of stimuli like changes in the weather, dust sprays and cigarette smoke. This finding may lead to new and better understanding of this chronic condition.

How cochlear implants affect speech perception

Children fitted with cochlear implants may find it hard to hear changes in the pitch of voices. Pitch gives speech its melody and, along with changes in loudness and the length of syllables, contributes to the prosodic patterns that convey meaning – particularly when it comes to new information or key words. Rosemary O'Halpin, of the Cochlear Implant Programme, has studied how children with implants use pitch, loudness and duration in their hearing and production of prosody.

When listening to artificially-generated speech, most of the children could not hear pitch changes of less than half an octave – a level of change which is significant in prosody. However, some of them could still identify significant words in normal speech using prosody. Maybe, therefore, children with cochlear implants do not rely on pitch cues in their perception of prosody, turning instead to syllable and word duration. Since important aspects of prosody are conveyed by pitch, in English, children with cochlear implants might be disadvantaged during the early stages of language acquisition. These findings should inform the type of speech production and perception training they receive.

WATCH THIS SPACE

A major initiative was launched by the HRB in 2001 with the announcement of a €12.7 million dedicated investment in five-year research programmes across the full spectrum of health research. Successful researchers from the clinical and biomedical sciences were asked to address the translation of advances in basic biomedical sciences into research that will benefit patients. Researchers in health services, epidemiology, public health and primary care, were asked to address issues of relevance to health policy and health services in Ireland. And, for the first time in Ireland, funding was made available for a dedicated research programme in nursing and midwifery research. These programme grants are nearing completion and this section gives us a taste of the research conducted under these awards – to get a full flavour of the findings you will have to read next year's "*Picture of Health*"!

The DNA damage checkpoint and cancer

The human DNA damage-dependent checkpoint pathway is believed to function as a tumour suppressor pathway. In fact, because of its role in the maintenance of genome integrity, mutation of this pathway may be an early step in oncogenesis for some types of tumours. Professor Noel Lowndes, NUI Galway, and his team are working to learn more about this pathway that will therefore be important for a complete understanding of the oncogenic process. This will lead to both better diagnosis of cancer type and possibly to the isolation of therapeutically important drugs tailored to specific tumours.

A functional and computational genomics strategy to identify novel mechanisms of injury and therapeutic targets in diabetic nephropathy

Approximately 33 per cent of diabetes patients will develop diabetic nephropathy (DN) and it is now one of the leading causes of end stage renal failure requiring dialysis or transplantation in western society. It is a significant cause of morbidity and mortality in Irish society and a major consumer of fiscal resources in the Irish health service.

Research on the management of diabetic complications has highlighted the potential for multidisciplinary research to elucidate new drug targets and suggest novel therapeutic strategies. That is why Professor Finian Martin, UCD, and his team are seeking to shed new light on the genetics, pathogenesis and treatment of both renal and extra-renal diabetic complications in a bid to stem the rising tide of diabetes-related morbidity and mortality.

The provision and use of health services, health inequalities, and health and social gain

How can the Irish health services be improved so that care can be delivered more efficiently, effectively and equitably to patients? What are the factors producing marked differences across population groups in the incidence of disease, disability and premature mortality? What are the potential supports that will improve the quality of life for both the general population and those experiencing illness and disability? As a result of HRB-funded research, Professor Brian Nolan and his team at the ESRI have recently published a report that attempts to answer some of these questions.

Mechanisms of action and therapeutic potential of lipoxins in renal disease

Inflammatory diseases such as arthritis, pneumonitis, glomerulonephritis and inflammatory bowel disease cause significant morbidity and mortality in the community and in the clinic. If inflammatory diseases are to be treated effectively it is imperative that biomedical researchers develop new therapeutic strategies as a matter of urgency. Hence, scientists at UCD led by Prof Catherine Godson, are currently exploring the mechanisms subserving the bioactions of Lipoxins, which have been proposed to act as "braking signals" for inflammatory processes. The research team hope that the data generated from these studies may open a new avenue that will, in part, facilitate the development of novel anti-inflammatory and anti-fibrotic therapeutic strategies.

The benefits and risks of fluoride on the island of Ireland

Fluoridation of water supplies in Ireland has been the subject of debate for over 50 years. Today, approximately 73 per cent of the Irish population reside in communities with fluoridated water supplies. Although, fluoride toothpastes were introduced to the Republic of Ireland (RoI) and to Northern Ireland (NI) at the same time in 1970, the public water supplies of NI are still not fluoridated. Professor Denis O' Mullane, and his team are quantifying the benefits and risks of fluoride to dental health and to a specific aspect of general health, osteoporosis, making use of the clear difference that exists between the RoI and NI in exposure of the public to fluoride. The implications of the research findings will inform the debate currently taking place.

Characterisation Hepatitis C induced immunological subversion and its implications for treatment response

There has been an explosion in our knowledge of the hepatitis C virus and our ability to treat hepatitis caused by this infectious agent. There is a growing need for the development of new diagnostic and prognostic tests. A team of Immunologists, led by Professor Cliona O'Farrelly, are currently using DNA Microarray Technology to identify genetic signatures, for patients who respond/don't respond to standard drug therapy. They are hopeful that, one day, this approach will allow the prediction of responders/non-responders to standard treatment, thus avoiding unnecessary suffering for patients who are unlikely to respond.

Nursing decision making: An integrated programme of research to maximise the effectiveness of clinical nursing resources

Professor Anne Scott, DCU and her team have been looking at a quantitative Minimum Data Set for Ireland that will describe patient problems, nursing activities, interventions and patient outcomes through the use of this data set in mental health and general nurse settings. It aims to provide insight in to how organisational and interpersonal factors contribute to the nursing decision making process and will identify how effective clinical decision making can be promoted.

Programme on cell regulation by cyclooxygenases: novel therapeutic targets in cancer and inflammation

Led by Professor Des Fitzgerald, UCD, this research programme brings together many researchers with diverse backgrounds with the aim of integrating basic and clinical research, from X-ray crystallography to human studies, bringing modern technologies to bear on several conditions where proinflammatory prostaglandins (PG's) play a role, such as inflammatory bowel disease (IBD), colon cancer and arthritis. It also looks at how PG's may affect the heart.

Toward therapeutic intervention at the genetic level in degenerative diseases of the retina

Retinitis Pigmentosa is the most prevalent cause of registered blindness among those of working age in Ireland. The purpose of this programme is to expand on existing knowledge around the aetiology of this disease. Professor Peter Humphries, TCD, and his team aim to develop therapeutics, targeting primary disease mechanisms and secondary mechanisms of neuronal cell death that will be applicable to a broad sector of the patient population.

Host-bacterial interactions within the gut in health and disease

The intestinal flora account for 1-2 kg of human body weight and consists of over 400 different species of bacteria. Some of these bacteria are beneficial and help humans digest food, alleviate disease, and regulate fat storage. A multidisciplinary team of scientists, led by Professor Fergus Shanahan at UCC, are currently developing a detailed picture of how these gut bacteria interact with the host at the molecular level. One approach involves using germ-free animals to determine the host response to putative probiotics. The outcomes of this research will help to tackle an unexplored area that is of relevance to a range of intestinal (for e.g. IBD, Crohn's disease and colon cancer) and extra-intestinal disorders such as atopic asthma and eczema.

All-Ireland Transfusion Research Network

The increased demand, diminished supply of donor blood and demographic changes in the population has put the blood supply in the North of Ireland and especially in the South of Ireland in grave danger. Despite these setbacks, it is imperative that a safe and secure blood supply is maintained. Dr Anthony Staines and his colleagues are currently addressing these concerns by establishing an All-Ireland Transfusion Research Network. This Network will link clinicians, blood bank staff, assist with audit of practice, develop new instruments with which to monitor activity, and improve blood stock and supply management.

Ageing, Health and Healthcare: Maximising quality at the interface between individuals and the healthcare system

Older people are the main users of health and social care services. With an expanding older population, generic research on ageing, as distinct from research on separate specific diseases most associated with older people, is essential for planning and delivering health and social services. It is also crucial to develop a broader scientific understanding of the ageing process. A programme led by Professor Hannah McGee, RCSI, seeks to simultaneously inform science and practice relevant to ageing and to build capacity in this important domain for the future through the Irish setting.

Secondary prevention of heart disease in general practice: a randomised controlled trial with qualitative, economic and policy analyses of an intervention to produce improved and sustained outcomes

The optimal method of delivery of secondary cardiac care in general practice was not yet identified when Professor Andrew Murphy and his team at NUI Galway commenced work on their HRB funded research programme. They are contributing to the identification of such an approach in a health care system without universal access to primary care or universal patient registration. The findings from this programme grant will be generalisable to the management of other chronic diseases in the community, such as diabetes. The study will also improve health professionals' understanding of secondary prevention of coronary heart disease and of patients' perspectives in respect of its management, taking account of aspects of their quality of life.

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