A SELECTION OF IRISH HEALTH RESEARCH 2006

FEATURING

Confronting cystic fibrosis
Easing the burden of diabetes
The price of better health
Brainwaves
Affairs of the heart
Tackling cancer

A PICTURE OF HEALTH

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A Selection of Irish Health Research 2006

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A PICTURE OF HEALTH

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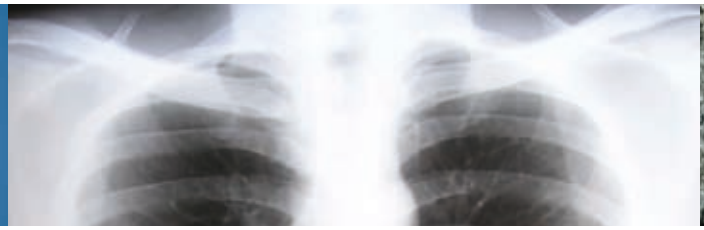
RESEARCH TO EASE YOUR BREATHING

An Irish team has helped identify two new promising drugs for chronic lung disease.

Too much of a good thing is bad for you, the old saying warns. And that is especially true of mucus.

We need the secretion to lubricate our airways, among other functions, but produce too much and it can kill you. This is what happens in cystic fibrosis (CF), for instance, when the airways become clogged and prone to recurring infections.

There is currently no way to stop excessive mucus production, and the best that can be offered is something to treat the complications. So, people with CF take antibiotics to fight the frequent infections, while people with chronic bronchitis typically use asthma drugs to ease their airways.

But now, two new drugs are showing considerable promise for people plagued by excess mucus. The developments are thanks in part to HRB-funded research led by respiratory consultant Prof Gerry McElvaney of Beaumont Hospital and the Royal College of Surgeons in Ireland.

Talk to him about it, and you can hear the excitement in his voice. “This is looking very promising, not just for cystic fibrosis, but other chronic lung diseases. And we have two avenues of approach, so I’m very hopeful.”

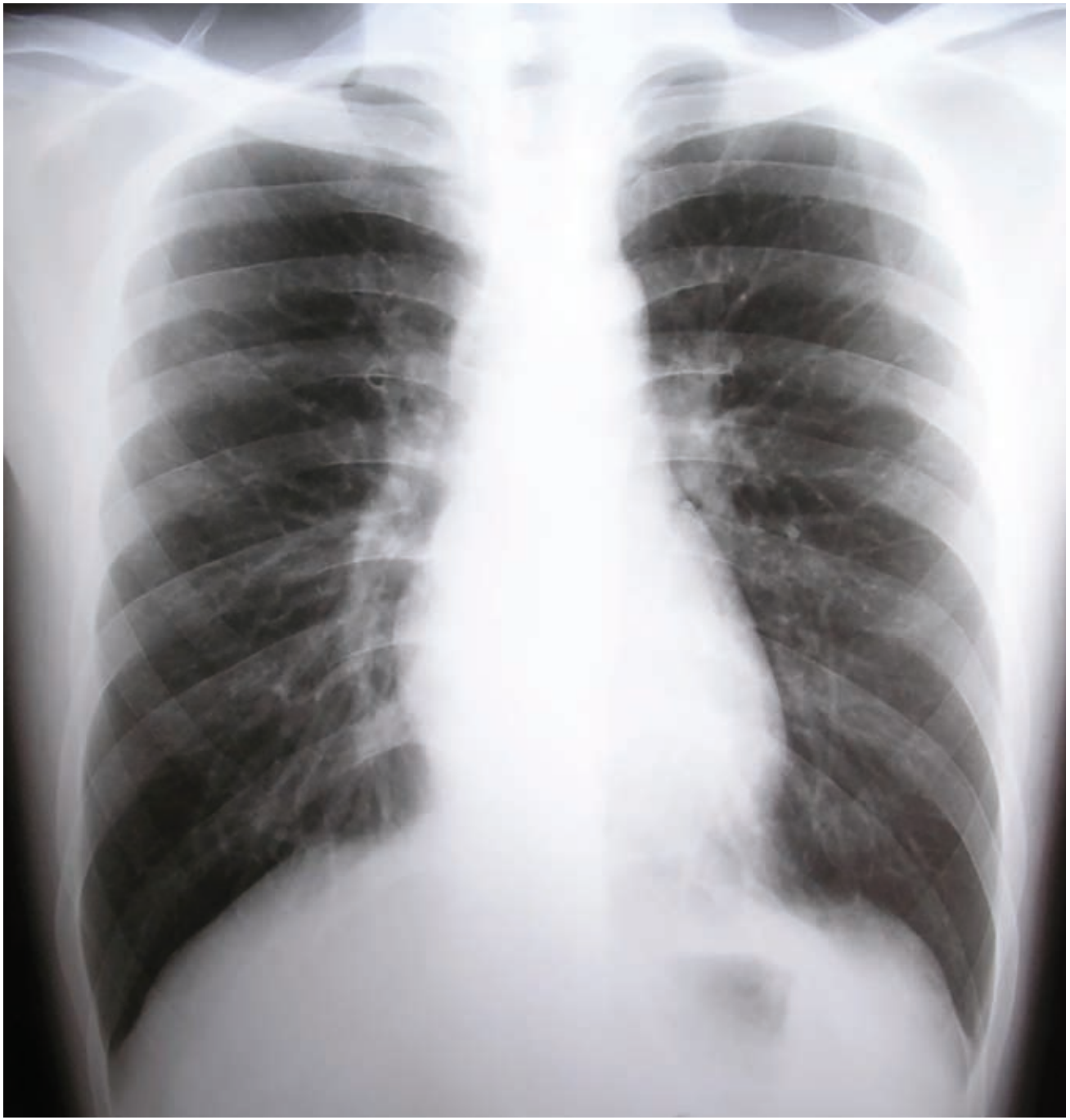
Making mucus

Mucus production is a complex process, involving many signals, receptors and pathways. Scientists have now pieced together much of the biochemical detail including, for instance, the involvement of an ion channel protein, known by the handy name of hCLCA1, and something called the epithelial growth factor receptor, or EGFR, which intriguingly, also plays a role in cancer.

Prof McElvaney's team has added considerably to our knowledge of both proteins and their role in CF and mucus production. First, the ion channel protein story.

McElvaney showed that this hCLCA1 protein is more active in the airways of people with CF than in healthy people. Next, his team identified several chemicals that block this hyperactivity in CF patients, including an established anti-inflammatory drug, talniflumate. Researchers elsewhere have shown this drug also works in other chronic lung conditions.

Talniflumate is one of the non-steroidal anti-inflammatory drugs (NSAIDs), a group that includes aspirin and ibuprofen, but it also exhibits other actions including effects on mucin production. Discovered over 20 years ago by an Argentine pharmaceutical company, it has long been approved for use around the world.



> **In the past, the best we could do was treat the symptoms and the complications of chronic lung disease. Now it looks like we may soon be able to treat the root cause.**

A US biopharmaceutical company, Genaera Corporation (www.genaera.com) has now licensed the drug for use in lung conditions, and rebranded it as Lomucin. Being well established, the drug has moved quickly to clinical trials, with Ireland leading the way in the cystic fibrosis trials.

"We did a safety study of talniflumate with CF patients here in 2005. That led to the phase II clinical trial that began earlier this year [2006], where we're looking now at efficacy, but also safety, again in CF patients", Prof McElvaney explains. A second CF clinical trial should start in Germany in late 2006.

It's not the first time an anti-inflammatory drug has been tested in cystic fibrosis. "A few years ago, we thought NSAIDs were the 'next big thing', but there were difficulties with ensuring appropriate dosing and they never became widely used", McElvaney explains.

However, so far they have seen no serious issues with talniflumate. It will be 2007 at the earliest before the results are available, but he is hopeful that at last they might have a drug to reduce mucus production in CF patients. Meanwhile, he is also pursuing a second avenue: the EGFR protein. McElvaney's team has recently shown that, if you stimulate this protein in the lungs of someone who has cystic fibrosis, you increase mucus production. The team then teased out the biochemical signals involved, which allowed them to identify chemicals to block the mucus signals. Among these inhibitors are some drugs previously known from cancer research, and a number of pharmaceutical companies are now interested in this aspect of Prof McElvaney's work.

Cancer drugs often have serious side effects, so McElvaney has helped refine the drug designs, making them more effective at reducing mucus production and less toxic.

He now expects to start a clinical trial in early 2007, probably jointly with a California group, and probably with chronic bronchitis patients, though he says the approach could yet prove useful in CF and perhaps even asthma.

"In the past, the best we could do was treat the symptoms and the complications of chronic lung disease. Now it looks like we may soon be able to treat the root cause." The two new approaches are still in development, and they are not a cure. But Gerry McElvaney sounds understandably hopeful.

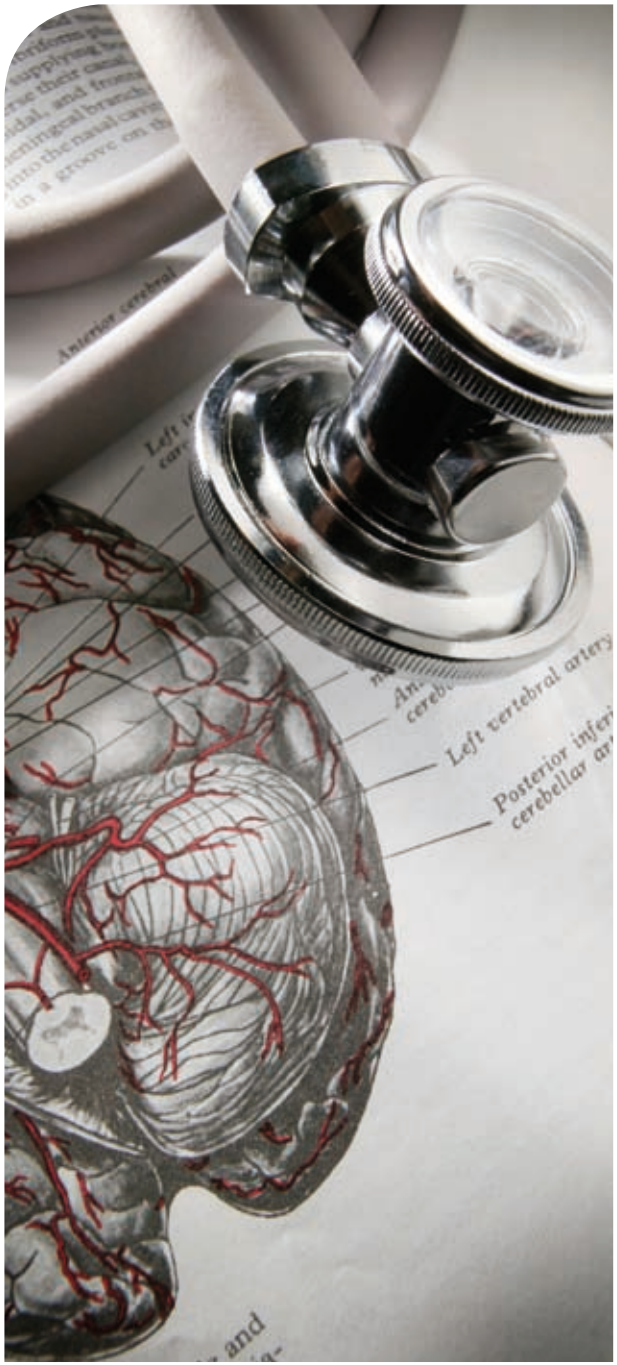
Prof McElvaney thanks the cystic fibrosis patients who are taking part in the clinical trials. The trials are funded by Genaera Corporation and run in conjunction with the CF Foundation (North America).

NO help for inflamed lungs?

IN OTHER research, scientists at UCD are looking for ways to undo the damaging inflammation that can follow a lung infection. And they've had initial success with two very different approaches: a dietary supplement, and gene therapy.

Diseased lungs – whether damaged by asthma, cystic fibrosis, or even smoking – are vulnerable to infection. When infection hits, the immune system floods the lungs with killer immune cells and molecules. The resulting inflammation is a two-edged sword, however: it may see off the infection, but damage lung tissue in the process. So Prof Paul McLoughlin, at UCD's College of Life Sciences, wants to limit, or even undo, the damage caused by inflammation.

Nitric oxide gas (chemical symbol: NO), is essential for normal lung function, McLoughlin says.



"Previously, we've shown that diseased lungs have less nitric oxide than normal. So we are looking at ways to increase the levels in damaged lungs."

Working with laboratory rats that have a long-standing lung infection, they first tried a dietary supplement, arginine, which increases NO production. "We saw a positive effect, and it did prevent some damage, but we think we can achieve more."

Hence the more radical approach of gene therapy, to give lung cells an extra gene for making NO. "We use a harmless virus that was engineered in Prof Tim O'Brien's laboratory in NUI Galway to contain the gene for a nitric oxide enzyme."

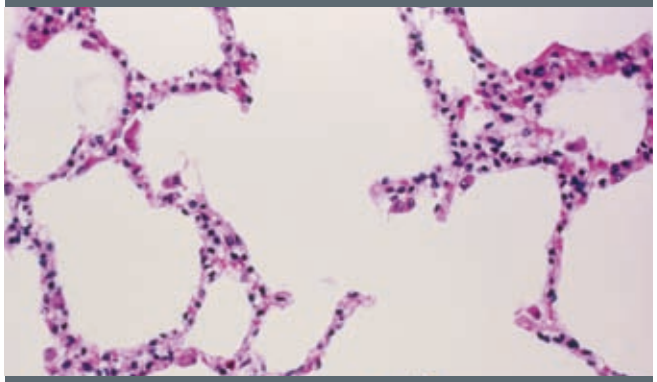
Preliminary gene therapy trials for cystic fibrosis in the past were not effective. This is because, to correct the genetic defect in cystic fibrosis, you need to transform a large number of the target cells, and keep repeating the treatment because the cells are regularly shed.

"Our idea is very different. Nitric oxide is permeable, so we may need to transform only a small number of cells. And this could be very long-lived cells, so you wouldn't need frequent treatments."

Results to date in the laboratory are promising. McLoughlin adds that, as so often in science, progress is slower than they had hoped. But watch this space. ■

↘ CYSTIC FIBROSIS IN IRELAND

Cystic fibrosis is an inherited condition affecting about 40 children born here each year.



A tiny misprint in one gene means the transport of sodium and chloride ions in and out of certain cells is faulty. As a result the glands that produce mucus, saliva and intestinal fluids do not work properly. People with CF typically have thick, sticky mucus. This affects their breathing, and digestive and reproductive tracts, leaving them prone to recurring infections that can be life-threatening.

A new Irish online register of people with CF (www.cfairegistry.org) has already registered over 1,000 people. For more information contact the Cystic Fibrosis Association of Ireland (www.cfireland.ie).

EASING THE BURDEN OF DIABETES




New Irish research shows that diabetes can cause anxiety and depression, but it's also possible to control the condition without losing quality of life.

Diabetes. It's just one word, but for many people it can seem like a long sentence – a life sentence, that leaves them hostage to their blood sugar levels, obliged to watch their diet and alcohol intake, and generally curtail their social life, to say nothing of the endless round of visits to hospital specialists, with all the travelling and waiting that entails.

At least, that's the general perception. Yet new research from UCC shows that it doesn't have to be like that. Organising care at local GP, rather than hospital level can enable most people with diabetes to take control of their illness, and receive appropriate care without compromising their quality of life.

Indeed, the 'quality of care' in one GP-led, or primary care scheme was at least as good as that achieved by a conventional hospital-led scheme. What's more, the primary care approach empowers patients and their GPs, and suggests an effective way forward for managing this large and growing health problem.

If there is one good thing about diabetes, it is that, unlike most other diseases, control of the condition rests with the person themselves. Maintain a healthy diet, take regular exercise, follow any prescribed courses of medication, and you should be able to prevent any complications. That means you need to fully understand your condition, and work with your diabetes care team.

But being in control of your own condition can also be a downside. Not everyone copes as well as others, especially as being diagnosed with a chronic condition like this brings its own stresses and anxieties.

Then there is the question of how best to organise the country's diabetes care teams, which because of the disease complications, can include a wide range of medical specialists, from cardiac, kidney and eye consultants, to dieticians and chiropodists. It's a question that raises long-term resource issues for health managers, and quality of life implications for patients.

New survey

At UCC, public health expert Prof Ivan Perry was concerned about the quality of life and psychological well-being of diabetes patients. "Not enough is known about this. But it's natural to think there might be some trade-off: that if someone is trying to achieve the 'gold standard' in controlling their blood sugar levels, it's probably at the cost of freedom in their everyday life."

Perry is also interested in how we manage the care of chronic diseases such as diabetes, but also asthma and even depression. "For many of these diseases we're essentially providing lifelong care. The hope is that the patient will become an 'expert patient', responsible for managing their own condition."

The UCC study surveyed over 2,000 patients with Type I or II diabetes, attending three different diabetes care teams: a traditional hospital-led scheme in the southwest; a hospital/GP shared care scheme in Dublin; and a primary care scheme in the Midlands.

When they got an unusually high response rate (71%) to their postal questionnaire, Perry realised he had hit on something. "Quality of life is a real live issue for people. The questionnaire coincided with a postal strike, and we even had people driving long distances to deliver their questionnaire by hand!"

In-depth interviews with a small sample of respondents revealed three distinct 'types' of diabetes patient. The 'reactive manager' monitors their blood glucose and adjusts their diet and exercise regime to maintain control. The 'passive follower' follows their prescribed regime, but doesn't react to changes; while the 'nonconformist' does not follow the prescribed diet and exercise regime, but does take their medication.

> **"Diabetes care teams and medical staff need to recognise that there are these three patient types, especially if they are to help people to manage their condition."**

"Diabetes care teams and medical staff need to recognise that there are these three patient types, especially if they are to help people to manage their condition", Perry advises.

Patient well-being

In terms of stress and psychological well-being, the larger survey revealed a hidden burden. Anxiety and depression are at least twice as common among people with diabetes as in the general population: 28% reported mild-to-severe levels of anxiety, and 20% reported similar levels of depression.

Smokers and those with diabetes complications were worst affected, and women were on average more anxious than men. This is something that family, and medical staff and care teams need to understand and take into account, says Prof Perry.

People's biggest worries were about the future, being able to work, and being able to enjoy a meal and a drink, the survey found. Those who were well-off, who had health insurance and a job and were married, had the best 'quality of life' scores. Older people also scored higher than younger people, possibly because they had come to terms with their condition. People with complications, and those who have to take daily insulin injections scored lowest.

In addition to surveying well-being at a personal level, the study also assessed quality of life and quality of care in three different schemes. Traditionally, when someone is diagnosed with diabetes they are referred to hospital and placed under the care of a consultant. There will be some correspondence with their GP, but their care is primarily hospital controlled. For the study, the UCC team surveyed patients attending a hospital care team in the Cork-Kerry region.

In this traditional hospital-led approach, patients may have to visit the hospital several times a year, with all the travelling and waiting that entails, and they may be seen each time by a different doctor from the team. For anyone living some distance from the hospital it's less than ideal.

Less common is a 'shared care' approach. Here, the workload is shared between hospital and GP clinic, there are agreed protocols for referrals and other procedures, and patients often carry their own records between the hospital and the GP. But while the workload is shared, according to Prof Perry, it's presumed the hospital is the source of expertise and will retain control. The UCC study surveyed patients attending one such scheme in Dublin.

A new and different approach is to organise care at GP level: assembling a multi-disciplinary primary care team, with a specialist diabetes liaison nurse, and with expert resources such as dieticians, ophthalmologists and chiropodists shared among the participating GP clinics. The team may not be linked specifically to any one hospital, but can refer patients to specialists if problems arise.

This type of structured GP care would have obvious benefits for people in rural areas, and one such scheme developed in the Midlands about a decade ago, in response to the lack of an endocrinologist in the region.

But can it provide the same quality of care as a scheme centred around a hospital team? And does being treated locally improve people's quality of life?

Primary care

The answer in this case, to both questions, is a resounding Yes. When Perry and his team compared quality of life and quality of care scores for patients, they found that those attending the Midlands primary care team enjoyed significantly better quality of life and quality of care than patients in the hospital and shared hospital-GP schemes, with the shared scheme scoring better than the traditional hospital one.

Several factors could be important. "Our impression is that the relationship with your own GP is very important. And being cared for locally in a good setup also helps." The arrangement also empowers both the GP and the patient.

> **"Anxiety and depression are more common among people with diabetes than in the wider population."**

Perry points out, however, that this is a survey and not a randomised, controlled scientific trial. He also stresses that the Midlands primary care team is very well organised.

The result is a vindication for GP Dr Velma Harkins of Banagher Health Centre, who pioneered the Midlands diabetes team. "We established the team over a decade ago, with the then Midlands Health Board, when there was no endocrinologist for the four counties of Laois, Offaly, Longford and Westmeath." Then, it was a novel approach, but the team got funding to cover a practice nurse, chiropodist, dietician and ophthalmologist, and more recently a specialist diabetes nurse.

The UCC result was not news to Harkins: the team audits their own results each year and so are confident that their quality of care meets international standards, she said.

The scheme now covers over 3,000 people with diabetes. "When we began first, someone who was

diagnosed with diabetes had to wait 18 months to see a specialist. Now most patients can quickly be treated locally, and anyone with problems can be fast-tracked to the specialists in the hospitals."

Perry likewise believes that the way forward for managing diabetes will be allowing both GPs and hospitals to play a role. "We shouldn't assume the care has to be hospital-led. Primary care is at least as good – possibly better – and there is less travelling for patients." In any case, Perry adds, with the huge rise in the number of people with diabetes in Ireland, the hospitals couldn't cope on their own.

The debate in Ireland is often polarised between hospitals and primary care, says Perry, yet it isn't an 'either/or'. "We will always need tertiary care for the complications. But internationally, the trend is for chronic conditions to be managed in the community."

Already, a number of structured primary care schemes similar to that in the Midlands are starting elsewhere around Ireland, many of them drawing on the success and expertise of the Midlands team. ■

↘ DIABETES IN IRELAND

There are nearly 210,000 people with diabetes in Ireland, according to the most recent estimate, in an Institute of Public Health report (June 2006). That's about one in 20 of us, but with no patient register this is still an estimate. Worryingly, as many more people again have diabetes but don't know. Some 250,000 people have 'pre-diabetes', or impaired glucose intolerance, half of whom will develop diabetes within five years if they don't change their lifestyle. All told, we're talking 13% of the population.

Two types of diabetes

TYPE I (insulin-dependent) diabetes occurs if the body produces no, or insufficient insulin. It usually appears early in life, and someone with this condition generally has to take insulin for life. In Type II diabetes, the body still produces insulin, but the cells no longer respond to the hormone. This condition usually develops in older people, and the general treatment is diet, exercise and medication.

It's not just a person's blood sugar levels that are affected: left untreated, diabetes can damage a person's heart and blood circulation system, leading to heart problems, blindness, kidney failure, foot ulcers and gangrene.

It is also a costly disease: patients with secondary complications need access to heart, kidney and eye specialists, and sometimes even kidney transplants and leg amputations. According to one estimate, 10% of our healthcare budget already goes on diabetes and related illnesses.

And the problem will worsen: the number of people with diabetes is set to double over the coming decade, because there will be more of us, and we will be older and more obese. By 2020, perhaps one in four of us will have, or be at risk of diabetes.

What to watch for

FEELING tired, thirsty, and rundown? Losing weight, and suffering with blurred vision, and recurrent infections? Do you often pass urine? Then you might just have diabetes.

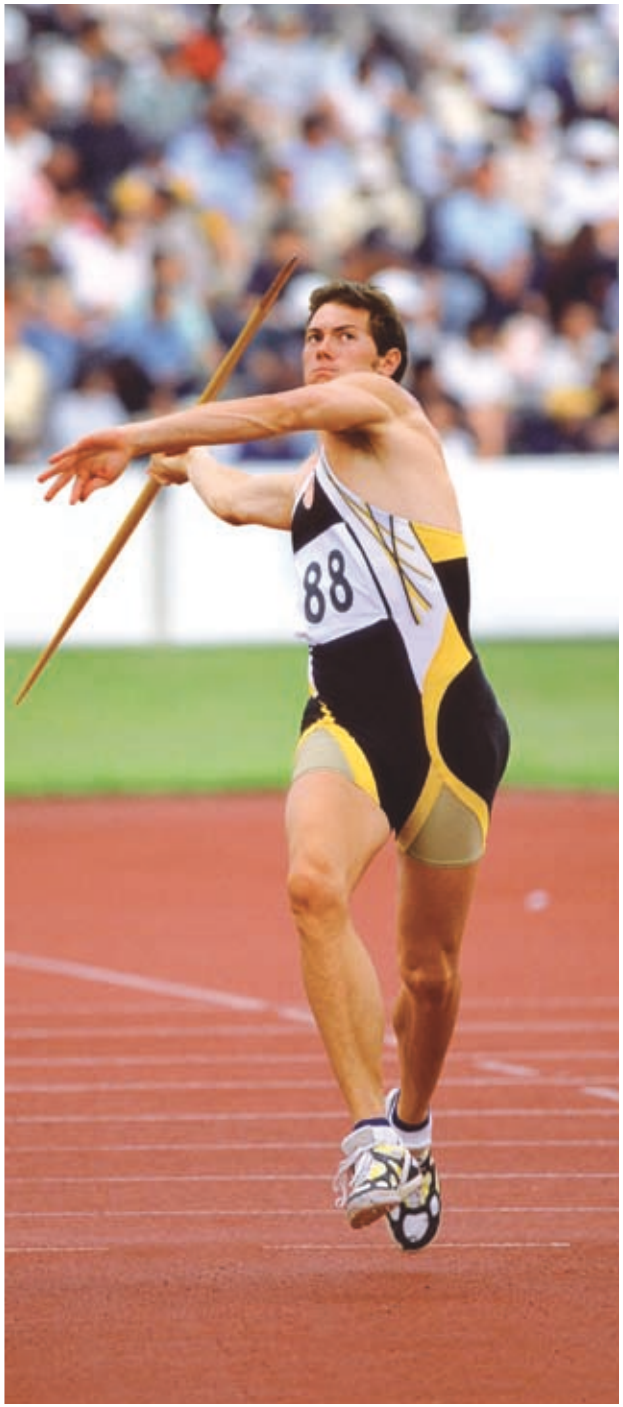
Some people are more at risk than others, especially if there is a family history of diabetes, if they are overweight (about 80% of people with diabetes are overweight), if they don't take much exercise, and if they had diabetes during a pregnancy, or if they had a large baby. The chances of developing diabetes also increase as we get older.

For more information, contact the Diabetes Federation of Ireland (www.diabetes.ie, or their helpline: 1850 909 909).

Key findings

The UCC study, led by epidemiologist Prof Ivan Perry, found that:

- Being diagnosed with diabetes can add significantly to your stress and anxiety levels, and leave you more prone to depression. Something patients, family and friends should know.
- Structured primary care can be as good as, if not better than, hospital-led care. Something the health system should acknowledge.
- There are different types of diabetes patient –'reactive', 'non-conformist' and 'passive' – and they need different forms of support. Something for GPs and patients to bear in mind.



THIS WON'T HURT A BIT

Consultation charges deter patients, probity checks for dentists would deter 'irregularities', and elderly people need more dental check-ups.

Some people don't see enough of their dentist, it seems, while other people may be seeing too much. And many ill people don't visit their GP because of the cost. That's according to two fascinating studies into how our dental and medical charges might be influencing our behaviour, whether as patient, dentist or doctor.

From bin collection charges to water rates and medical fees, we know that financial incentives and charges can affect people's behaviour. But could they also affect our health? If you have to pay every time you visit your doctor or dentist, are you less likely to visit, for instance? Even if you are feeling ill or your teeth hurt? Might you be tempted to go more often than needed if the service was free?

Open wide

UCC health economist Dr Noel Woods is interested in our relationship with our dentist. Thanks to the latest National Survey of Oral Health (2002), he knows the state of the nation's teeth, and therefore how often we should be visiting a dentist. And he knows how often people with a medical card are visiting a dentist, and the treatment they get, from the database of the Dental Treatment Services Scheme.

Dental visits are free for medical card holders, yet intriguingly, Woods found that this group visits their dentist much less than expected: just 19% of card holders visited a dentist in 2001, compared with about 45% of PRSI patients, even though the latter pay a charge for most treatments. No evidence, then, that GMS patients are abusing the system. On the contrary, Woods concludes that "medical card holders don't value their oral health very highly" and underutilise the scheme.

Significantly, elderly people were least likely to visit a dentist. "This isn't about aesthetics and having perfect teeth. Ill-fitting dentures can affect an older person's ability to eat, and their diet and nutrition." So he wants daycare centres to provide dental check ups, in addition to the services they currently provide, such as chiropodists. "GPs could also remind older patients to visit the dentist."

Woods also wondered if some patients visit the dentist more often than they need. Put another way: since dentists can claim a fee every time they see a medical card holder, is there any evidence that dentists exploit this 'incentive'?

"Some patients, especially 16-24-year-olds, go more often and seem to receive more services than they need," Woods says. Arguably, young adults might value their oral health more than older people. Or perhaps the national survey that Woods relies on has underestimated their needs?

But Woods also found that, in areas where there are many dentists competing for patients – the Southern HSE area, for example, is particularly well served, thanks to the many graduates from Cork's dental college – medical card holders tend to receive more treatments per visit than average.

This suggests that, where competition is tight, "a few dentists may be responding to the financial incentives, and acting economically rather than clinically". It could simply be that they recall patients every six months, he suggests, when some international surveys suggest that a longer interval would suffice in many cases. Economists call this situation 'supplier-induced demand'.

Woods stresses he has not proved any irregularities, merely revealed a trend. "But if your dental delivery system provides economic incentives to providers, with no probity checks, then you're wide open for exploitation." The situation is compounded by what economists term 'asymmetric information': in other words, the dentist knows more than you do, putting them in control. And it is by no means unique to Ireland: when 'over-provision' was identified in the British NHS, Woods says, they introduced a fraud detection unit, probity checks, and even a redesign of the system.

The cost of dental services for medical card holders is about €50 million a year. Woods' analysis suggests that some €5 million (about 10%) could be 'over-provision'. "That's a drop in the ocean, alongside the overall healthcare budget. But it's still €5 million. And anything that is irregular, and especially any medical treatment that is not needed, is unethical."

Thanks in part to the UCC study, new probity checks were introduced to the Irish system in Spring 2006. In an agreement with the Irish Dental Association, which represents dentists, there are now regular random checks on dentists in each region. "It would be very costly to redesign and change the system. Hopefully, the probity checks will ensure that dental services are provided entirely on need."

> GPs could remind older patients to visit the dentist and daycare centres could provide dental check ups.

The doctor will see you now

In a complementary study, Dr Andrew Murphy, professor of general practice at NUI Galway, asked if consultation charges deter people from visiting their GP. Thanks to the different systems operating north and south of the Border, he could conduct a kind of natural experiment: comparing a system where consultations are free (Northern Ireland), with the Republic of Ireland, where 70% of people pay, typically €35-55.

Questionnaires were sent to over 22,000 people attending 20 matched practices in the North and the Republic, including urban and rural, and large and small practices.

Significantly, 26% of people in the Republic said there were times when they had a medical problem but did not visit their GP because of the charge. Worryingly, Murphy says that the people most affected were those with poor health, long-term illness and the symptoms of depression. A small percentage of people who don't have to pay any consultation charge were also deterred by cost, possibly costs associated with travel, childcare or time off work.

The same phenomenon is seen in other countries with similar healthcare charge systems, Murphy says, including New Zealand, Canada, Australia and especially the US.

Prompt and effective primary care at GP level can identify problems early and reduce the need for more costly hospital care later on. Prof Murphy argues that we need to make sure the system does not deter people from visiting a doctor until it is too late, and "that the safety nets work".

Intriguingly, his survey also found that in the Republic a majority of both fee-paying and medical card holders think that it is reasonable to pay for consultations. In Northern Ireland, there was more support for the introduction of charges for missed appointments.

While the UCC dental study suggests that some dentists may be exploiting the fee per visit system (where the fee is claimed from the Dental Treatment Services Scheme), Murphy found no evidence that GPs take advantage of fee-paying patients.

Paying patients were actually less likely to have a GP-initiated visit, or receive a prescription, than medical card holders. "GPs seem to be more concerned with their patients' ability to pay, than with opportunities for income generation."

The survey found other differences between the systems on either side of the Border: in Northern Ireland, visits are mostly by appointment, and for two-three days' time (not counting urgent appointments, when most people are seen on the day); in the Republic there is generally open access, so patients see their GP more quickly, but spend longer in the waiting room.

In the North, 45% waited at least two working days to see their doctor of choice. In the Republic, the figure was 8%. As a result, people's satisfaction with their GP practice was somewhat higher down South (84%, compared to 81%).

Patients have one concrete suggestion for GP practices: 30% of them, North and South, would like later opening hours and weekend clinics!

Two significant changes have been introduced since this questionnaire was circulated in 2003: the doctor-only medical card in the Republic, and a new GP contract in the North, which stipulates a 48-hour maximum wait for an appointment. Prof Murphy would like to repeat the survey in a year or two, to see if these measures mean more people now see their doctor sooner and visit their doctor when they are ill, and are not deterred by cost. ■

↘ GET YOUR TEETH INTO THIS

How long does an average dental filling last? UCC health statistician Dr Michael Cronin has studied data about fillings, and how often they are replaced, courtesy of the Dental Treatment Services Scheme that covers medical card holders (the same database his colleague Dr Woods used for the economic study).

Of the €50 million spent each year by the scheme, 30% goes on fillings. So it's important we know the factors that affect how often a filling is likely to be replaced, and that we have some benchmark for quality of work.

Intriguingly, Cronin found that a filling is less likely to be replaced if the tooth is a pre-molar, if you are a woman, have not had root canal work, attend a middle-aged dentist, and live in certain areas.

Molars (those teeth at the very back) are difficult to reach and drill, while the ceramic fillings used in front teeth are not hard-wearing, hence the in-between pre-molar fillings last longest. Women? Perhaps, Cronin speculates, they put off visiting the dentist for longer than men. Root canal work is a risk factor because this major procedure can upset neighbouring teeth, while fillings by younger and older dentists seem to require replacement more often than those by middle-aged colleagues.

And the regional differences? As in the economic study, if there are more dentists in an area, more people will visit them, and go more often. And the more often someone visits a dentist, the more likely it is that a filling will eventually be replaced. "Once you drill into a tooth and fill it, you weaken it, and sooner or later that filling will need replacement. It's a vicious cycle, until you end up losing the tooth", Cronin says.

As well as producing some fascinating results, and a benchmark for quality that can now be used in the DTSS probity checks, this is a valuable piece of statistical analysis: previously, statisticians had to 'follow' each individual tooth in a study, but Dr Cronin developed a 'bootstrapping' way to take account of the fact that a person's teeth are all 'connected', so to speak, so now statisticians can 'follow a mouthful'.

UNCOVERING THE CAUSES OF A CRIPPLING CONDITION

How exercise and certain genes may put some people at risk of motor neurone disease.

When Dr Orla Hardiman starts talking about her latest research into motor neurone disease, she becomes so animated it's hard to keep up. Especially as she covers everything from genes to marathon running and the population genetics of the Irish.

Hardiman has every reason to be excited. A consultant neurologist at Dublin's Beaumont Hospital and senior lecturer at the Royal College of Surgeons in Ireland, she leads a major international team which recently identified a gene that causes motor neurone disease (MND) in some people.

Their major breakthrough is helping shed light on the root causes of this crippling condition, and could one day deliver a new treatment. Much of the information for the study comes from a detailed register of Irish patients that Hardiman has established.

The scientists discovered that some MND patients have a mutation in a gene called ANG. Significantly, all the affected patients are Irish or Scottish, or of Irish or Scottish descent. The gene can also run in families: where a family had two cases of MND, the scientists found that both people had the ANG mutation, but healthy family members did not.

> Patients attending specialist clinics have a longer life expectancy, better quality of life and fewer hospital stays.

The ANG gene codes for a protein involved in forming new blood vessels. Hardiman says it plays a role in some other diseases, but this is the first time it has been implicated in a disorder of the central nervous system. "It's a whole new mechanism, that may have something to do with the body's response to low oxygen conditions."

Other evidence supporting the low oxygen, or hypoxic, theory comes from mice: knock out one of their hypoxic genes, and they develop a condition similar to MND. This led Dr Matt Greenway, a research fellow working with Hardiman, to search for, and find, another similar hypoxic gene in some Irish MND patients.

Taken together, the findings shed light on possible causes of MND, and perhaps even other neurological conditions, and the College of Surgeons has already filed a patent with a view to searching for a potential drug.

The latest study was a major international collaboration, involving other teams from Northern Ireland, England, Scotland, Sweden and the USA. All told, they analysed DNA samples from 1,600 patients, and as many more healthy controls. "It's the biggest ever motor neurone disease study, and we couldn't have done it five years ago. All this is only possible now thanks to the sequencing of the human genome, and the latest developments in computing and software."

Referring to the ANG gene's association with Irish and Scottish patients, Hardiman says the result highlights the importance of studying diseases at the individual and population level. "We know that different ethnic groups have different genetic markers, and some of these may make some people more susceptible to a particular disease. You can't ignore ethnicity when you're studying the susceptibility to disease."

Tantalising clues

The MND register that Hardiman established is also producing some fascinating information. Begun a decade ago, the database now contains detailed information on over 1,200 patients, including their symptoms, medical treatment and history.

From this, Hardiman has discovered that there are real benefits to attending specialist clinics. "Patients who attend a specialist clinic on average have a longer life expectancy, by about 6-9 months, and a better quality of life and fewer hospital stays."

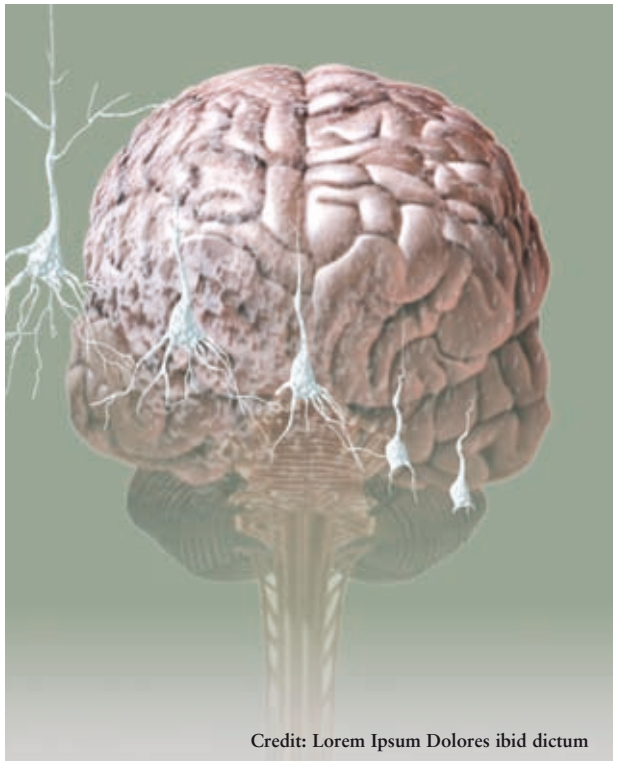
Intriguingly, the database has revealed a geographical trend in Ireland, with MND incidence somewhat higher in the west than in the east. This mirrors other genetic trends in the Irish population (such as blood groups), and may reflect historic and prehistoric influxes of people from Britain and Europe.

It was generally thought that MND did not affect a person's mind but, Hardiman says, specialists increasingly recognise that there can be subtle effects and some patients can suffer cognitive decline, something she and her team are also exploring with the information from the patient register.

Another tantalising clue comes from people's athletic history, and might tie in with the low oxygen theory. "A disproportionate number of our patients were athletic in the past. And there are at least twice as many cases of MND among marathon runners as you'd expect."

A large US study found no connection, but Hardiman wondered if exercise might be important for just a subgroup of patients. From the register, she has evidence suggesting that it is important in men with the limb-onset form of the disease. The sample was too small to be conclusive, however, so another HRB project is underway pooling data from Northern Ireland, where a patient register modelled on the Republic's one was recently set up.

Yet another tantalising clue comes from an association between MND and haemochromatosis.



Credit: Lorem Ipsum Dolores ibid dictum

This genetic blood disorder, common in Ireland, means your body absorbs too much iron from the diet. It, too, could be linked with the body's response to low oxygen.

Hardiman and another research team in England found an association between MND and haemochromatosis, but again, the numbers involved are too small to be conclusive. However, an Italian study also found similar results, suggesting the association is real. The challenge now is to understand what this means.

Overall, the MND research has been tremendously fruitful, especially given that Hardiman leads a relatively small team, with limited resources and working with a small number of patients. As a full-time consultant, she must do her research on the side, and she bemoans the paucity of contracts that would allow consultants to do more clinical research.

Attracting funding is also, she says, a constant struggle. "It can be very hard to sell the benefits of a database and population genetics, especially for a rare disease." That said, she is grateful to the HRB for its support, and also to industry sponsors, the Charitable Infirmary Charitable Trust, the Beaumont Foundation and the Irish MND Association (where she is medical patron), which have all supported the programme.

Despite the struggle, it is, she says, exciting and satisfying work, and she is already applying for funding to chase some of those tantalising leads on genes, exercise and geography. And then she's gone, rushing to her next appointment. ■

North-South collaboration

THIS research was part-funded by the HRB and the R&D Office, Belfast, as a North/South collaboration involving Dr Orla Hardiman, with Dr Victor Patterson, consultant neurologist, Royal Victoria Hospital, Belfast, and HRB clinical research fellow Dr Matt Greenway, RCSI. They also collaborated with Prof Andrew Greene and Dr Sean Ennis from the National Centre for Medical Genetics at Our Lady's Hospital Crumlin.

When motor neurones die

MOTOR nerve cells in your brain and spinal cord control your muscles, so when these cells begin to deteriorate and die the result is muscle wasting and weakness . . . and motor neurone disease. Symptoms often start in the arms and legs, but sometimes in the face.

In Ireland, two people die every week from this debilitating condition, which at any one time affects about 250 people here. MND typically hits people in middle-age, and occasionally younger adults; men are twice as likely to get it as women.

There are actually several forms of MND, the commonest being amyotrophic lateral sclerosis (ALS), or Lou Gehrig's disease, named for a US baseball star who died of the condition.

MND is a progressive condition. The causes of which are unknown. There is no cure and, currently, just one drug (riluzole) has been licensed for use in ALS, and it offers only a modest improvement in life expectancy.

For more information contact the Irish MND Association (www.imnda.ie, or tel:1800 403 403).

↘ WHY FISH OIL IS GOOD FOR YOUR BRAIN

Scientists are learning how memories are made and how brain diseases develop.

How our brains work remains one of the great scientific puzzles. For instance, how does your brain take the ink patterns on this page and turn them into meaning? What is a memory? How are memories stored? And why does it all sometimes go so horribly wrong, in diseases such as Alzheimer's and Parkinson's?

A major international research effort is underway to understand how the brain works, what causes brain diseases, and how we might protect our brains from degenerative conditions. And Irish scientists are playing their part in this effort.

One important finding comes from Trinity College Dublin (TCD), where neuroscientists have teased out how fish oil benefits our brains.

"EPA definitely protects the nerve cells", says research fellow Dr Aileen Lynch of TCD's physiology department. EPA being an Omega-3 fatty acid, found in fish oil, grains and pulses, and known to scientists as eicosapentaenoic acid.

The TCD team, led by physiology professor Dr Marina Lynch, has been studying EPA's effects on rats for some years now. "We basically mimic the damage you'd expect with age, for instance", Dr Aileen Lynch explains.

They previously found that EPA can protect brain cells from the damage that typically happens when we grow old, or ill with infection, or develop a degenerative brain disease. Aged rats are fed the Omega-3 as a supplement in amounts equivalent to the supplements typically sold in health food shops. And the scientists see the benefits after about four weeks. In some cases, they found that EPA can even restore normal function.

Now, Dr Lynch has discovered that EPA works because it has many anti-inflammatory effects. Notably, it increases production of a potent anti-inflammatory immune compound called IL-4.

"One advantage of IL-4 is that it's small enough to cross the blood-brain barrier", Lynch adds, which is always a concern when you are designing a drug to reach the brain.

Once we identify the mechanisms involved – easier said than done – it should be possible to design a drug to regulate the process, and that could be good news for people with degenerative brain diseases. Meantime, her work provides another good reason for eating lots of oily fish.

Parkinson's disease

At UCC's department of anatomy, several scientists are researching the cause of Parkinson's disease – what Dr Kieran McDermott describes as "one of the great conundrums".

People afflicted by this degenerative disorder suffer tremors and their movements slow and even become difficult to start. "We know this is because people lose a certain type of neuron in a small region called the mid-brain. But we don't know why these neurons die."

Very similar neurons – both types use the same neurotransmitter, dopamine, and so are called dopaminergic neurons – are also found in the hypothalamus, yet are largely unaffected. And there lies the conundrum.

McDermott and his colleague Dr Aideen Sullivan are comparing both regions, and have found that the hypothalamus has ten times more support cells, or glial cells, than the mid-brain. “Glial cells detox things, so they do protect the neurons.”

With fewer support cells, perhaps the neurons in the mid-brain are more vulnerable to some toxin? Or perhaps the glial cells produce something they need to survive? Questions the team hopes to answer as their work progresses.

There is currently no cure for Parkinson’s disease, merely drugs to control the symptoms. One avenue being pursued is transplanting neurons to replace those that die. Internationally, some transplants of foetal tissue have been tried, but these were controversial and the benefits were short lived.

But what if we could ‘grow’ replacement nerve cells in the laboratory? To do that successfully, McDermott says, we need to understand fully all the factors that neurons need for survival, including perhaps glial cells but also other growth factors.

In a related project, Dr Aideen Sullivan has improved the survival rate of neurons grown in the lab, using gene therapy to provide them with an essential protein. Her team is now studying how these nerve cells behave and survive when they are transplanted into rats that have a condition similar to Parkinson’s.

Alzheimer’s disease

A different mechanism is at work in Alzheimer’s disease, where patients accumulate deposits of a protein called amyloid beta. UCC biochemist Dr Cora O’Neill is studying the enzymes that produce this protein. Among many findings, her team has discovered a key difference: in an Alzheimer’s brain, one enzyme (called BACE1), works twice as fast as normal. “It’s not that there is twice as much enzyme. We think maybe the cells lose control of its speed somehow.”

Her team is now applying for additional HRB funding to search for chemicals that would slow the enzyme down to normal speed. If successful, it could open a promising new avenue for tackling this disease.

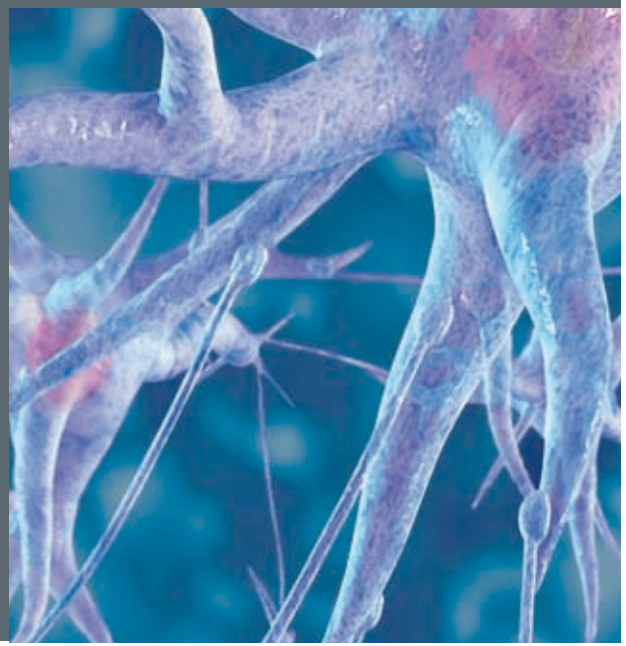
The main characteristic of Alzheimer’s disease is that people progressively lose their memories. So, understanding how memories form and are stored will help shed light on this disease, as well as telling us much about how our brains work.

At NUI Maynooth, psychologist Dr Sean Commins is interested in the nerve cells in the parts of our brain that are involved in processing and storing memories. “Our current theories suggest that information is stored in the hippocampus for a short while, and then transferred to the neocortex for more long-term storage”, he explains.

Now, he has shown for the first time that there are indeed specific functional connections between these two brain regions, a finding that supports current theories of memory.

By measuring the electrical impulses that travel among the nerves there, he has also shown that these neural connections can respond to stimuli and change, just as you’d expect if they are involved in processing memories.

It’s a first step, he says, in experimentally confirming our ideas about how long-term memories form. Something to think about next week – when you try to remember everything that you read here.



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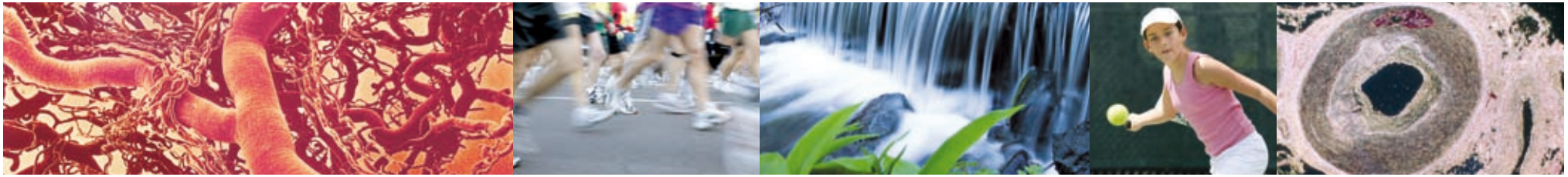


New treatments to keep blood moving and so prevent coronary heart disease and stroke could flow from Irish research.

A new drug that might prevent clots and a possible therapy for blocked arteries, are among the results of the latest Irish research into heart disease.

Cardiovascular disease is Ireland's biggest killer. It kills about 10,000 people here every year, according to the Irish Heart Foundation, accounting for one-third of all deaths. The two main causes are coronary heart disease or blocked arteries (atherosclerosis), and stroke caused by a clot (thrombosis).

Stroke alone kills 2,000 people every year – that's more than breast, lung and bowel cancers combined! It's also a significant cause of disability, and some 30,000 adults in Ireland are currently left disabled by a stroke.

Deaths from cardiovascular disease, though still unacceptably high, have actually fallen significantly in recent years. In fact, the death rate here nearly halved between 1985 and 2000, thanks to improved treatments and interventions, and the fact that many people have quit smoking and improved their cholesterol and blood pressure levels.

That positive trend could be about to change, however, as obesity and diabetes levels rise dramatically, and fewer people take sufficient exercise… all factors that put people at risk.

Not surprisingly, there is tremendous interest in discovering the causes of cardiovascular disease, and identifying new approaches and therapies to fight it, and many Irish health research teams are part of this international scientific effort.

Unblocking arteries

An artery starts narrowing when fatty, cholesterol plaques develop on the inside of the blood vessel. The muscle cells in the artery will often grow over the plaque, making it even bigger and the blood channel narrower, and the plaque can even acquire its own rich blood supply. If that happens, the plaque becomes prone to rupturing and can lead to dangerous clot formation, in addition to blocking blood supply, causing angina and putting the person at risk of a heart attack.

Two surgical techniques have been used with considerable success in recent years to unblock arteries. Inserting a wire stent that pushes the artery walls apart and keeps the channel open. And if that doesn't work, surgeons can try a 'bypass': grafting in a stretch of healthy blood vessel to bypass the blockage.

The problem, especially with a stent, but also eventually with a bypass, is that the blockage often recurs and so any benefit is short-lived. Now, scientists at the Regenerative Medicine Institute (www.remedi.ie) in NUI Galway, have developed a therapy that could prevent the blockages from re-forming.

Led by Prof Tim O'Brien, they aim to restore arteries to a healthier state, using gene therapy to deliver a key enzyme. The enzyme enables cells to manufacture a small gas molecule, nitric oxide (chemical symbol: NO).

NO plays a key role in regulating blood flow, and has long been an important target for many drugs – Viagra, for instance, exploits NO to improve blood flow to a certain part of the male anatomy, and likewise angina drugs exploit its ability to increase blood flow.

> **"The answer to heart disease is often NO, and NO again!"**

Significantly, there is less nitric oxide in blocked arteries than in healthy blood vessels. So Tim O'Brien's idea is to help the cells there to produce more of the crucial gas, by giving them an enzyme. "We use a crippled version of the common cold virus to deliver the gene for a nitric oxide enzyme", he explains.

To manufacture nitric oxide, cells can deploy a range of enzymes (called nitric oxide synthases, or NOS), and O'Brien's team has discovered that these have different effects on blood vessel cells. "You have to be careful which enzyme you choose."

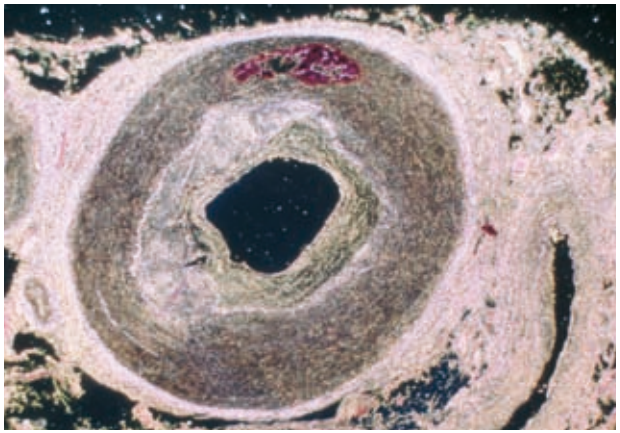
In pre-clinical tests, O'Brien identified the most beneficial form of the enzyme. The group then successfully used their engineered virus to deliver the gene for this enzyme to blood vessels in laboratory animals. NO levels rose and, most heartening of all (no pun intended), the channel in the animals' arteries became less narrow.

"This looks really promising. Especially as the enzyme we chose also promotes healing of the blood vessel wall. It could be a really useful technique to combine with a stent or graft [bypass]."

One advantage of O'Brien's approach is that the gene, and the enzyme, does not have to be successfully inserted into all of the cells in the region. "Nitric oxide gas is very permeable. So even if only some of the cells are transformed, the gas can still permeate and benefit surrounding cells."

Having identified the best enzyme to protect blood vessel walls, the Galway group next plans to test their strategy using a different virus that should produce more long-term benefits. If this is successful, and regulatory approval is given, trials with people could be underway within five years.

At Dublin's Tallaght Hospital, cardiologist Prof Ian Graham is also interested in nitric oxide and



atherosclerosis. "Nitric oxide seems to have a 'protective' effect on arteries", he explains. When NO levels fall, the artery walls can become 'sticky' and damaged.

He has now confirmed that people with atherosclerosis have higher levels of a natural byproduct, known as ADMA, that directly blocks NO production. Could this be why their NO levels are low?

Graham compared 260 people who have atherosclerosis with a similar group of healthy people. Significantly, he found that the ADMA levels dropped when people took a statin drug to regulate their cholesterol levels. Graham's finding suggests that statins may also help to heal arteries by improving nitric oxide levels. But it's not clear yet if the drugs merely cut ADMA levels, or if they also lift nitric oxide levels.

At UCD Prof Therese Kinsella is also interested in why some blood vessels become narrow. She studies the signals that tell the cells lining a blood vessel to grow and multiply, so that they end up constricting the channel.

Significantly, she has found subtle but important differences between us humans and mice and rats. As mice and rats are widely used in studies of human diseases, Kinsella says it's important that scientists realise there can be differences. In particular, researchers testing possible new drugs – to treat narrowing of the arteries, for instance – should test them on human cells and tissue, and not just on lab animals, she warns.

Clot busters

Unwanted blood clots that can cause a stroke are also the focus of much Irish cardiovascular research. And at the Royal College of Surgeons in Ireland, Prof Niamh Moran and her team have identified a molecule that can prevent such unwanted clots forming. Moran is very hopeful that this could be the basis of a new drug for people at risk of a thrombosis.

The line between blood that is ready to clot instantly at the first sign of a cut, yet can still flow freely around the body, is a fine one – a yin and yang balance between the forces, or agents, that promote clotting, and those that prevent it.

Scientists still do not fully understand all the agents, signals and processes involved in blood clotting, but we have learned much in recent years, thanks in part to Irish researchers, especially teams at the RCSI and UCD.

We know, for instance, that small blood cells called platelets are important. Platelets are normally silky, but when they sense damage and are 'activated', they dramatically change their appearance and become 'sticky', and capable of forming a clot.

This shape-shifting takes just a few seconds. Seen under a microscope, it's as if smooth round balls have flattened into something resembling a fried egg: a bump in the middle holds the cell's 'machinery', and the rest is spread out in an apron around it, perhaps in a bid to cover a leak or cut. The spreading can continue for some time after initial activation.

Dr James McRedmond, research fellow and cell biologist at UCD's Conway Institute, is analysing the genes and proteins "that make a platelet a platelet". Thanks to the latest developments in gene chip technology and proteomics, he is compiling a list of the thousands of genes that are switched on in platelets, and also the proteins they contain, both before and after they've been activated.
"It's pretty much the first time anyone has looked at this in platelets, so we are finding lots of proteins that we didn't know were there", he explains.
The next step will be to analyse the patterns and identify the key changes, to develop a clearer picture of what happens when a platelet switches from smooth to sticky.

At the College of Surgeons Prof Niamh Moran has developed an international reputation for work on platelet activation. With painstaking detail, her team has pieced together many of the signalling, receptor and structural molecules involved.

Just a few years ago, her team discovered that there is a biochemical switch that controls a platelet's change from silky to sticky. They also discovered that nitric oxide – there's that gas again – could reset the switch, restoring sticky platelets to their normal silky state.

More recently, Moran has been studying the integrin molecule that makes platelets sticky. "It spans the cell membrane. A big bit that's like Velcro pokes outside the cell. A smaller bit on the inside takes the message to become activated."

Significantly, Moran's team has also stumbled on a molecule that prevents integrin taking that message and activating the platelet. "This is very exciting for us. We had manufactured a range of small peptides to see which bit of the integrin molecule was important, when we found one of them actually prevents activation."

> **"The new drug could be designed so it is activated only when a clot starts forming."**

They have now modified the structure to improve its potency, produced a peptidomimetic version (pure peptides are digested in the stomach, and so of limited interest as drugs), and patented their discovery.

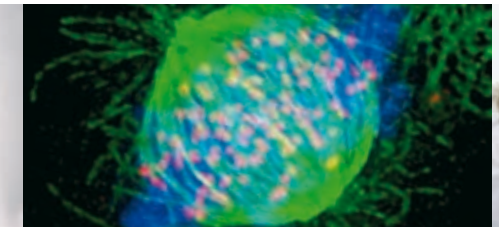
Moran has a neat biochemical trick in mind to ensure that their drug becomes active only when needed. "Someone who is at risk of thrombosis would take our drug in its inactive form, and it would only be activated if a clot starts forming."

Significantly, the integrin also plays a key role in several other conditions, including inflammation, and cancer, where it helps make tumour cells mobile.

"Ours is curiosity driven research", says Moran. "But we are also developing a tool to dissect what's happening in the cell." And a tool that could yet yield a new drug to prevent thrombosis, and possibly related drugs for other conditions too. ■

THE GREAT CANCER COVER UP!





Transplant patients should cover up well in the sun. That's one of the messages from Irish cancer research.

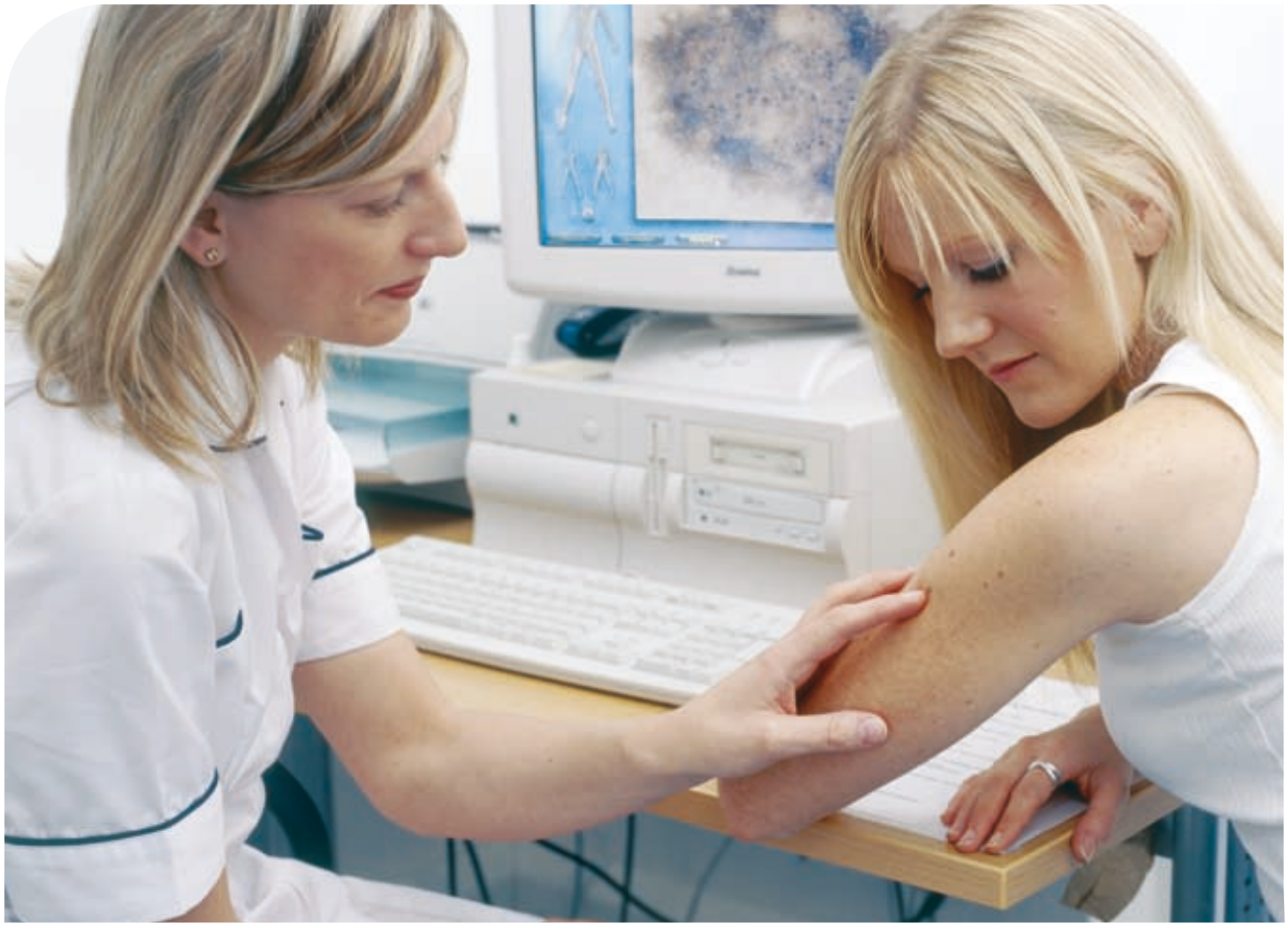
How does aspirin help prevent bowel cancer? Why should transplant patients slap on factor 60 every time they go out? Why are breast cancer cells so disorganised? And what makes some cancer cells able to 'up sticks' and move around the body?

These are just some of the questions that cancer researchers around Ireland are tackling. It's part of the major ongoing international effort aimed at improving our understanding of cancer, and identifying new and better therapies.

One group that is very susceptible to skin cancer are transplant patients. In fact, new Irish research shows that kidney transplant patients are 200 times more at risk of skin cancer than healthy people.

Dermatologist Dr Fergal Moloney, who studied the incidence of skin cancers among some 2,000 kidney transplant patients at Dublin's Beaumont Hospital, says the increased risk is primarily because their immune-suppressing drugs leave their immune system less able to detect and destroy the early cancer cells in time.

It's also because, thanks to those same drugs, patients are now surviving longer – some kidney recipients have survived 25 years – giving them time to develop skin cancer. And the cancers they get, most commonly squamous-cell cancer, tend to be more aggressive than usual, again because their immune system cannot hold the cancer in check.



Transplant patients today have a better understanding of the need to protect their skin from too much sun, he says, but despite advice, a quarter still do not apply suncream on a sunny day. “We continue to see lots of skin cancer in the clinic, and some patients can develop dozens of cancers.”

Exposing your skin to the sun, even in Ireland, Moloney says, can result in damage to the DNA. “Normally our immune system holds this in check, so the damaged cells don’t progress to cancer. But immunosuppressant drugs can reduce your immune surveillance by about 50%, leaving you vulnerable, especially to skin cancers.”

Comparing data for kidney transplant patients with data on the wider population, in conjunction with the National Cancer Registry, Moloney found that older patients can develop skin cancer as early as two years after transplantation. Younger patients develop skin cancers more frequently: within six years of their transplant, they are 200 times more likely to develop skin cancer than a healthy person of the same age.” Hence, he recommends that all transplant patients have their skin screened regularly, ideally by a dermatologist.

Moloney, whose wide-ranging study also looked at genetic variations in skin colouring and in how immunosuppressant drugs are metabolised, says there are four key messages. First, we should all avoid sunburn and too much sun. “You never know when you’ll need a transplant, and it’s the amount of exposure you have before your transplant that is really important.”

Second, transplant patients should remain active and enjoy outdoor activities, but they should all cover up, even on overcast days: that’s hat, long sleeves, and a broad spectrum, factor 60 (yes, 60!) sunblock on face, hands and the ‘vee’ of the neck, applied 30 minutes before going into the sun.

Third, transplant patients should become familiar with their body, and know what to look for. And finally, women should have an annual smear test, because immunosuppressant drugs mean they are also more susceptible to genital warts.

One reason people develop skin cancer is because UV radiation in sunlight damages our DNA. Some chemotherapy drugs can cause similar damage,

> **“We should all put sun block on all exposed parts every time we go out.”**

notably cisplatin which is often used for ovarian tumours.

Thanks to evolution, our cells contain a special enzyme (DNA polymerase-eta), that allows them to tolerate this UV damage. But not everyone has this enzyme: people with a rare genetic disease called xeroderma pigmentosum variant lack the enzyme, and are very susceptible to skin cancer caused by sunlight.

At NUI Galway, Dr Michael Carty wondered if other people who develop skin cancer might likewise have some defect in this enzyme. But he and doctors at University College Hospital Galway have screened 40 skin cancer patients so far, and all had the normal gene. Further tests suggested there might have been less enzyme in some tumours, so Carty's next step is to see if some cancers develop because there is less enzyme activity, for whatever reason.

The more we know about this enzyme, Carty says, the more we will understand skin cancers, and the better we will be able to predict how someone's tumour might react to chemotherapy drugs like cisplatin.

Anti-inflammatory and anti-cancer?

Surpisingly, some non-steroidal anti-inflammatory drugs (NSAIDs) also have anti-cancer effects. Aspirin, for instance, can help prevent bowel cancer. Unfortunately, aspirin can have troubling side-effects, and so do some other NSAIDs. Remember Vioxx? Withdrawn from the market because it increases the risk of heart attack and stroke.

It's thought these drugs work against cancer because they inhibit an enzyme called COX-2. So the search is on for safer COX-2 inhibitors. And to that end, several researchers at UCD are studying what the enzyme does in healthy and cancer cells.

Research fellow and gastroenterologist Dr Glen Doherty has discovered that in bowel cancer cells, COX-2 reduces the levels of a molecule called DRAK2. The molecule has been studied in blood cells, but this is the first time it has been seen in a cancer.

Doherty has now discovered that DRAK2 is involved in telling cells when they are past their 'best before date', and should remove themselves by, essentially, committing suicide. But with less DRAK2 in the bowel cancer cells, this doesn't happen, and the cells live longer than they should.

This could explain why the anti-inflammatory drugs help prevent cancer: by inhibiting COX-2, they lead to higher DRAK2 levels and so more cells die. Doherty is hopeful this new information will lead to safer, more effective drugs.

One of the big worries with any cancer is metastasis: when some of the cells become mobile and can leave the original tumour site to invade other parts of the body. So a drug to block this would be a valuable addition to our anti-cancer armoury.

Now, researchers at UCC have identified a molecular switch involved in this process. Project leader Dr Rosemary O'Connor says the work sheds valuable light on what's happening inside the cells, and it is already helping to improve the design of anti-cancer drugs.

Current anti-cancer drugs are a big improvement on the 'blunderbuss days' of trying to kill as many cells as possible by hitting them hard with something toxic. Today, our improved understanding of the molecular chemistry of cancer has led to more refined approaches, that are more effective, less toxic and with fewer side-effects. Herceptin, for instance, used against certain breast cancers, targets a particular receptor on the cancer cells.

Dr O'Connor studies a similar receptor, called IGF-IR, which is important in a range of cancers. It's more active in cancer cells and it seems to be part of the switching mechanism that tells tumour cells to multiply and move.

There is already commercial interest in this receptor, with several companies testing inhibitors that block the receptor, and some even at clinical trial stages.

Enter Dr O'Connor's team. With HRB funding and additional support from Cancer Research Ireland, they have discovered how IGF-IR works in metastatic cells: that it interacts with a scaffolding protein in the cells, and that this interaction controls the switch that ultimately enables tumour cells to multiply and move around.

By creating special laboratory strains of cancer cells, they showed that if this interaction cannot happen, the cells are less likely to become mobile; conversely, when lots of scaffolding protein is present, the cells proliferate and migrate even faster than usual.

Thanks to the UCC study, companies developing drugs that target the receptor now know their molecule should specifically block the interaction with the scaffolding protein. The Cork team is already helping to design better tests that might be used to screen patients who would respond well to a drug, and to design new drugs that might prevent a wide range of tumours from metastasizing.

Disorder and disease

At UCD, Prof Finian Martin is studying why breast cancer cells are so disorganised. "Normal, healthy breast tissue has a very organised three-dimensional structure", he explains. But tumour cells lose this facility, and instead form disorganised groups that can eventually invade neighbouring tissue.

To learn how this happens, Prof Martin's team starts by observing healthy breast tissue and how it is organised. "We grow normal breast cells on a special protein scaffold in the laboratory." Then they disrupt the cells, and watch what happens as these ordered, three-dimensional structures start becoming disorganised, as happens in cancerous tumours.

By comparing differences, they hope to understand the changes, providing information that could one day lead to new and better therapies, perhaps even ways to make breast cancer cells behave normally again.

The group recently discovered that a natural hormone, hydrocortisone, and a protein known as

JNK have to interact if breast cells are to organise correctly. When they remove JNK from their laboratory cells, the cells start behaving like cancer cells: growing and multiplying uncontrollably, losing their shape and sense of direction, and becoming more mobile.

The next step – there always seems to be a next step in cancer research – is to see if JNK is also lost in real breast tumours, and not just in their laboratory model. If so, then a drug to protect JNK could open a new avenue for breast cancer therapy. ■

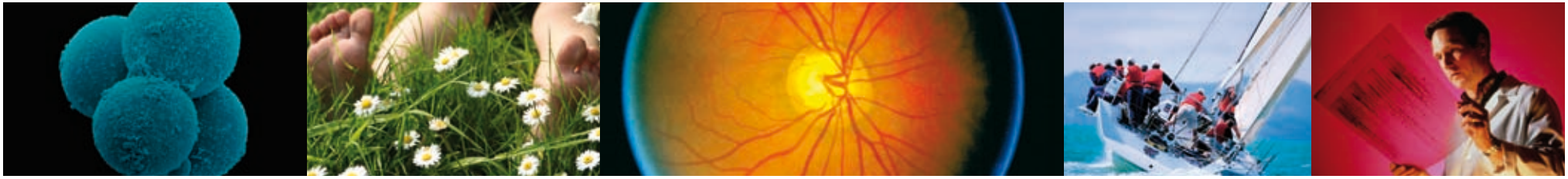
↘ CANCER IN IRELAND

EACH year in Ireland some 22,000 people develop a cancer and 7,500 die from the disease. But those numbers could double over the next 15 years, according to a report published in June 2006 by the National Cancer Registry (www.ncri.ie).

The number of new cancers each year could rise to about 43,000 by 2020, because more of us are living longer and have more time to develop cancer, and because some cancers are becoming more common. The incidence of prostate cancer could nearly quadruple (a 275% increase predicted between 2000 and 2020), cancer of the kidney could nearly treble, and melanoma cases will more than double.

For more information see also the Irish Cancer Society (www.cancer.ie). Its cancer helpline at 1800 200 700 is staffed Monday - Friday 9.00am - 5.00pm.

IN SHORT...



This section describes briefly, individual project findings from research into a variety of health-related research topics, including mental health, eye disease, arthritis and innovative medical technologies.

Medical Innovation

The gel that heals

From a drug's unusual side effect comes a new gel that helps wounds to heal faster. Phenytoin is widely given, either orally or intravenously, to treat epilepsy and convulsions, but it also stimulates cells to proliferate and often causes enlarged gums.

Now, research pharmacist Dr Clare Meaney and colleagues at RCSI are exploiting this: they combined phenytoin with a special hydrogel, producing a preparation that can be spread on a wound or cut. Surgical wounds and lesions in animals healed faster when treated with the gel. Clinical trials are starting at a Dublin hospital, and the team has now patented their invention.

Bioinformatics

An array of cancer genes

Imagine being able to see at a glance which genes are switched on in cancer cells, and which ones are switched off? Gene chip micro-arrays allow scientists to do just that, but, with hundreds even thousands of genes involved, it's nearly impossible to spot meaningful patterns amongst all the data.

So UCD's bioinformatics group, under Prof Des Higgins, have developed a suite of statistical tools to help researchers analyse micro-array results, and even compare the results from different cancers, or spot differences between cancer cells and healthy tissue. The tools, based on two off-the-shelf techniques ('between group analysis', and 'co-inertia analysis'), have been customised specifically for micro-array studies. In the long-term, such tools could help researchers to develop semi-automated diagnostic tests for cancers. More information at http://bioinf.ucd.ie/

Mental Health

Stress and depression

New drugs to treat depression could come from research into stress hormones. According to UCC psychiatry Prof Ted Dinan, when we're under stress, our body responds by producing cortisol, and people suffering with chronic depression have more cortisol than normal. For 'everyday' stress (traffic, exams, infection . . .) the cortisol levels are controlled by corticotropin releasing hormone (CRH).

But now, Dinan's research has confirmed that something different happens during depression: another stress hormone, vasopressin, comes to control the cortisol levels, and what's more, the person's body over reacts and produces too much cortisol. So, a drug that prevents cells over-reacting in this way might be useful in treating depression. And prompted by Dinan's research, one pharmaceutical company is now developing a vasopressin-blocker for clinical trials.

Immune disease

Crystal therapy for arthritis?

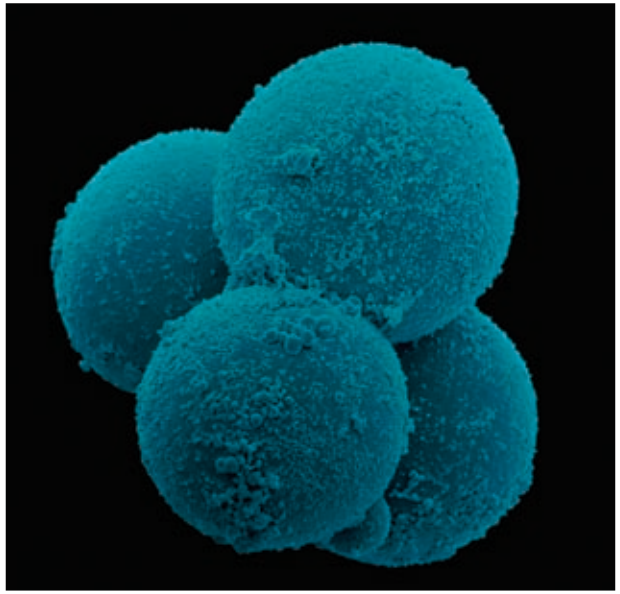
Up to 70% of osteoarthritis patients have calcium crystals in their joints. The crystals make the arthritis worse, by prompting the joint to produce more of the

prostaglandin molecules that cause the damage. At the Royal College of Surgeons, Dr Eamonn Molloy found that two forms of an enzyme (called COX), are involved in producing these extra prostaglandins. So patients who have these calcium crystals might do better on drugs that knock out the two versions of the COX enzyme. Some non-steroidal anti-inflammatory drugs (NSAIDs) block only one form. Molloy also discovered that some prostaglandins can have beneficial as well as harmful effects. Hence researchers designing new drugs should aim to block only the harmful activity.

Social Science

Drug user profiles

The term 'drug user' is widely used as a catch-all, but not all drug users are the same. And, says psychologist Dr Paul Cahill, treatment programmes should be tailored to the needs of the drug user.



From information on nearly 7,000 people in the National Drug Treatment Reporting System, he and colleagues at the University of Ulster identified six user types, including multi-combination (15%), methadone (14%), recreational (13%), and experimental (8%), but the biggest group by far, accounting for nearly half of all users, were those being treated for heroin addiction.

The study sheds valuable light on the profile of drug users here, and treatment programmes should be tailored to the various drug user groups, says Dr Cahill, who is now with the Health Research Board. For instance, with most treatment services focused on heroin, other types of user may not be getting appropriate treatment.

BRIEF COMMUNICATIONS

Clinical Microbiology

A virus that kills cancer cells

TCD microbiologists have produced a virus strain that kills cancer cells in mice and are now working towards clinical trials in cancer patients

A virus infection is normally bad news, but what about a virus designed to kill cancer cells? Viruses operate by invading a cell, where they produce lots more virus particles, before bursting out and, in the process, killing the cell. It's this cell-killing behaviour that Prof Greg Atkins is exploiting, by designing a virus to infect and kill cancer cells. A number of clinical trials with such viruses are underway in other countries, but, Atkins says, these involve DNA viruses, which run the risk that the virus could integrate into the patient's DNA and actually trigger a cancer.

So the TCD virologists have chosen an RNA virus, Semliki Forest virus, which, because it cannot integrate, should be much safer. They've designed several SFV strains that are deliberately disabled, so that they can't cause problems or infections, and with extra genes that make them more effective cancer killers. Their most recent strain carries the gene for an immune system molecule, the cytokine IL-12, which packs a double whammy: it stimulates the immune system, and it causes tumours to suffocate by preventing them from developing a blood supply. Trials in mice with tumours were very successful: all the tumours stopped growing, and in some mice the tumours completely disappeared (the numbers varying with the strain of mouse and type of cancer).

Atkins is very hopeful that this virus therapy could be used in some of the many cancers that don't respond to drugs or radiation. Thanks to HRB funding, the team has shown their approach works, and they've now won commercial funding from Enterprise Ireland and SFI that will allow them move towards clinical trials in patients whose tumours have become resistant to other therapies.

Medical Technology

See an embryo breathe

A team at UCC has developed a system sensitive enough to monitor a tiny pre-implantation embryo

Imagine being able to detect the almost negligible amount of oxygen consumed by a handful of cells. Well, bioengineers at UCC have developed two systems capable of doing just that. Designed to assess early embryos before they're implanted (and which might consist of from one to at most 100 cells), the systems could be used in research

laboratories (e.g. with mouse embryos), with pedigree cattle embryos in dairy herd improvement programmes, say, and even with human embryos in IVF clinics. Currently, before an embryo is transferred, an embryologist will assess its condition by inspecting it under a microscope. Though simple, this is subjective. Now that could change, thanks to research by Prof Dmitri Papkovsky and his team at UCC and the Tyndall Institute.

Their first design comprises an integrated biochip, while the second uses a tiny glass capillary set-up. Both systems rely on new fluorescent oxygen probes which the team developed and patented. They are coupled to a standard laboratory reader and can produce a result with up to eight samples in under an hour. According to Prof Papkovsky, the challenge is finding a balance between a system's sensitivity and complexity. Their biochip prototype could monitor five mouse embryos, and they believe has the potential to monitor single embryos. The more sensitive capillary device can monitor an individual mouse embryo, but was less convenient to use. The team now aims to develop both designs and ultimately hopes to produce disposable commercial devices that would be robust, efficient and cheap to use.

Immune system

Timing, converts, and infection

Irish research suggests that timing of an anti-inflammatory drug could be crucial, especially for infants

The more we know about our immune system, the more complex we realise it is, and the more it seems we need to know.

Take inflammation, for instance. Scientists have discovered some subtle checks and balances in the system, including an elegant negative feedback system: in the presence of dead cells (as happens with infection and inflammation), some blood cells become reprogrammed, converting from pro-inflammation to anti-inflammation. The switch probably evolved to dampen our immune response and minimise the risk that inflammation will escalate out of control after the initial response that is needed to fight off infection

But what happens when the reprogrammed cells leave the blood and move into other tissues, where they mature into immune cells? And is reprogramming the same in adults and newborn infants, who after all, have different immune systems?

At Crumlin Children's Hospital research centre, immunologist Prof Denis Reen studies this reprogramming, using blood samples from adults and umbilical cord blood for newborn cells. He has discovered that the results are indeed different in infants. In particular, their reprogrammed blood cells can mature into immune cells that are more anti-inflammatory than adult ones.

This could depress an infant's immune response, Reen says, and may explain why some infants are susceptible to infection. The finding also has implications for the timing of drugs. "These days, our first reaction to inflammation is to try and bring it down. But if we intervene with an anti-inflammatory drug, we could go in at the wrong time and get the wrong response."

Stopping shock and inflammation

Drugs to treat septic shock and chronic inflammation could come from Irish research into how our immune system works

TCD scientists may have discovered a way to stop septic shock. This terrifying condition develops when the body's immune system over reacts to bacterial infection, such as pneumonia, meningitis and MRSA, and causes multiple organ failure. Some 200,000 people die in Europe each year from septic shock, which can develop in hours and, once begun, is nearly impossible to stop.

TCD immunologist Prof Luke O'Neill has been teasing out the biochemical steps involved, starting when immune cells detect the presence of the invading bacteria. Half of all cases involve a bacterial molecule called endotoxin. O'Neill has now discovered how this triggers a chain reaction in immune cells ending with "basically a bugle call to wake the entire immune system".

Crucially, he has identified the particular switch that is triggered. This involves a protein known as TRAM and his team has now figured out how TRAM is turned on. The discovery has been patented, and TCD biotech campus company Opsona hopes to identify a drug to interfere with this process. “Ideally, this would turn the volume down, since you don’t want to turn the immune system off completely.”

Meanwhile, Dr Paul Moynagh, a colleague of Prof O’Neill’s and based at UCD, is investigating a related aspect of the immune system: chronic inflammation. This happens when immune cells flood into an infected tissue or organ and, if it’s not resolved, can lead to the kind of damage seen in arthritis and multiple sclerosis.

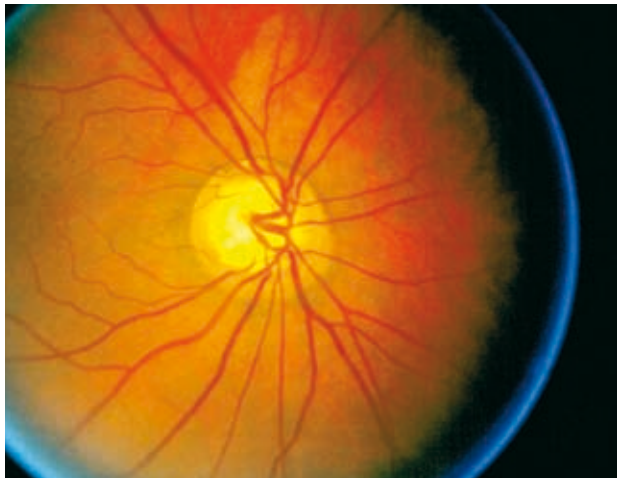
Moynagh has now characterised the mechanisms involved in one inflammatory pathway, involving the Pellino family of proteins. He has also designed a molecule to inhibit this pathway. This successfully blocks inflammation in cells growing in the lab, so it might lead to a new type of anti-inflammatory drug. Moynagh’s next step is to see if the molecule also works in laboratory animals that have inflammation.

Eye disease

An eye for research

Promising research may lead to a drug treatment for a progressive form of blindness

They are turning a blind eye to research in UCC, the better to understand it and hopefully develop a treatment. Specifically, Prof Tom Cotter and colleagues are studying the degenerative eye disease,



retinitis pigmentosa (RP). This develops when certain cells in the eye die, by committing suicide. Strange though it may seem, cell suicide is a vital process in our bodies, where it helps to control cell numbers and organ and tissue development. Normally it is regulated by caspase enzymes. But Cotter’s team has discovered that under the disease conditions of RP another set of enzymes are involved, the calpains.

Now, with Spanish collaborators, they are designing small molecules to block these calpains, in a bid to prevent eye cells committing suicide inappropriately. Already they have had some success using these compounds in eye cells grown in the laboratory. The next step is to see if they can modify one of their new molecules so that it can safely cross the blood-brain barrier, and if successful, would test this on animals, before considering it for clinical trials.

This promising project is just one of a number of HRB studies into the causes of blindness. At Dublin’s Mater Hospital, Prof Colm O’Brien is studying glaucoma, when changing conditions in the eye can again trigger cells to commit suicide inappropriately, and his work has shown that calpain enzymes are again implicated in this disease. At UCD, Prof Paul Engel is studying the defective enzyme that is the root cause of one particular form of retinitis pigmentosa, RP10.

Mental Health

Learning to help yourself

There is international interest in a Cork initiative designed for people at risk of ‘deliberate self-harm’

Training in inter-personal problem solving may help people who are at risk of self-harm, or even those who already harmed themselves. ‘Deliberate self-harm’ is on the rise, and in Ireland nearly 9,000

people a year end up at hospital after harming themselves. Many harm themselves repeatedly, and sadly, many will go on to commit suicide, yet patients find it hard to stay the course at conventional mental health clinics. Now, a major study in Cork suggests that training in inter-personal problem solving skills could be helpful.

Nearly 450 people took part in the trial, and half were assigned to the six-week course. According to lead psychologist Dr Breda McLeavey, who is based at Cork University Hospital, they learned how to spot problems early, and how to identify options and make decisions. Initial results are promising – the participants say they found it useful, and attendance was good – but it will be late 2006 before analyses reveal if the programme did improve problem solving, reduce depression and the chance of them harming themselves again.

This is the biggest study of its kind, according to McLeavey, and there is considerable international interest. If the approach proves successful, she expects the programme would be implemented nationally.

Neuroscience

The blockage that could be a breakthrough

Treatment for a wide range of brain disorders, from epilepsy to stroke and Alzheimer's disease, could one day come from biochemical research at TCD

There is a naturally occurring molecule in your brain that is important in memory and learning, and in maintaining and restoring brain function. It's called TRH (thyrotropin-releasing hormone), and needless to say, there's considerable medical and commercial interest in it. But there is a big problem: no sooner is TRH made in your brain, than a special TRH-degrading ectoenzyme (TRH-DE) starts destroying it, usually within minutes.

To get around this, one pharmaceutical company produces a modified TRH that is less susceptible to degradation, and which is now used to treat spino-cerebellar degeneration. But a TCD team, under Dr Julie Kelly and Prof Keith Tipton, is taking a different tack: they want to block the enzyme with a inhibitor. Inhibition is a tried and tested approach, according to Dr Kelly, who cites the ACE inhibitors now widely used for high blood pressure. And blocking the enzyme should be a more natural way to lift someone's TRH levels, than giving them synthetic hormone. Moreover, because the enzyme acts only on TRH and nothing else, an inhibitor should have few if any side effects.

The team has now designed and synthesised a dozen potential inhibitors, and is working to refine their designs. If they can produce an effective inhibitor that can also safely cross the blood-brain barrier, it could be used to treat a broad range of brain disorders and diseases. Their findings have been published in the international journals, and at least one commercial company is now interested.

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