PROGRESS

The research magazine of Parkinson's UK

Issue 8: Winter 2010

Impulsive and compulsive behaviour – potential side effects of medication

The second Parkinson's UK research conference

What's the role of inflammation?

Tracking the earliest signs of Parkinson's

Contents

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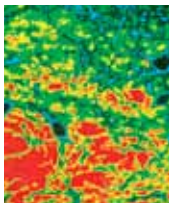


Front cover image
Enhanced light micrograph of dopamine-producing nerve cells (red) in brain tissue Catherine Pouedras/Eurelios/SPL

Welcome

2010 has been a very exciting year for research in Parkinson's UK. I was delighted to be involved in two research events that brought home just how much progress we're making towards achieving our ultimate goal of finding a cure for Parkinson's.

First, at the World Parkinson Congress, I had the chance to meet people with Parkinson's together with researchers from all over the world. There was such a wide range of topics and so many things to see and hear that I could have done with a double! You can read some extracts from the diary (on page 8). It was a great opportunity to meet with other bodies that fund research, including the Michael J Fox Foundation, to discuss the studies we support and how we can work together in the future.

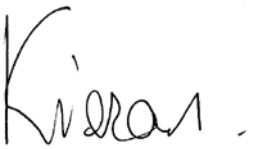
In November we held the second Parkinson's UK Research Conference in York. It was great to see over the two days how much research is being carried out in the UK and it made me realise how important the Parkinson's UK investment is in stimulating Parkinson's research. The meeting also had an international flavour with two of our keynote speakers travelling from the US and Sweden to share their work. Find out more on page 10.

Our cover feature is on impulsive and compulsive behaviours, such as pathological gambling. Reading Mark's story was a powerful reminder of the many difficult issues that people with Parkinson's can face. It also shows the tremendous ability people have to get through tough times. This inspires the research we do.

Some of you asked about taking part in Parkinson's research projects, so we've included details inside the back cover of how to find out about studies that are looking for participants. There's also a link on the contents page to questionnaire about the magazine – please keep the feedback coming.

2010 has been an encouraging year, and I'm really looking forward to 2011. We'll continue to fund groundbreaking research to improve the treatments available for Parkinson's and move ever closer to a cure. We will also be developing our Research Support Network (see page 33) that will bring together Parkinson's UK members and supporters. The network will help to raise funds and boost the profile of Parkinson's research with the general public, researchers and politicians.

All the very best,



Dr Kieran Breen
Director of Research and Development

Kieran

Impulsive and compulsive behaviour:

The trouble with reward and motivation

Most people with Parkinson's have more than movement-related symptoms to deal with. Changes to mood and cognition and other non-motor problems can also develop due to the death of a specific set of dopamine-producing nerve cells. For some people, there can be serious side effects associated with taking certain medications to combat these symptoms. These symptoms are mainly, but not exclusively, associated with dopamine agonist drugs. They include a group of conditions known as impulse control disorders.

Dr Iracema Leroi is a consultant psychiatrist in the northwest of England, who has recently completed a Parkinson's UK Senior Research Fellowship. Here she gives Progress the background to these distressing complications.

Impulse control disorders (ICD) include behavioural changes such as excessive gambling, compulsive shopping and 'hypersexuality' (a pathological interest in sex). Up to 17% of people with Parkinson's may experience these side effects. While they are more likely for people taking dopamine agonist drugs, some people have had similar experiences with other Parkinson's drugs, such as levodopa.

Our understanding of the importance of impulse control disorders has increased over the past decade. In 2003, a study of almost 2,000 people with Parkinson's found nine cases of pathological gambling among those taking dopamine agonists. In 2005, another study reported that 11 people had developed the same problem within a month of starting dopamine agonists. When the specific medication was reduced, or stopped altogether, most of the problems cleared up. As a result, some high profile legal cases against pharmaceutical companies have been launched. Now all dopamine agonists used in the UK come with warnings about the risk of developing impulse control disorders.

Pathological gambling is one of the most commonly reported impulse control disorders associated with Parkinson's. And its effect on people's lives is certainly one of the most dramatic. Typically, people affected experience a change in their behaviour and start looking for opportunities to gamble. They may form addictions to using scratch cards or buying lottery tickets, betting, internet or casino gambling and stock market trading. In whatever form this

pathological gambling takes, it is often very difficult for the affected person to control. This impulse control disorder can involve increasing amounts of money and risks. It may continue even when things start to go horribly wrong as a result of this behaviour.

Pathological hypersexuality is another common impulse control disorder, first described in a study of people with Parkinson's in 1983. It can result in an increased sex drive and more frequent erections for men. Pathological hypersexuality may also expand the range of sexual behaviours. For example, people sometimes develop new sexual orientations, practices and even fetishes. This type of behaviour is associated with dopamine replacement therapy and often comes with changes in mental state. These include feeling less inhibited or having 'hypomania', which is a flood of energy, ideas and feeling mildly 'high' or irritable.

Pathological hypersexuality can also occur alongside other impulse control disorders, such as pathological gambling. When dopamine replacement therapy is reduced or stopped, the hypersexual behaviour often stops too.

Other impulse control disorders, such as compulsive shopping or binge eating, may overlap with both hypersexuality and pathological gambling. At the moment, if a person is diagnosed with Parkinson's and is male, young and has a 'thrill-seeking' personality, they are seen as more likely to develop an impulse control disorder. However, the problems are not only experienced by this group of people.

For more information

People who are experiencing problems with their drugs should contact their specialist or Parkinson's nurse as soon as possible. Sometimes people who experience this behaviour may not realise they have a problem, so if carers and family members notice any unusual behaviour, it's important they discuss it with a healthcare professional as quickly as possible.

To find out more, call our helpline on **0808 800 0303** or see our information sheet Impulsive and compulsive behaviour, available at **parkinsons.org.uk** or to order for free by calling **01473 212 115**.

References

Weintraub D et al (2010) 'Impulse control disorders in Parkinson's disease – a cross-sectional study of 3090 patients' *Arch Neurol*; 65:589-595.

Too much of a gamble...

Mark Robson is 54 and lives in Oldham, near Manchester. He almost lost everything as a result of pathological gambling. Mark took part in Dr Leroi's research study.

Continued on next page

Mark and Sam

In 1998, Mark was diagnosed with Parkinson's. In November that year he was perscribed a dopamine agonist called pergolide. At first, the dose was low. But it was gradually increased to 4mg per day.

He wasn't aware of it when his personality started changing, but his wife noticed something wasn't right. He became less outgoing and started to overeat. Mark soon had no control over the amount of food he was consuming, putting on 5 stone.

"I then started gambling in 2004, which was totally out of character for me. At first, I used interactive TV games and then casino sites on the internet. I was juggling money on five different credit cards and taking out extra loans. I probably spent at least 20 hours a day gambling online. It carried on for 16 months."

Mark remortgaged the house to pay for his habit, but had managed to keep the financial situation a secret from his wife up to this point.

He remembers how he became increasingly sneaky. He lied to get the money to gamble, spent money needed to pay the mortgage and stole about £20,000 from his wife's business. She was eventually declared bankrupt. In all, Mark gambled away at least £200,000.

During this time, Mark was seeing his specialist at Oldham hospital. But, because he wasn't aware of the link between his behaviour and the medication he was taking, he didn't tell the doctor about his gambling addiction. The penny didn't drop until Mark saw a newspaper article about someone else with Parkinson's who'd had a gambling habit and linked this to his medication.

Mark got back in touch with his specialist and was told to come in straight away. After talking about the link between dopamine agonists and compulsive behaviour, he was taken off pergolide gradually, over about four weeks. The urge to gamble disappeared.

Sadly, Mark's marriage had broken down by this point and in 2006 he got divorced. He'd been unable to work since 2000. Feeling suicidal, Mark was referred for psychiatric counselling. In the end he was hospitalised for two months before going to live with his father in Fleetwood for three years.

It took several attempts to get the right medication to treat Mark's Parkinson's. And all the while he was taking anti-depressants and struggling to get his life back together.

In 2009, Mark and his former wife got back in touch with each other. Mark had hired a solicitor to prepare a case against the drug manufacturers and he needed her support. The couple reconciled and remarried in November 2009. They recently celebrated their first wedding anniversary.

Parkinson's UK research on impulsive and compulsive behaviours

We're currently funding two research teams as part of our themed research programme into impulsive and compulsive behaviours and impulse control disorders. We initially announced these studies in the summer 2008 issue of Progress. Dr Paola Piccini is leading a team based at Imperial College London and at the National Hospital for Neurology and Neurosurgery. In one study, the team are using brain imaging to investigate addictive behaviours in Parkinson's.

Previous research has suggested that impulse control disorders may be a result of problems with the reward pathways in the brain. So the team are using imaging to compare what's happening inside the brains of people with Parkinson's who have addictive behaviours with those that don't. Participants in the study are being shown a range of 'rewarding' images such as money, appetising food and even Parkinson's drugs, both on and off medication.

Results so far suggest that participants with addictive behaviours have a stronger response to the rewarding images than those who don't. This may suggest that these people are more likely to develop behavioural problems due to their drugs

and may allow us to predict who is more likely to have problems when prescribed specific types of medication.

A second study by the team is looking at whether there are any links between disturbed sleep or excessive hoarding and impulsive and compulsive behaviours. Early results from the study show that overall levels of anxiety and depression, as well as poor sleep, are linked with impulsive and compulsive behaviours. We'll update you on both projects after they finish in 2011.

Meanwhile, Professor Anthony David is developing a treatment programme in which trained nurses can step in to help people with Parkinson's and their carers deal with impulsive and compulsive behaviour problems. At the moment the only treatment is to limit the use of a person's medication, but this will have an adverse effect on the effectiveness of the drugs to control the Parkinson's symptoms.

The programme involves helping people to understand the nature of the problems, manage stress, minimise harm and access the right support services. So far, nine people with Parkinson's have entered an individualised treatment programme. We look forward to the results and letting you know how they got on.

World Parkinson Congress

2010 was a great year for getting people together. The research team was privileged to attend the second World Parkinson Congress in Glasgow at the end of September. Over 3,000 people from 66 countries came together to combine their knowledge and experience in the fight against Parkinson's.

We had four days of the latest reports from the lab and the clinic, along with workshops and discussions involving people with Parkinson's, researchers and carers. It would be impossible to describe all of the presentations, so here are just a few excerpts from the Progress diary.

Wednesday 29 September

Smell is definitely one of this year's hot topics. Losing the sense of smell may be one of the early signs of Parkinson's. Dr Harry Robertson from Dalhousie University is working on a brain imaging technique which, along with the loss of smell, could flag up the people most likely to develop the condition, enabling earlier treatment. We know that at least 50% of people with Parkinson's lose their sense of smell before they are diagnosed.

While previous studies had identified some genes that may be associated with Parkinson's, Dr Haydeh Payami from the Wadsworth Centre in New York went further to see how specific genes may interact with the environment. It turns out that if you have a specific set of genes and also drink a lot of coffee over a whole lifetime, you're at less risk of developing Parkinson's. This information not only tells us about coffee but, more importantly, shows

that there is a definite interaction between a genetic susceptibility to getting Parkinson's and other factors that may play a role to spark this off.

Thursday 30 September

There was a good Q&A workshop with some of the researchers. A Parkinson's UK member asked about whether levels of proteins like alpha-synuclein and LRRK2 in the blood can be used to monitor the condition. In fact we've just given funding for an innovation grant to look into this (see page 22 for more detail).

Friday 1 October

Cognitive behavioural therapy for people with Parkinson's has been shown to help people with problems such as anxiety and depression. It aims to teach people how to deal with things such as physical symptoms or coping with psychological problems. Dr Karen Anderson of the University of Maryland told us about work showing that it can successfully help to change people's response to a situation even if the situation itself doesn't change. In other words it could give people back some control over their lives.

The feedback from both the Parkinson's UK members and researchers was very enthusiastic. Unlike usual research conferences, it gave the researchers and the people living with Parkinson's a chance to meet and hear each other's points of view. The researchers felt that it put their work into perspective while the members really appreciated the amount of research that was being carried out around the world to improve the treatments that can be used for Parkinson's and ultimately find a cure for the condition.

Steve Ford, Chief Excutive, Parkinson's UK

York 2010

We held the second Parkinson's UK Research Conference in November. Around two hundred scientists and clinicians gathered together in York for two days to share their latest discoveries. In all, we heard 27 talks and saw almost 120 presentations in every area of Parkinson's research, from the latest in the biology of dopamine-producing nerve cells to the benefits of physiotherapy and exercise for people with Parkinson's. We also officially launched the innovative new five-year research strategy that we told you about in issue 7 of Progress.


Mark


Valerie


Deniz

York 2010 followed on from the success of our first research conference, in 2008. We had two goals. The first was to bring the UK Parkinson's research community together to discuss current and future work. This was a great opportunity to help the development of collaborations that will push Parkinson's research forward to bring us even closer to a cure. And it was really encouraging that even more people wanted to come and present their work than in 2008. Our second goal was to develop and support the next generation of Parkinson's researchers. Our career development

awards and PhD studentships exist because we're very keen to nurture talented researchers in the early stages of their careers. We want to ensure that UK research remains at the forefront of improving life for people with Parkinson's. So it was really exciting to have many of the posters and several of the oral presentations given by these skilled young researchers. (Read more about some of them on pages 12-15 of this issue.)

Highlights of the conference included the talks from our three keynote speakers, Dr Valerie Voon, Dr Mark Cookson and Dr Deniz Kirik. Valerie, from the University of Cambridge, updated us on impulsive and compulsive behaviour, which affects up to 17% of people with Parkinson's. Problems include pathological gambling, hypersexuality or compulsive shopping and are mainly associated with dopamine agonist medication. Valerie's work showed that dopamine agonists can make people more likely to make risky choices and quick decisions although this can also be seen to a lesser extent with other Parkinson's drugs. You can read more about imuplsive and compulsive behaviour in this issue's cover feature on page 4.

Mark is based at the National Institutes of Health in the US. He told the conference about how variations in many different genes may contribute to people's risk of developing Parkinson's. The aim of genetic research is to understand more about which genes are involved in Parkinson's. Understanding how and why nerve cells die will help us to develop new drugs to treat Parkinson's by slowing down or stopping the progression of the condition.

Deniz from Lund University in Sweden spoke about the potential of cell replacement and gene therapies to treat or ultimately cure Parkinson's. Although they are some way off being ready for general use, they may well become more effective treatments for Parkinson's than medication – targeting the condition rather than the symptoms. Some initial clinical studies are already taking place (see Roger Barker's project on page 30). So it was great to hear from Professor Maya Sieber-Blum from Newcastle who presented her work on cells that might be useful for future cell replacement therapies. She showed that stem cells which are located at the base of skin hairs can be turned into dopamine-producing nerve cells that seem to be very like the ones that die in Parkinson's.

On Monday afternoon Dr Ellen Poliakoff of the University of Manchester spoke about how gym training may help people with mild to moderate Parkinson's. At the end of the ten-week period of the study, the participants were able to react faster to a stimulus using a computer-based test which assessed their mental awareness.

And then on Tuesday morning Nazir Rampersaud, from the University of London presented his very exciting research into exendin-4 (a drug currently used to treat diabetes) that helps rats to recover from symptoms that are similar to early stage Parkinson's. Based on some initial results from a Parkinson's UK-funded innovation grant, early clinical trials of exendin-4 are already underway. But we still need to understand its beneficial effects better before it could be available to treat Parkinson's.

Parkinson's UK Director of Research and Development, Dr Kieran Breen, summed the meeting up:

> "Our mission is to inspire, nurture and develop the next generation of Parkinson's researchers. It was fantastic to see so many talented and enthusiastic researchers here in York, and to know that Parkinson's research in this country is in safe hands."

You can get more news from York 2010 online at parkinsons.org.uk/researchconference where you can download the full programme and listen to interviews with our three keynote speakers.

New research

Our three-year research grants include PhD studentships and career development awards to train and keep excellent researchers in Parkinson's. Our project grants help researchers follow up earlier results with an in-depth study.

Are Lewy bodies the bad guys in Parkinson's?

Lewy bodies are clumps of protein found inside the nerve cells that die in Parkinson's. They're mainly made up of alpha-synuclein but also contain other proteins in smaller amounts. Exactly how and why Lewy bodies form is still unclear, but research into Alzheimer's has shown that de-activating small fragments of toxic proteins can protect nerve cells from dying. So we've awarded a three-year PhD studentship of £84,096 to Dr Jody Mason and Dr Neil Kad at the University of Essex for student Roya Zohrabi to find out whether dopamine-producing nerve cells can be protected in a similar way.

Roya

Recent evidence suggests that the protein alpha-synuclein helps healthy nerve cells to release dopamine, which is vital to allow nerve cells to communicate. But in Parkinson's, alpha-synuclein starts to band together into larger fragments called fibrils. These fibrils then join together with other proteins to become Lewy bodies. However, researchers think that it's the fibrils that are actually toxic to the dopamine-producing nerve cells.

If this is true, then Lewy bodies may in fact be the cell's attempt to protect itself by gathering the fibrils together out of harm's way. However, the nerve cells still die, so preventing the fibrils forming in the first place may actually protect them.

Taking this approach, Roya will try to apply the promising findings from Alzheimer's research to Parkinson's. She will first study how alpha-synuclein fibrils form inside cells grown in a lab dish. She'll then go on to search for small proteins, known as peptides, that can stop or reverse alpha-synuclein from joining up into fibrils. So at the end of the project we may well have some good candidates for new drugs to treat Parkinson's.

"Parkinson's continues to affect millions of people worldwide, so I think it's vital that we develop new ways to understand how unhealthy protein build-up can cause nerve cell death", says Roya. "I'm really glad that this studentship will give me the chance to contribute to cutting-edge, rewarding research that could lead to future drug treatments for Parkinson's"

Two more studentships

We've also awarded PhD studentships for projects to be carried out by Dr Maeve Caldwell at the University of Bristol and Dr Stephanie Cragg at the University of Oxford.

The Bristol team will be take samples of skin cells from people with variations in the genes for LRRK2 and Parkin, both of which are linked to young onset Parkinson's, They will use these to make stem cells and then transform them into dopamine-producing nerve cells that are almost identical to the ones found in the brain. They aim is find out how easily this can be done, and how well the resulting nerve cells hold up when exposed to chemicals that cause Parkinson's-like symptoms in animals. Their research will help lead us closer to the development of stem cell therapy that may be able to replace lost dopamine-producing nerve cells for people with Parkinson's.

Dr Cragg's team will be working to increase our basic understanding of some of the factors that may influence the release of dopamine from nerve cells. Dopamine is the chemical that is decreased in Parkinson's and studying what other factors may modify this could help us to develop more effective therapies to overcome of the symptoms of Parkinson's.

All about LRRK2

LRRK2 – pronounced lark 2 – is the most common gene associated with the cause of Parkinson's. But despite recent breakthroughs in research, we need to understand more before better treatments can be developed.

Dr Patrick Lewis at the Institute of Neurology at UCL in London has been given a Parkinson's UK Fellowship of £250,000 over three years to find out more about the role of LRRK2.

Research breakthroughs have found that a mutant form of LRRK2 can cause the death of dopamine-producing nerve cells in the brain. Research has also shown that blocking a part of the LRRK2 protein (called a kinase) from working, can stop these cells from dying. This points the way toward treatments that target the kinase. Other parts of the protein could also potentially be targeted by drugs which may slow down or stop the progress of Parkinson's.

"But in order to fully understand how LRRK2 can go wrong, we need to have a thorough understanding of what it does normally, and how variations change its behaviour," says Patrick. "To do this I'm going to study purified LRRK2 using biochemical approaches that we have experience with here at the UCL Institute of Neurology."

"It's becoming increasingly clear that LRRK2 is important in Parkinson's for a lot of affected people, and not just those with inherited Parkinson's. So, figuring out how it works and how to change this is a promising route to developing potential novel therapies. Although it will be some time before drugs which target LRRK2 are ready for testing in the clinic, we hope that these can ultimately be used to slow down, or alter the progress of Parkinson's."

This project was based on some initial results gained from an innovation grant awarded to Patrick last year. It shows that a relatively small investment by Parkinson's UK in a piece of innovative research can help to develop our next generation of researchers.


Patrick

The true costs of Parkinson's

Healthcare costs money, and resources are limited. So it's crucial to know how much particular treatments and services cost and which give best value for money. But this is a complicated calculation and government funding for many conditions, including Parkinson's, is often based on inaccurate information. Dr Emma McIntosh from the Health Economics Research Centre at Oxford University has been awarded a three-year fellowship of £250,000 to find out the true costs of Parkinson's.

Emma aims to find the answers to two questions: first, which treatment benefits do people with Parkinson's and their carers most value, and second, how much do these treatments and services actually cost? Parkinson's is a complex condition, and the impact it has on people's lives is often hidden, so the answers are hard to measure. Emma will develop existing techniques for analysing costs and benefits to allow for these difficulties.

A crucial and often neglected issue is what people living with Parkinson's actually want from their treatment. Measuring improvements in a person's day-to-day quality of life is difficult in the clinic, so the question is often ignored. Also, it isn't easy to put an economic 'value' on this. Emma will survey people directly about what they most value from their current treatment and what they'd most like from any future therapies.

One of the ways to investigate the costs of different treatments is to look at the reasons people are admitted to hospital. Emma can then compare this with the resources needed for community care.

Much of the support for people with Parkinson's comes from unpaid carers. It's important to find out what support and resources these carers need. Emma will try to put a figure on the economic impact of Parkinson's on carers. As Parkinson's is a condition that needs funding over time, this is essential.

By the end of the fellowship we'll have obtained evidence to show what people with Parkinson's and their carers most want, along with information on the costs of different treatments. So when we campaign for better services for people with Parkinson's, we'll have the numbers to back up our case. This is particularly important when funding is limited.

"One of my key aims is to identify treatments and services that should be given the most resources, according to the needs of the people living with Parkinson's," Emma says. "We need to find this out from people with Parkinson's themselves, in order to improve their lives. We can then make sure the results are available to government bodies such as NICE (the National Institute for Health and Clinical Excellence). They'll then have accurate information when deciding whether to fund existing and possible future treatments."

Rebecca and Emma

Keeping it real – a better model of Parkinson's

Alpha-synuclein is a protein that's naturally found all over the brain, which seems to play a critical role in the development of Parkinson's.

We know it makes up the main part of Lewy bodies, which are the sticky clumps of protein found inside dying dopamine-producing nerve cells. But we're still missing information about how alpha-synuclein changes as Parkinson's develops. To find out, we've given Dr Richard Wade-Martins at the Oxford Parkinson's Disease Centre a three-year grant of £212,058.

What we know about alpha-synuclein so far comes from genetics, and from studying people's brains after they have died. Unfortunately, looking at the brain after death doesn't tell us what happened in the earlier stages of a person's condition. For this reason, animal models are vital for understanding how Parkinson's progresses, and particularly for studying how proteins behave.

At the moment, the majority of animal models rely on treatment with toxic chemicals that kill dopamine-producing cells. While this leads to some of the movement-related Parkinson's symptoms in the animals, it lacks other important features, such as Lewy bodies. So, using these chemicals can't tell us what is happening as the cells start to die, only after.

Dr Richard Wade-Martins and his team have been working to develop mice that have the same type of alpha-synuclein that humans do. The idea is that the animals may go on to develop Lewy bodies, which can then be studied in detail.

Richard

"Our preliminary research shows that these mice have alpha-synuclein in all of the key brain areas affected in people with Parkinson's, which is encouraging," said Richard. "We plan to investigate any changes in how the nerve cells work before Lewy bodies develop, and what happens as the animals grow older. We'll do some detailed brain imaging of the mice and compare any changes that we find with human brain tissue.

"We'll also track any build-up of alpha-synuclein from the earliest stages. This will help us find out how it affects both dopamine use, and the animals' ability to perform a range of motor tasks."

Results from the study should be able to tell us which comes first – changes to alpha-synuclein or changes to the way the dopamine-producing nerve cells work. This will help us understand the earlier stages of Parkinson's better, and is an important part of the search for a cure. We'll also be left with a more realistic model of Parkinson's, which will help future research to identify how we may be able to target drugs to slow down or halt the death of the nerve cells.

Innovation grants

Parkinson's UK Innovation Grants fund high-risk, high-reward research projects that test new ideas. Our aim is to speed up the route to a cure.

Reducing inflammation

Inflammation is one of the body's natural defences. When we get an infection, a cut or an insect bite, the temporary redness and swelling that appears is part of a longer chain of events to heal the damage. Inflammation helps repair or remove damaged cells. In the long-term however, it can harm the body, and recent research suggests that it may play a role in Parkinson's. So we've given Dr Peter Teismann at the University of Aberdeen a grant of £34,989 to find out more about the effect of inflammation on the dopamine-producing nerve cells that die in the brains of people with Parkinson's.

We don't yet understand everything about inflammation. But we do know that it can sometimes play a key role in conditions such as rheumatoid arthritis or Alzheimer's. And recent research has shown that people who regularly take the anti-inflammatory drug ibuprofen are a little less likely to develop Parkinson's.

Previous work by Peter's team has found that a toxic chemical causes some of the symptoms of Parkinson's in animals may also result in inflammation in the brain. However, the team has

also discovered a specific combination of other chemicals that can actually protect dopamine nerve cells from dying. And they may do this by reducing inflammation. So they're working on developing a drug that could halt Parkinson's based on this chemical combination.

The catch is that a drug that completely prevented inflammation wouldn't necessarily make the best treatment. We need the good effects that inflammation can have to help us recover from illness or injury. So the team will use this project to alter the combination of chemicals and test these first on nerve cells grown in a lab dish. They can then move on to investigate whether they have an effect in an animal model of Parkinson's. They want to find out which combination of chemicals will keep the nerve cells protected but allow the helpful elements of inflammation to continue.

At the end of the project we will know more about how inflammation affects the nerve cells that die in Parkinson's. We may also have a completely new target for developing a drug that can slow or stop dopamine-producing nerve cells from dying.

Too much iron

Iron is essential and helps the brain to work normally. It's used for several vital processes, including brain development and for producing certain chemicals that nerve cells use to communicate with each other. However too much iron in the brain can cause damage to nerve cells. Past research has found that dopamine-producing nerve cells in people with Parkinson's contain excess iron, but we don't yet know why. Dr David Dexter at Imperial College London is using a one-year grant of £35,000 to help find out.

It may be that excess iron is involved in the death of the dopamine-producing nerve cells that occurs in Parkinson's. Excess iron is also found inside nerve cells in other conditions associated with the death of nerve cells. For example, the nerve cells affected in Alzheimer's also contain more iron than usual.

We already know that inflammation increases the amount of iron inside other (non-nerve) cells in the body. But the question David's team are investigating is whether inflammation is a trigger that increases iron within dopamine-producing nerve cells. Inflammation is known to play a part in Alzheimer's and recent research suggests it's also involved in Parkinson's.

> "You've probably heard health stories in the news about 'free radicals' – they're natural by-products made inside cells as a result of generating the energy they need to function", says David. "However, free radicals can also be very toxic to cells when they react with iron because this reduces a cell's ability to make enough energy.
>
> "Healthy cells are able to remove free radicals. However cells that contain excess iron may have this balance disrupted. Cells that are affected by inflammation for an extended period of time may enter a vicious circle. They can't make enough energy to remove the free radicals, which in turn react with iron to cause more damage."

In this project, the research team will try to discover more about how inflammation might increase the amount of iron inside dopamine-producing nerve cells. They will study the effects of blocking the action of various different chemicals that are likely to be involved, in nerve cells grown in a lab dish. Finding out what causes the excess of iron could give us a new target for drug treatments that could slow or stop the progress of Parkinson's by protecting the dopamine-producing nerve cells.

Could diet help stop Parkinson's?

Protecting the dopamine-producing nerve cells that die in Parkinson's would be a huge leap towards a cure. But current drug treatments only treat symptoms. They can't stop these cells from dying.

We've given a one-year grant of £34,939 to Dr Jeff Davies at the University of Swansea. His team is working to find out more about a recently discovered protein called ghrelin, which could be crucial in developing a new treatment for Parkinson's.

Ghrelin is a hormone made naturally by the stomach, which regulates hunger. It also seems that gherlin in the blood can protect the nerve cells destroyed in Parkinson's.

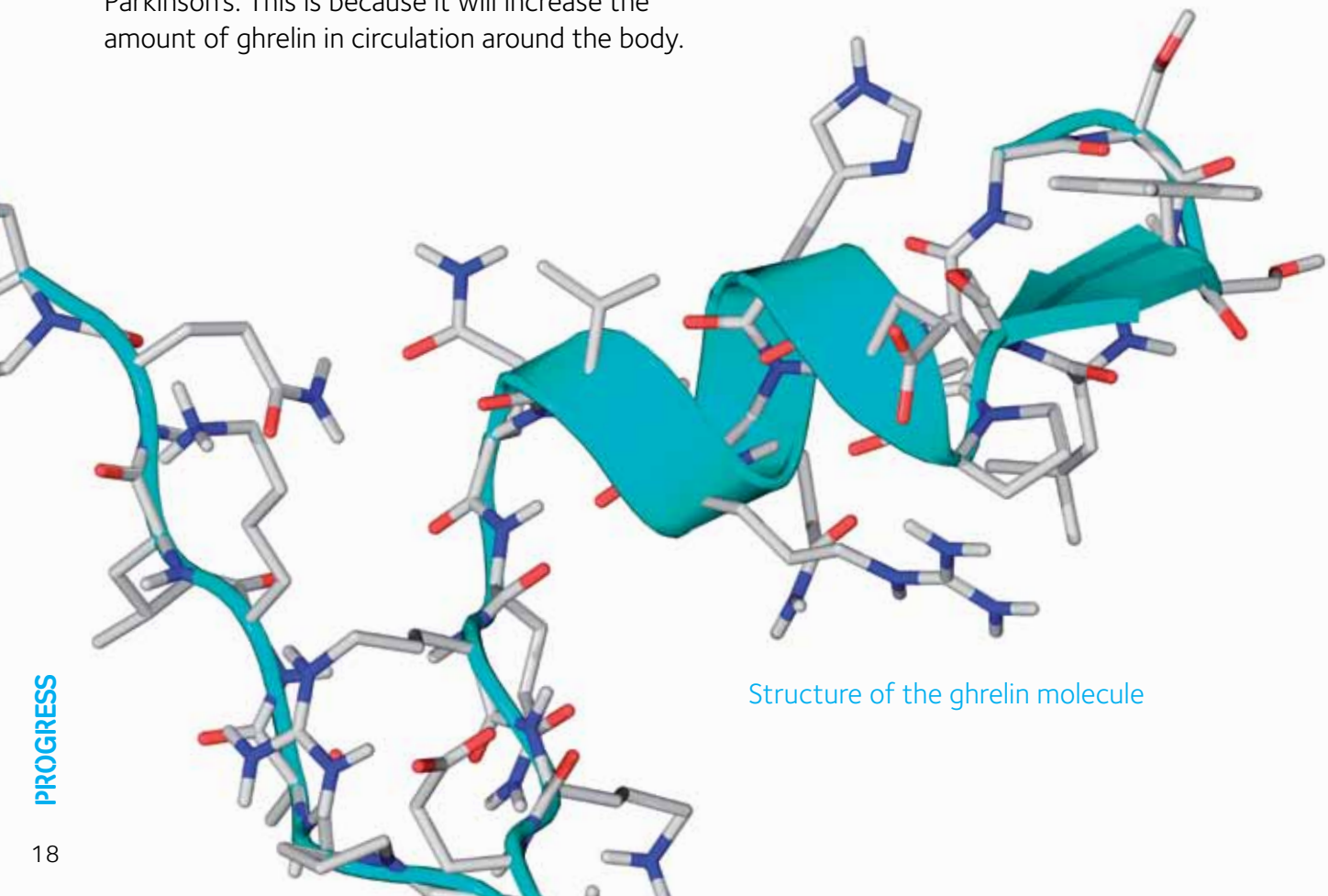
Scientists have previously suspected that restricting the number of calories people eat and drink may help to treat the symptoms of Parkinson's. This is because it will increase the amount of ghrelin in circulation around the body.

However, Jeff's team has discovered that keeping ghrelin levels constantly high may in fact be harmful to dopamine-producing nerve cells. So, we need to understand how ghrelin can be protective for nerve cells in some cases, but harmful in others.

Jeff's team suspect that eating food at regular intervals might increase the natural up and down rhythm of ghrelin levels in the blood. And this may be the key. The team plans to test whether it's the regular rhythm of ghrelin that protects the nerve cells and whether disrupting this rhythm may result in more nerve cell death.

Early results suggest that keeping ghrelin levels high activates inflammation in the brain. In the short term, inflammation is a helpful part of an active immune system. In the long term, it can have the opposite effect and actually increase the rate at which the nerve cells die.

"Our initial results are really exciting," says Jeff. "We have a lot of potential here to develop a novel therapy for Parkinson's that could perhaps be controlled by diet, or by a drug to regulate levels of ghrelin in the blood. If we can do that, it really could significantly improve the lives of people living with Parkinson's and ultimately slow down or halt the death of the nerve cells."



Structure of the ghrelin molecule

Predicting Parkinson's

Did you know that 60% of people in the UK now have access to the internet everyday? With this many people online, scientists are interested in how the internet could help to help identify people who may be at risk of developing Parkinson's.

Dr Alastair Noyce has been working with a team at Barts Hospital and the London School of Medicine and Dentistry and the Institute of Neurology to develop a computer program that could predict who might develop Parkinson's. Their grant of £35,000 will fund a study to find out how well the programme works.

Alastair

Movement-related symptoms of Parkinson's develop when 60-80% of nerve cells that produce the chemical dopamine have died in the brain. It's at this stage that people are usually diagnosed. But a lot of people who go on to develop Parkinson's report that they have experienced other non-movement related symptoms before their diagnosis. These include constipation, losing their sense of smell, anxiety, depression and sleep disorders.

On their own, these problems are often found individually in older individuals. But, when taken together, they may give us a way of identifying people who are at greater risk of developing Parkinson's or those in the early stages of the condition. Using these symptoms as a guide, Alastair's team have put together a questionnaire. Alastair explains more:

> "We aim to recruit 1,000 people who have not been diagnosed with Parkinson's or any similar condition, and who are between the ages of 60-80 years. We'll ask them to complete a quick questionnaire.

"We'll then look at the results using a computer program we've developed based on our analysis of how strongly these non-motor symptons have been associated with Parkinson's. Loss of sense of smell is thought to happen fairly early in the progression of Parkinson's. Therefore, all the participants will also have their sense of smell tested. Over time, we hope to develop a tool that will accurately identify people at risk of Parkinson's.

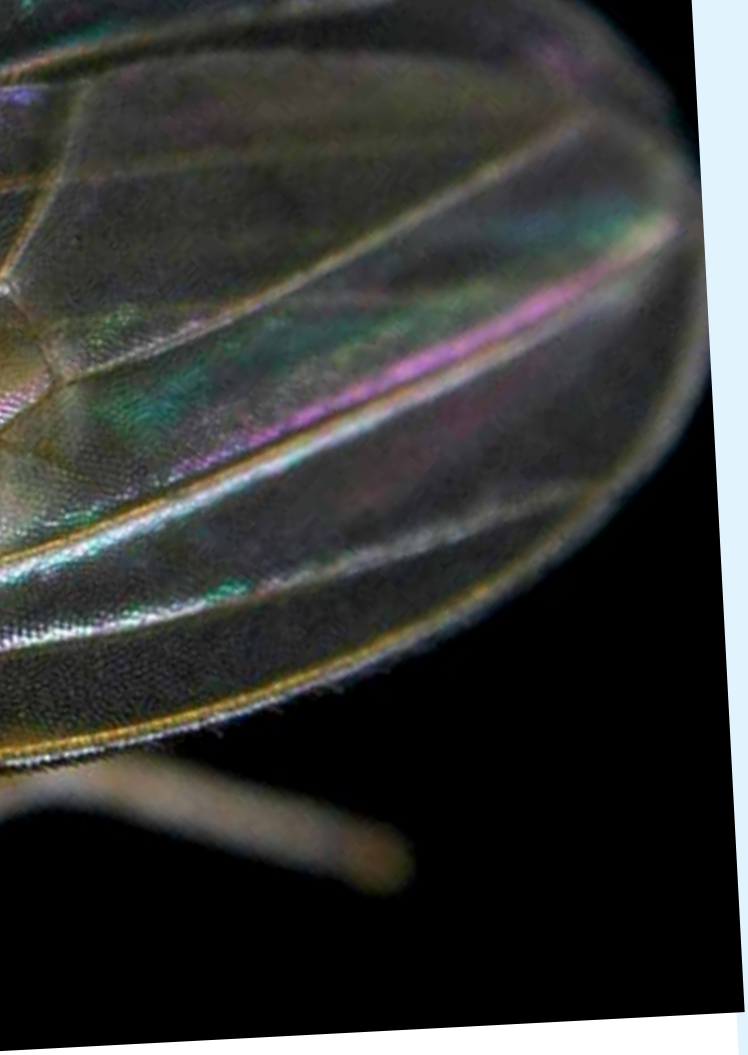
"By the time motor symptoms show up, it's impossible to stop the condition from progressing with current medication," continues Alastair. "However, if it were possible to identify the people most at risk of Parkinson's or who were in the very early stages, we could develop drugs to intervene before the movement problems occur. It may then be possible to slow down or even halt the condition. Finding the at-risk group and designing these drugs are two major priorities in Parkinson's research."

Keeping an eye on flies to help visual problems in Parkinson's

Fruit flies can tell us a lot about human genetics and how nerve cells work. In particular, the eyes of a fly are simple and fairly easy to study. Many people with Parkinson's have problems with vision. And it turns out that changes in three of the genes involved in the inherited form of Parkinson's may also lead to damage in the structure of fly eyes. So it's important to find out what effect these genetic variations have on the activity of these nerve cells. In this six-month project, Dr Christopher Elliot and his team at the University of York will use their grant of £33,587 to carry out the first study ever in this area of Parkinson's research.

Although Parkinson's is often thought of as mainly a movement disorder, many people experience eye trouble including difficulty reading, dry eyes and even hallucinations. Nerve cells in the eye contain the chemical dopamine. This is the same chemical that is used by the nerve cells that die in Parkinson's that are located in the part of the brain that controls movement. And there is some evidence that people with Parkinson's have problems in the retina which is at the back of the eye.

In both fruit flies and humans, dopamine plays a role in adapting the eye to bright light. But we don't yet know whether the genetic variations involved in Parkinson's changes how the dopamine-producing nerve cells in the eye work. LRRK2 is both the most common gene behind inherited Parkinson's and is also found naturally in



the fly, so it's an ideal gene to study. If changes in this gene interfere with the working of the dopamine-containing nerve cells affected by Parkinson's, what effect will they have on the dopamine-producing nerve cells in the eye?

The team will record the electrical signals generated by nerve cells in the eye in response to light – a procedure called an electroretinogram. They'll also study the visual part of the fly's brain to find out whether therapies that help Parkinson's symptoms might also help eye problems. They'll use the electrical signals produced by the eyes of fruit flies as a quick way to test potential drug treatments.

At the end of the project the team should have enough evidence to develop an in-depth study on how it may be possible to use the fly eyes to screen for more effective drugs to treat Parkinson's.

An objective measure of dyskinesia

It's a distressing fact that about 50% of people who take levodopa for more than five years will develop dyskinesia. This results in uncontrolled movements that can affect people just as much of the symptoms of their Parkinson's.

At the moment it's quite hard for doctors to help people manage dyskinesia very effectively. So to help change the situation, Dr Stephen Smith at the University of York is working on a computer-based system that should make it much easier to adjust people's medication. His one-year grant is for £33,935.

We can find out how much dyskinesia impacts on quality of life by asking the people affected and their carers. But there is currently no accurate way to measure how severe the dyskinesia is physically. So Stephen has been developing a simple tool that doctors can use to help them make an objective assessment. It'll get its first test run during this project.

Six participants will take part in the study and they will wear wireless sensors on their arms and legs for a 24 hour period. The sensors will be able to pick up movements automatically to record how strongly and how often they happen. The recordings will then be analysed on computer using Stephen's software that aims to tell the difference between dyskinesia and ordinary movements.

After this pilot study to demonstrate whether the system can work, the team aim test it out in a larger clinical trial. And the end result, we hope, will be a system that can easily measure dyskinesia. We can then use this information to optimise a person's medication. We hope it will improve life for everyone affected by Parkinson's.

Tracking the early signs of Parkinson's

Catching Parkinson's in its earliest stages is one of the major goals of current research. But at the moment there is no single test available in the clinic to tell us whether a person may be in the early stages of Parkinson's. Therefore, there is no chance to start treating the condition before the majority of dopamine-producing nerve cells have died in a part of the brain that controls voluntary movement. However, we do know that the protein LRRK2 is central to the condition. So it may be possible to develop an early warning sign based on monitoring LRRK2 activity. Dr Richard Wade-Martins at the Oxford Parkinson's Disease Centre has been given a grant of £35,000 over 12 months to investigate.

LRRK2 may be one of the keys to help us understand the death of dopamine-producing nerve cells within the brain. Recent research in animals has shown that when LRRK2 is over-active, the protein alpha-synuclein is more likely to stick together. Alpha-synuclein is the main component of Lewy bodies – clumps of protein found inside the dying nerve cells that are characteristic of Parkinson's. Another new discovery is that preventing LRRK2 from working can protect the dopamine-producing cells, stopping them from dying so quickly. The fact that LRRK2 seems to play such a key role in Parkinson's suggests that it may be an attractive prospect for monitoring the early stages of the condition.

Dr Javier Alegre-Abarrategui, a neurologist and scientist in Richard's lab who has a leading role in this research project, told Progress:

"Long before nerve cells in Parkinson's patients start dying, protein molecules inside them show abnormal properties. Like on a billiard table where the first strike hits one ball and then sets the others off. We believe abnormal activation of LRRK2 to be one of the first strikes in Parkinson's.


Javier

"We know that LRRK2 is only activated when two molecules bind together to form a pair. So we're working on designing a biological marker to label the active form of LRRK2 that should make it easier to see and even count. It's been done successfully in other research areas, but never before in Parkinson's. Because we know that overactive LRRK2 may play a role in the formation of Lewy bodies, we hope that monitoring LRRK2 activity like this could tell us whether Lewy bodies are starting to form."

A test like this could one day be used to find active LRRK2 in the blood or spinal cord fluid of people at risk of Parkinson's. It could also help us to develop new advanced scanning techniques. These would allow us to treat people at the earliest possible stage, even before the symptoms have developed. It could also make it faster and easier to find a drug that can stop LRRK2 from working abnormally, and so perhaps find a ultimate cure for the condition.

Ongoing and completed research

What worms can tell us about Parkinson's

PhD student Neda Masoudi is two years into her project with Dr Anton Gartner at the University of Dundee. The research team is using the humble nematode worm to understand what may cause dopamine-producing nerve cells to die in Parkinson's, and how it may be possible to protect them. Although the human brain is, of course, more complex than the worm's, the nerve cells communicate in similar ways.


Neda

Nematode worms have a total of just 302 nerve cells, but eight of these are almost identical to the dopamine-producing nerve cells that die in Parkinson's in people. So the worm can help us investigate what happens in the early stages of the condition. We can more easily pick apart how the cells interact and can quickly and cost-effectively test drugs that might prevent nerve cell death. This is one of the priorities of our five-year research strategy.

Variations in the LRRK2 gene are present in some people with inherited Parkinson's. But new evidence shows the gene may also be involved in the non-genetic form of the condition. Understanding what the gene does will provide vital information about the causes of Parkinson's.

"In one part of the project, we've been looking at the effect on worms of not having the worm-equivalent of LRRK2," says Neda. "And we have also set up a test that lets us screen for potential drugs that can change LRRK2 activity. These drugs may be useful in future to slow or halt the progression of Parkinson's.

"We've also been trying to identify other new genes involved in Parkinson's. It's exciting, because we think we've uncovered a gene that might protect against damage to dopamine-producing nerve cells. I'm looking forward to this final year of the project, when we'll really understand how different genes may be involved in nerve cell death." Watch this space!

Individual treatment

You may remember that in issue 6 we told you about Dr Ashwani Jha, a clinician with a strong interest in Parkinson's. We awarded him a three-year career development award of £173,953 to find out whether it's possible to tailor treatments to each individual's symptoms. One year into the project at UCL's Institute of Neurology, he tells Progress how it's going.

Ashwani

It's well known that the rhythm of signals used by nerve cells in the brain to communicate with each other is changed in Parkinson's. Successful treatments – whether drug-based or surgical, such as deep brain stimulation – can help to change this unusual electrical activity and reduce symptoms. But we don't yet understand exactly how this brain activity relates to specific symptoms.

"This is a really important issue," explains Ashwani. "People with Parkinson's have a great range of symptoms. The ideal treatment should target areas of the brain associated with each symptom."

In the past year, Ashwani and his team have scanned and recorded the electrical activity of nerve cells on the surface (the cortex) of the brain. Because the participants have previously had electrodes placed within the brain for treatment with deep brain stimulation, the team has also been able to record activity from deep within the brain. The team has investigated whether changes in the electrical activity in this area can be easily measured in the cortex. The aim is to identify patterns of electrical brain activity that match specific symptoms.

"So far, we've recruited 13 participants from London and Oxford, which means we're on-target to examine the 25 people we need in the study," continues Ashwani. "We've asked participants to perform a set of tasks that activate different brain regions involved in starting a movement, a key problem in Parkinson's. We then measure the effect of deep brain stimulation on the electrical signals, to find out what changes in nerve cell activity help to reduce symptoms for each person. We can treat individual symptoms more effectively if we can understand what is happening in the brain."

Ashwani and the team have presented their findings so far at two international scientific meetings and are ready to publish them to let others know about this exciting work. We'll keep you posted on this project, which is part of our commitment to develop a way to more accurately diagnose and monitor Parkinson's and ultimately to find a cure for the condition.

Taking a grant and running with it

We've probably all got the message that exercise is good for you! But for people with Parkinson's, putting it into practice isn't always so easy. Movement-related symptoms and a fear of falling can get in the way. So too can barriers such as the lack of appropriate facilities and support, the cost of exercise and travel and a lack of knowledge about Parkinson's by fitness instructors. To address the issue, in 2008 we gave an innovation grant of £14,750 to Prof Cath Sackley at the University of Birmingham. Together with a team led by Prof Helen Dawes at the University of Oxford, they carried out the 'PDEx' study to find out whether a specially developed exercise programme could help people with Parkinson's.


Cath

PDEx was a small pilot study designed to compare the standard care given to someone in the early stages of Parkinson's to an individualised exercise programme at a community leisure centre. This provided the appropriate support for people with specific mobility problems. The overall goal of the research was to find out what effect the training would have on people's mobility, strength, levels of physical activity and fatigue, the number of falls they had and how they felt about their general health. But first the team needed to find out whether the programme was feasible for people to take part in.

Participants in the study either started the three-month programme straight away, or were assigned to a 'control' group who carried on as usual for the first three months and did the specialised programme later on. This made sure no-one missed out on the exercise while allowing the research team to compare the programme to standard care.

Results showed that participants completed the exercise programme without any ill effects. Prof Sackley told Progress:

> "We were really pleased, because gym attendance for the programme was very good. This indicates that the programme could easily be implemented throughout the UK to provide rehabilitation away from a hospital environment.
>
> "This study gave us encouraging data, so we needed a larger study in order to find out whether there will be any differences between the exercise and control groups using various ways of measuring benefit."

PD Rehab is a large trial now being co-ordinated by Cath's and Prof Carl Clarke's group in Birmingham with funding of £1million from the Health Technology Assessment Programme. The team used the data from our innovation grant to help secure the funds and take this important work on to the next stage of improving life for everyone affected by Parkinson's.

On site:
Take part in research!

Our Research Support Network is a group of Parkinson's UK members, all with a keen interest in research. Within the network, a team of grant reviewers is involved in choosing which research projects to fund. They visit scientists all around the UK, and produce key information about research projects for other network members, Parkinson's UK staff and people affected by Parkinson's.

Tony Wells is a retired bus driver who's been a network member for the last two years. He tells Progress what he's been up to and why he got involved in this area of our work.

How did you get involved with the Research Support Network?

"I'm 61 now, and I was diagnosed with Parkinson's when I was 53. Soon after that I joined the charity and also my local branch at Harlow. They've got some really good organisers there, so there's a lot of support.

"There was an advert for the research network in one of the Parkinson's UK magazines and it appealed to me. I'm reasonably mobile and I enjoy helping people, so I decided to do as much voluntary work as I can. I came along to the induction day and it took off from there."

What sort of things have you worked on?

"I got rather enthusiastic and I've been on quite a few different site visits to places like Nottingham, Birmingham, Newcastle and London. A lot of the teams are multi-national, so they all exchange ideas. There are a lot of partnerships out there and overall, the progress since I've been doing this is astronomical. It really makes you feel better when you go to these projects, because you're asking questions and getting good answers. It's good to know that progress is being made. And best of all was when I was invited onto a selection committee..."

Was that for this year's career development awards?

"That's right. I remember that day well, because I actually had to help interview people, including doctors and scientists. Dr Patrick Lewis was one of them. He was describing things very well I thought, but I didn't understand everything, as some of it was very technical. So I said to him, if I invited you to a local branch, how would you explain your objectives to them in layman's terms? I think that was my job there really – to get people to say in plain English what they're actually doing. And he explained himself very well."

Tony

What do you think is the most interesting area of research right now?

"Obviously the main goal is to find a cure. But we've got to find the causes and better treatments in the short term as well. So, the most important thing at the moment is to get as much data as you can from people with Parkinson's. You've got to find out which people are more susceptible to getting Parkinson's. You need to find out about people's family background, and how Parkinson's may be diagnosed earlier. If you can get data in the early stages, you're on the way to finding the causes, which helps develop treatments, and then eventually a cure."

Where will the network take you next?

"I've taken a certain interest in the patient/carers side of things and so I've just started on a steering committee for a project on assistive technologies. I'm in a team that includes a Parkinson's nurse and other professional people. We'll meet at Guy's Hospital in London four times a year. And the idea of that is to let patients and carers know that there's help available for them in all sorts of ways. This is a long-term condition and I think that family carers need as much help as the patients."

What do you get out of being a member?

"I enjoy talking to professors and doctors. I listen to them, they listen to me and they take a lot of my questions on board. Since I got Parkinson's, I've learned to use a computer, and found out what a lot of the medical terms really mean. I think I'm more intelligent now than before I had Parkinson's! My motto is: 'It's not about what you can't do, it's what you can do. Do what you can handle, and what you can't do, well, there's another day.'

"As the Parkinson's has got worse I've gradually slowed myself down a bit. But I still take an active part in things, and I get tremendous support from the staff here at Parkinson's UK. I pass the information on as much as I can to local branches to let them know that there's a lot of people helping those with Parkinson's."

See page 33 for information on joining the Research Support Network.

News from the brain bank

The Parkinson's UK Brain Bank, based at Imperial College, London, is the UK's largest human brain bank dedicated to Parkinson's. Funded by us, the brain bank provides tissue to researchers around the world, who are working on a cure for Parkinson's. In the last issue, we updated you on the success of our 2009 Brain Donor Appeal. This inspired more than 2,300 people, with and without Parkinson's, to sign up to become brain donors. Here we meet a family who have signed their names to the Parkinson's brain donor register.

Paul with his family

Paul Sharpington is a Metropolitan police officer from Bexleyheath in London. As a busy PC, Paul is used to meeting people from all walks of life. He is aware that many people have to face particular problems on a daily basis, including living with conditions like Parkinson's. Paul's wife Jane is a teaching assistant in a local primary school with one-to-one responsibility for children with special needs.

Paul was surprised when he heard about the Parkinson's brain bank through our 2009 appeal – he wasn't even aware that you could register to donate your brain for medical research. As a committed blood donor for many years he knew that this was something for the whole family to consider doing. So Paul and Jane spoke with their two sons, Jamie (16) and Alex (13), about the brain bank, and the boys were keen to sign up too.

"As a family we are all very aware of the importance of giving back to society," Paul told Progress. "We are very happy for as many of our body parts and organs as possible to be used for medical research, and if our brains can help to find a cure for Parkinson's in the future, we would be delighted.

"We now have a total of 427 brains being stored," said the Parkinson's Brain Bank Manager, Dr George Gveric. "382 are from people with Parkinson's and 45 are from people who don't have Parkinson's. And there are another 5,600 people who have signed up to the Brain Donor Register, which is really impressive.

"Parkinson's is a complex condition that keeps on developing over time. Animal models are useful and help us study some aspects of Parkinson's. But they can't recreate the many changes we see gradually spreading throughout the brain as the condition progresses. So it's absolutely vital that we can look at the whole brain as well as studying what goes on inside the nerve cells. And we need to do this with brains from people who don't have Parkinson's as well as from people who do, so that we can compare the two."

With the help of people like Paul and his family, researchers have already made some major breakthroughs For example, the first signs that the nerve cells that are affected by Parkinson's have problems with making energy and removing toxic by-products from the process were found using tissue from our brain bank.

So a big thank you from everyone at Parkinson's UK to Paul, Jane, Jamie, Alex and everyone on the Parkinson's UK brain donor register. Your support is helping us to find a cure and improve life for everyone affected by Parkinson's.

George

For further information on becoming a donor, please contact the Brain Bank Manager, Dr George Gveric:

call **020 7594 9732**
email **pdbank@imperial.ac.uk**
visit **parkinsons.org.uk/brainbank**

People who have already registered but whose contact details have changed, please help us to keep our records up to date by calling **020 7594 9732**.


Roger

Back to the future

Researchers from around Europe and Canada are about to start a new five-year clinical study into cell replacement therapy for Parkinson's.

The TRANSEURO team secured a grant of €12million from the European Union for the research, after Parkinson's UK funded a series of initial planning meetings. Dr Roger Barker at the University of Cambridge is co-ordinating the project.

It's now over 20 years since tissue transplants for people with Parkinson's suggested that a cure was 'around the corner'. Several clinical trials took place in which participants had surgery to implant foetal tissue in the brain. This would replace the dead nerve cells in the part of the brain that controls movement.

For a few people, it seemed to work well – their symptoms largely went away. But it didn't work for everyone, and worse, there was no reliable way to tell who would get better and who would not respond at all. Some people even developed additional involuntary movements from the graft (so-called graft induced dyskinesias). As a result of this and the negative outcome from two small double blind placebo-controlled trials of this therapy in the US, these types of clinical trials stopped.

However, the new international study aims to show that cell transplants can in fact work consistently for some people who have specific types of Parkinson's. The research will take place at centres in the UK, Sweden, France, Germany and hopefully Canada as well. The team plans to recruit at least 80 people with Parkinson's to take part. Roger told us:

"The early trials showed us that cell transplants can work for people with Parkinson's but it wasn't clear why it worked for some people but not for others.

"We hope that our new trial will prove that cell transplants can work safely and reliably – potentially paving the way towards treatments that use stem cells to replace the cells that have died in the Parkinson's brain."

Research supported by:

The George John and Sheilah Livanos Charitable Trust

As the UK's Parkinson's support and research charity, we are leading the work to find a cure and we're closer than ever. All of our research programmes are funded entirely through voluntary donations, whether it's the combination of small, but significant, donations by individuals or through larger contributions by charitable trusts, individual donors and organisations. The charity's members and branches also play a key role in raising funds for the vital research that we carry out.

In the last issue of Progress, we reported on a project being funded by the Freemasons' Grand Charity. Here, we provide details of a project at the University of Oxford that is partially supported by the George John and Sheilah Livanos Charitable Trust.

The study is investigating two of the major themes that have emerged in Parkinson's research in recent years – the roles of a protein called alpha-synuclein and a process called oxidative stress. Alpha-synuclein is a key factor within Lewy bodies that are present in the brains of people with Parkinson's. (There was an article on Lewy bodies in issue 6 of Progress.)

Oxidative stress is a process within the cells that produces free radicals. These are chemicals that take part in the everyday activity of the cells and they're usually kept at a low level using specific enzymes. But too many free radicals are thought to cause the death of nerve cells and may play a key role in Parkinson's.

The NOS enzyme plays a key role in regulating the amount of free radicals within the cell. In this study Dr Richard Wade-Martins and his team are studying how alpha-synuclein and NOS may combine to cause the death of dopamine-producing nerve cells. The motor symptoms of Parkinson's will appear when 60-80% of the nerve cells in a specific part of the brain have died. We think that NOS and alpha-synuclein come together in some way to alter the number of free radicals in specific nerve cells.

The goal of Richard's project is to help us understand more about the factors that cause Parkinson's. We need to know how and why certain nerve cells in the brain in Parkinson's die in order to find a cure. This study is helping to fill in some of the current blanks in our understanding. If successful, we will be able to work out how alpha-synuclein and NOS combine to potentially lead to the loss of nerve cells.

The project will be completed in May 2012, and the research team has already made some key findings.

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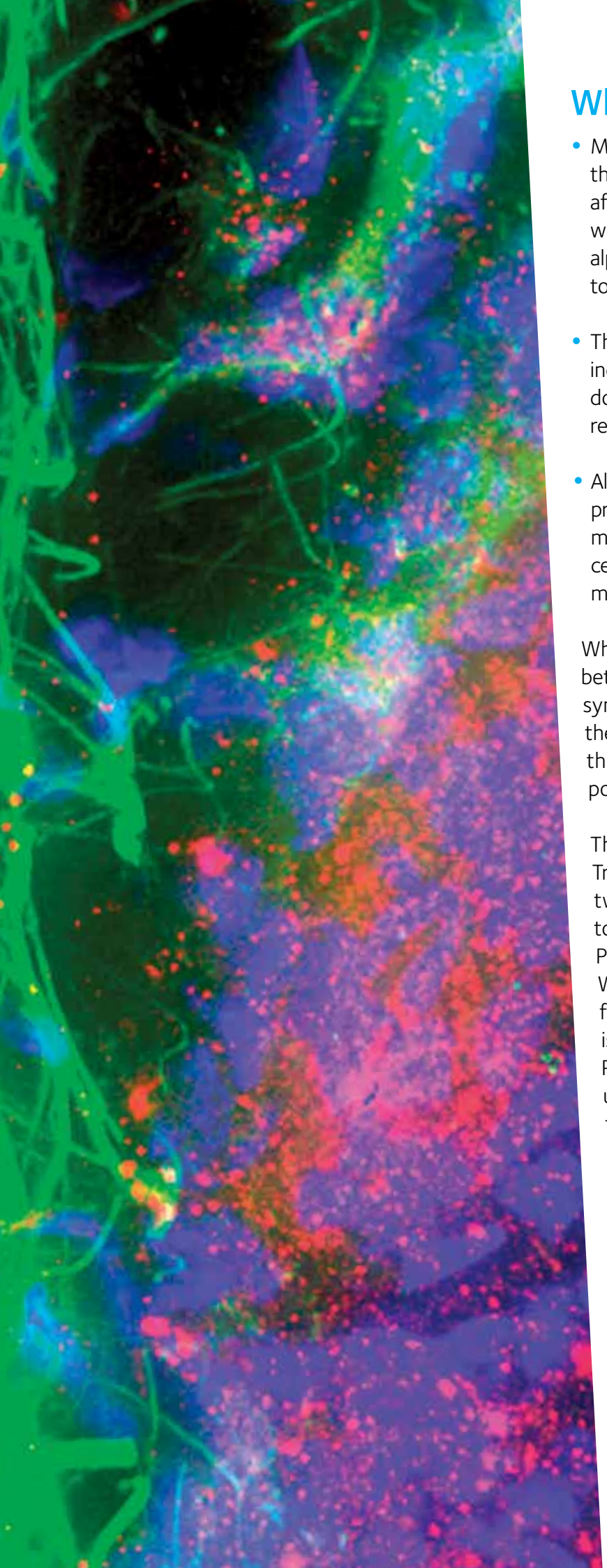

What has been found so far?

- MPP^+ is a neurotoxin that's thought to increase the levels of free radicals inside nerve cells and affects their ability to make enough energy to work properly. But, reducing the amount of alpha-synuclein in a nerve cell decreases the toxic effect of MPP^+.

- The activation of the NOS enzyme usually increases in response to MPP^+. However, this doesn't happen if alpha-synuclein levels are first reduced.

- Altering the amount of LRRK2 (another key protein involved in Parkinson's) inside nerve cells modifies the cells' ability to remove debris. In certain forms of Parkinson's, a change in the gene means that LRRK2 is not working properly.

When this project is finished, we will have a better understanding of the role of alpha-synuclein within the cell and whether it may be a therapeutic target. Potential drugs designed for this target could stop the disease process and possibly reverse it.

The George John and Sheilah Livanos Charitable Trust and the Freemasons' Grand Charity are two examples of how organisations working together can make a difference to people with Parkinson's. You can find details of Prof Nick Wood's project on the PINK1 gene, which is funded by the Freemasons' Grand Charity in issue 7 of Progress. These studies show how Parkinson's UK is working with donors to bring us closer to our ultimate goal – finding a cure for Parkinson's.

If you would like to know more about projects funded by Parkinson's UK or how you can help fund groundbreaking research like this then please contact us on **020 7963 9313**.

Research Support Network

Throughout 2010, the Parkinson's UK Research Team has been talking to our members, supporters and local groups about research. We've gained a lot of feedback and great suggestions on how we can get more people involved.

The top two things people tell us they want are:

- information about research to share with their carers, family, friends or local Parkinson's UK group. People especially want regular updates about clinical trials for Parkinson's, and the latest discoveries and results from research projects
- to volunteer for research. People want to be actively involved and help in our world-wide search for better treatments and a cure for Parkinson's

So in 2011, we're planning to build up our Research Support Network for everyone interested in Parkinson's research. We'll share lots of information with people who join the network to help spread the word and raise awareness about Parkinson's research.

We're also starting teams of volunteers who are united by their passion to make a cure a reality. Volunteer teams can play a part – however big or small – in the charity's research activities. The first teams are being set up in Wales, Eastern England and the East Midlands. You can get involved in a variety of different ways depending on your interests, skills and availability.

Become a Research Support Network volunteer!

If you're interested in being involved in our research activities and live in Wales, Eastern England or East Midlands, we'd love to hear from you. Please call Dr Lubna Arif, Research Liaison Manager, on **020 7963 9316** or email **larif@parkinsons.org.uk**

Lubna

Project index
Featured in this issue

Parkinson's UK ref	Article title	Lead researcher	Institution	Award type	£ awarded	Start date	Page
F-0606	The trouble with reward and motivation	Dr Iracema Leroi	University of Manchester	Senior Research Fellowship	£238,768	Jul 07	4
J-0704	Compulsive behaviours	Prof Paola Piccini	Imperial College London	Innovation	£310,319	Apr 08	7
J-0707	Compulsive behaviours	Prof Anthony David	Institute of Psychiatry, KCL	Innovation	£333,332	Jul 08	7
K-0903	Stem cells from the skin (York 2010)	Prof Maya Sieber-Blum	Newcastle University	Innovation	£34,936	Oct 09	11
K-0707	Gym training (York 2010)	Dr Ellen Poliakoff	University of Manchester	Innovation	£9,993	Jan 08	11
K-0702	Diabetes drug exendin-4 (York 2010)	Dr Peter Whitton	School of Pharmacy	Innovation	£7,092	Apr 07	11
H-1001	Are Lewy bodies the bad guys?	Dr Jody Mason	University of Essex	Studentship	£84,096	Oct 10	12
F-1002	All about LRRK2	Dr Patrick Lewis	Institute of Neurology, UCL	Senior Research Fellowship	£250,000	Upcoming	13
F-1001	The true costs of Parkinson's	Dr Emma McIntosh	University of Oxford	Senior Research Fellowship	£210,060	Feb 11	14
G-1003	Keeping it real – a better model of Parkinson's	Dr Richard Wade-Martins	University of Oxford	Project	£212,058	Oct 10	15
K-1001	Reducing inflammation	Dr Peter Teismann	University of Aberdeen	Innovation	£34,990	Sep 10	16
K-1004	Too much iron	Dr David Dexter	Imperial College London	Innovation	£35,000	Upcoming	17
K-1008	Could diet help stop Parkinson's?	Dr Jeff Davies	Swansea University	Innovation	£34,940	Dec 10	18
K-1006	Predicting Parkinson's	Dr Alastair Noyce	Queen Mary, University of London	Innovation	£35,000	Upcoming	19
K-1007	Keeping an eye on flies to help visual problems in Parkinson's	Dr Christopher Elliott	University of York	Innovation	£33,587	Upcoming	20
K-1005	Understanding dyskinesia - how wireless sensors could tell us more	Dr Stephen Smith	University of York	Innovation	£33,935	Oct 10	21
K-1003	Tracking the early signs of Parkinson's	Dr Richard Wade-Martins	University of Oxford	Innovation	£35,000	Upcoming	22
H-0709	What worms can tell us about Parkinson's	Dr Anton Gartner	University of Dundee	Studentship	£85,200	Aug 08	23
F-0903	Personalising treatment	Dr Ashwani Jha	Institute of Neurology, UCL	Training Fellowship	£173,953	Jun 09	24
G-0801	Research supported by: The George John and Sheilah Livanos Charitable Trust	Dr Richard Wade-Martins	University of Oxford	Project	£185,316	Oct 08	31

Recently started

Parkinson's UK ref	Project title	Lead researcher	Institution	Award type	£ awarded	Start date
G-1005	Developing bone marrow stem cell therapy for Parkinson's	Dr Alan Whone	University of Bristol	Project	£13,130	Jul 10
G-0910	Analysis of the functional consequences of alpha-synuclein phosphorylation at Serine 129 and its potential role in Parkinson's disease pathogenesis	Dr Mark Cooper	Institute of Neurology, UCL	Project	£208,751	Aug 10
H-1003	The control of striatal dopamine neurotransmission by axonal calcium channels and by striatal neuromodulators: insights for Parkinson's disease	Dr Stephanie Cragg	University of Oxford	Studentship	£92,993	Sep 10
K-1001	Assessment of a novel lead structure for the neuroprotective treatment of Parkinson's disease	Dr Peter Teismann	University of Aberdeen	Innovation	£34,990	Sep 10
H-1001	Using semirational design and single molecule imaging to generate antagonists of alpha-synuclein and understand their mechanism of action	Dr Jody Mason	University of Essex	Studentship	£84,096	Oct 10
H-1002	Generation of induced pluripotent stem cells from Parkinson's disease patients	Dr Maeve Caldwell	University of Bristol	Studentship	£87,476	Oct 10
K-0909	Does transcranial Direct Current Stimulation improve functional mobility in people with Parkinson's disease?	Dr Geert Verheyden	University of Southampton	Innovation	£33,608	Oct 10
G-1002	Development of Hsp90 inhibitors to combat neurodegeneracy	Prof Christopher Moody	University of Nottingham	Project	£120,895	Oct 10
G-1004	Understanding pathological spread in Parkinson's	Prof Tamas Revesz	Institute of Neurology, UCL	Project	£319,334	Nov 10

If you're interested in participating in a research study visit parkinsons.org.uk/researchstudies for a list of projects in your area, or call the Research and Development team on 020 7963 9326.

Progress is produced by the Parkinson's UK Research and Development team in collaboration with the Information Resources and Communications teams.

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