

The research magazine of the Parkinson's Disease Society

PROGRESS

Issue 6: Autumn 2009

Spotlight on Lewy bodies

Preventing falls in Parkinson's outside the home
Unravelling the mysteries surrounding Parkinson's
Helping people with Parkinson's feel more positive
Stem cells – a cure for Parkinson's?


Parkinson's
Disease Society

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Front cover image

Coloured transmission electron micrograph (TEM) of a section through a Lewy body. Lewy bodies are round clumps of material that can be seen inside damaged nerve cells and are a diagnostic feature of Parkinson's. They are largely made up of filaments of the protein alpha-synuclein (blue).
Credit: Lysia Forno/Science Photo Library

Welcome

Welcome to *Progress*, the Parkinson's Disease Society's research magazine. This issue contains details of some new and exciting research that is being funded by the Society, the latest results from completed studies and what these results mean for people with Parkinson's.



We continue to fund innovative research to develop better treatments and ultimately find a cure for people living with Parkinson's. Looking towards the future, our career development award scheme supports promising young researchers who will become the research stars of tomorrow.

Dr Tilo Kunath at the University of Edinburgh has recently received a fellowship from the Society for his research that uses the latest cutting-edge technology for Parkinson's stem cell research (see page 24). This new project builds directly upon his previous career development award that helped him establish one of the leading research groups working with stem cells for Parkinson's in the UK.

Identifying and treating the non-motor symptoms of Parkinson's is another top priority for people with Parkinson's. We have therefore invested over £1million into studying dementia in Parkinson's, to help us to detect it at an earlier stage and improve the treatments.

And finally, the Society has recently announced the funding of our largest ever research grant – the Discovery Award. This ambitious project brings several research teams together to tackle vital areas of Parkinson's. The aim is to develop ways of diagnosing Parkinson's earlier and developing new and better treatments that can slow or stop the condition progressing or ultimately reverse or prevent the death of nerve cells (see page 6).

Our research studies are completely dependent on voluntary donations. Only with your continued generous support will we be able to make the next crucial steps towards our ultimate aim of developing a cure for Parkinson's.



Dr Kieran Breen
Director of Research and Development

Spotlight on...

Lewy bodies

What are Lewy bodies?

Parkinson's is characterised by a loss of nerve cells in the region of the brain known as the substantia nigra. These cells produce the important chemical dopamine, which transmits messages between the parts of the brain that control movement. The loss of this chemical means that this part of the brain cannot function properly. The symptoms of Parkinson's occur when around 70% of these particular dopamine-producing nerve cells, in this specific part of the brain, are lost. Lewy bodies are round clumps of proteins that can be seen inside damaged nerve cells of people with Parkinson's and these may be associated with nerve cell death. They are formed within nerve cells before they die.

What do they look like?



Figure 1 Lewy bodies are made of proteins that clump together. They include the protein alpha-synuclein

Lewy bodies are not visible to the naked eye and so can only be seen through a microscope that magnifies the image (Figure 1).

Fact box 1: What research is the PDS supporting?

PDS-funded research is trying to understand how the protein found in Lewy bodies – alpha-synuclein – is involved in nerve cell death. Some of the ways in which this is being done include:

- the development of an animal model that mimics some of the symptoms of Parkinson's due to the death of dopamine-producing nerve cells. Researchers can use this model to find out how the formation of Lewy bodies are associated with the death of nerve cells and the role of alpha-synuclein in this process
- growing nerve cells in the laboratory and then switching off the alpha-synuclein gene. This allows us to look more closely at what happens to nerve cells and will tell us how important alpha-synuclein is within the cell
- finding out whether alpha-synuclein decreases the energy available within the cell. This energy is required to keep the cell alive, and to cope with factors that may spark off cell death

What are Lewy bodies made of?

Lewy bodies are made of proteins that clump together when the cells start to die. They include the protein alpha-synuclein. The gene which produces alpha-synuclein is involved in the rare inherited form of Parkinson's. This suggests that alpha-synuclein may play a role in nerve cell death, although the mechanisms by which this happens are not yet known. Researchers are trying to work out why the Lewy bodies are made and the importance of alpha-synuclein in the process (see Fact box 1).

Where does the name Lewy body come from?

The Lewy body was first discovered in 1912 by Friedrich Lewy, a German neurologist.

Why are Lewy bodies important?

There is no definitive test for Parkinson's. At present, the diagnosis of Parkinson's is made clinically by looking at the symptoms that a person is experiencing. In the early stages of Parkinson's, these symptoms may include tremor, stiffness and slowness of movement. People with Parkinson's may also experience difficulties with handwriting and with making facial expressions. However, there is an overlap with other conditions making it difficult to make a 100% correct diagnosis.

One of the definitive features that indicates that a person has Parkinson's is the presence of Lewy bodies in the brain. However, these Lewy bodies can only be detected by examining the brain under a microscope after the person has died. While someone is alive, a PET scan (see Figure 2) can detect a decrease in the level of dopamine from a specific region of the brain referred to as the basal ganglia. However, these scans are

expensive and not always available. Although a scan can help to confirm Parkinson's, the results are not 100% accurate in all cases. Ultimately, we would like to develop scanning techniques that will allow us to identify Lewy bodies while the person is still alive. This will confirm that a person definitely has Parkinson's and ensure they start receiving the correct treatment.



Figure 2 A PET (positron-emission tomography) scanner

Where can they be found?

Lewy bodies are found in damaged nerve cells in the brain of people with Parkinson's. However, Lewy bodies can also be found elsewhere in the bodies of people with Parkinson's. German researchers, Braak and colleagues, suggest that the changes that occur in Parkinson's may actually start outside the brain. Lewy bodies are first observed in the nerves surrounding the gut and then they progress through to the brain like a domino effect. They propose that Lewy bodies are first deposited in a section of the brain called the olfactory bulb and in the

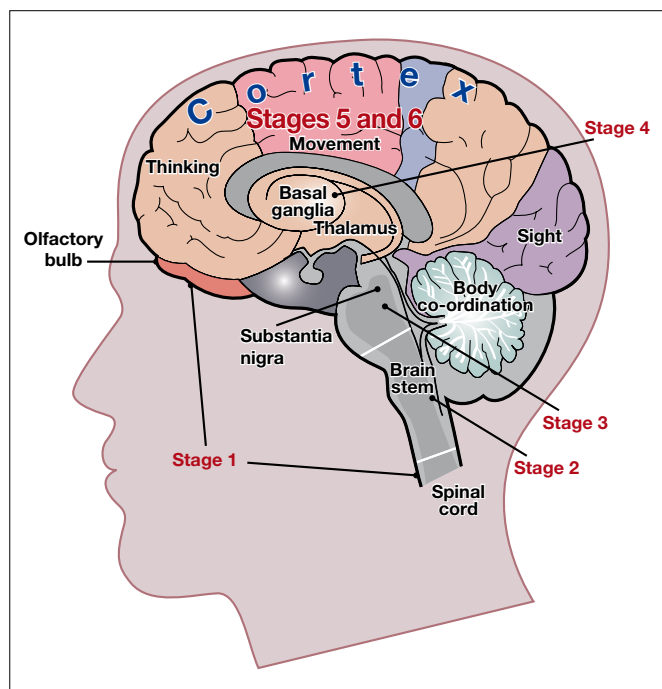


Figure 3 Regions of the brain affected by Parkinson's and the development of Lewy bodies.

lower brain stem (stages 1 and 2 of Figure 3, also see Fact box 2). Then the Lewy bodies move up from the brain stem to the substantia nigra, which is part of the brain where nerve cell loss occurs in Parkinson's (stage 3). It is interesting that the area of the brain that is first affected is the olfactory bulb. This is the part that is responsible for smell and a lot of people with Parkinson's lose their sense of smell before they develop the motor symptoms of the condition. In more advanced cases of Parkinson's, Lewy bodies then appear in the front part of the brain, which is called the cortex (stage 4, see Fact box 2) and become more widespread (stages 5 and 6).

Braak's observations of Lewy bodies spreading from the gut to the brain led him to question whether Parkinson's may originate outside the brain, caused by an unidentified agent that is capable, somehow, of travelling from the gut to the brain. It is important to stress that this explanation is unconfirmed and further research is needed to prove or disprove this idea.

Fact box 2: Some definitions (See Figure 3)

The **olfactory bulb** is part of the brain that is responsible for our sense of smell. It transmits information about odours from the nose to the brain.

The **brain stem** is the lower part of the brain where it connects to the spinal cord.

The **cortex** is the part of the brain that controls complicated tasks such as memory, attention, and language.

When do Lewy bodies start to form in the brain?

Lewy bodies start to form before the motor symptoms of Parkinson's are noticed. They are present in the brain when people begin to notice the non-motor symptoms of Parkinson's. People with Parkinson's experience a number of non-motor symptoms, such as loss of smell, depression and constipation. The period when these symptoms start is called the 'pre-motor phase' of the condition. We do not know the exact time period from when the nerve cells start to die and Lewy bodies form before the motor symptoms of Parkinson's appear. It is likely to vary significantly between people who develop the condition. However, research suggests that it is at least 6–8 years.

What is dementia with Lewy bodies?

Dementia with Lewy bodies (DLB) is one form of dementia that occurs in older people. The condition gets its name from the Lewy bodies that are found in certain parts of the brain after death. It shares symptoms with both Alzheimer's and Parkinson's. However, it differs subtly from both in the

exact symptoms and also in the changes that are seen in the brain after death. Fact box 3 lists some of the symptoms of dementia with Lewy bodies. About 75% of people with DLB will also develop some of the symptoms of Parkinson's. Another form of dementia that shares some of the symptoms of DLB is known as Parkinson's disease dementia. The Society is funding a major five-year research programme to understand this type of dementia in greater detail. To learn more about this project and also how Parkinson's disease dementia is different from dementia with Lewy bodies read pages 12–14.

Fact box 3: The symptoms of dementia with Lewy bodies

Symptoms include problems with:

- concentration and attention
- memory
- language
- the ability to recognise faces and objects
- the ability to carry out simple actions
- the ability to reason

For more information on DLB, you can get hold of a copy of our information sheet *Dementia with Lewy Bodies* by downloading it from www.parkinsons.org.uk or by obtaining a copy, free of charge, from:

Sharward Services Ltd
Westerfield Business Centre
Main Road
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Suffolk IP6 9AB
 Tel: 01473 212 115
 Fax: 01473 212 114
 Email: pds@sharward.co.uk

Presence of Lewy bodies after transplantation with healthy new nerve cells

Research has shown that foetal dopamine-producing nerve cells that were transplanted into the brains of people with Parkinson's survived for up to 16 years after the operation (see Fact box 4). However, some of the cells in the transplant eventually went on to develop Lewy bodies, which was totally unexpected. This suggests that some of the factors that spark off the development of Parkinson's may be able to transfer gradually from a sick nerve cell to a neighbouring transplanted healthy one in the brain. Researchers have long been debating whether Parkinson's results from a single factor that leads to the death of dopamine-producing nerve cells or whether it is a gradual process that spreads throughout the brain to affect previously healthy nerve cells. The researchers involved in these transplantation studies suggest that the factors responsible for triggering the death of nerve cells may be capable of spreading and affecting the new transplanted nerve cells.

Fact box 4: What is transplantation

- Transplantation refers to the process whereby the cells which die in Parkinson's are replaced with new healthy cells.
- The nerve cells can be obtained from a number of sources such as stem cells and human foetal brain tissue.
- The nerve cells can be injected into a specific part of the brain where they form connections with the neighboring parts of the brain.

Therefore, as new cells are transplanted into the brain, they eventually become exposed to factors that cause the formation of Lewy bodies and this eventually sparks off the death of the nerve cells. While these results

appear to support Braak's ideas about the progression of Parkinson's (page 4), further studies are required to examine the results of the transplant studies in more detail.

How is the PDS involved in transplantation studies?

The Society helped fund five people to take part in the first tissue transplantation trials

in the early 1990s. Two people involved in the trials showed improvements in their symptoms. However, not all of the participants benefitted and some people developed disabling side effects such as dyskinesias (random uncontrollable movements). The PDS has funded meetings of the researchers involved in the initial trials to allow them to analyse the results in detail. This could tell us why some people benefitted and others didn't.

Discovery award

£5million funding received to find a cure for Parkinson's

We can reveal that the PDS has received its largest single trust donation – £5million – to fund groundbreaking new research, aiming to crack the code and find a cure for Parkinson's.

The money will be provided over the next five years from The Monument Trust, one of the Sainsbury Family Trusts, which approached the Society with an offer to fund innovative new research to find a cure.

Scientists from across the UK were invited to apply for the newly created 'Discovery award' and seven of the best teams in the UK made the shortlist. The winning team from Oxford was chosen by a prestigious international review panel. The winning project will look at three key areas of Parkinson's research. Its aim is to discover how Parkinson's develops and progresses, what the early signs of Parkinson's are and how to pave the way for new and better treatments.

Read full details about the winning research, who is involved and where it will take place in the next issue of *Progress*.

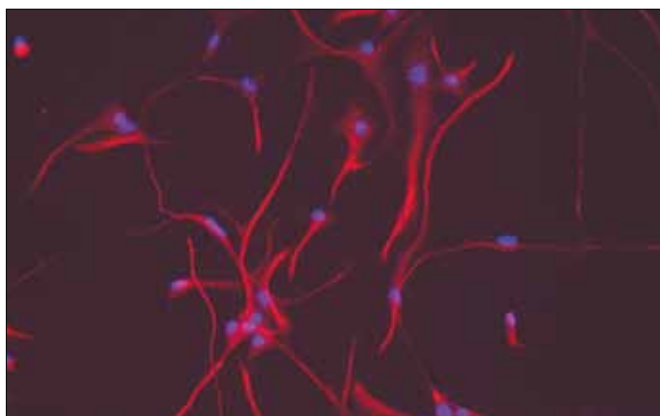


New research projects

At the Board of Trustees meeting in March 2009, six project grants, totalling over £1million, were given the go-ahead. These projects will mainly focus on getting a better understanding of the causes of the condition. It is only by gaining a better knowledge of why Parkinson's occurs that we can develop new treatments and ultimately a cure.

Understanding the causes of Parkinson's

In Parkinson's, there is a loss of dopamine-producing nerve cells in the region of the brain that controls movement. This cell death results in a decrease in the levels of the chemical dopamine, which prevents people from performing smooth, co-ordinated movements. There is currently no cure for the condition so it is important to improve our understanding of the factors that cause the decay of these nerve cells to move towards finding a cure.



Nerve cells grown in a lab

While the majority of cases of Parkinson's are not directly inherited, a number of defective genes have been found that have been associated with the rare inherited or familial form of Parkinson's. Inherited forms of Parkinson's account for up to 5% of people with the condition. In addition, there are likely

to be a number of genetic risk factors that make people more susceptible to developing the non-inherited form of Parkinson's. However, these need to be combined with external or environmental factors to trigger the death of nerve cells.

In 2004, groundbreaking research funded by the PDS led to the discovery of two genes associated with the inherited form of Parkinson's.

PDS-funded research has also played an important role in establishing that there are problems with the mitochondria that are contained within the nerve cells in the brain of people with Parkinson's. Like batteries, these provide energy for cells to function and ultimately keep cells alive.

Research has shown that at least three of the genes associated with the inherited forms of Parkinson's (DJ-1, parkin and PINK1) play a role in the normal working of the mitochondria. Therefore, mutations in the genes that are associated with Parkinson's will decrease the energy that is produced within the cells, which results in them losing the ability to work normally.

As dopamine-producing nerve cells are considered to be working 'flat out' under normal circumstances, any decreases in the energy available to them will have significantly harmful effects.

A zebrafish model of early onset Parkinson's

Lead researcher: **Dr Oliver Bandmann, University of Sheffield**

Cost: **£239,593 over 36 months**



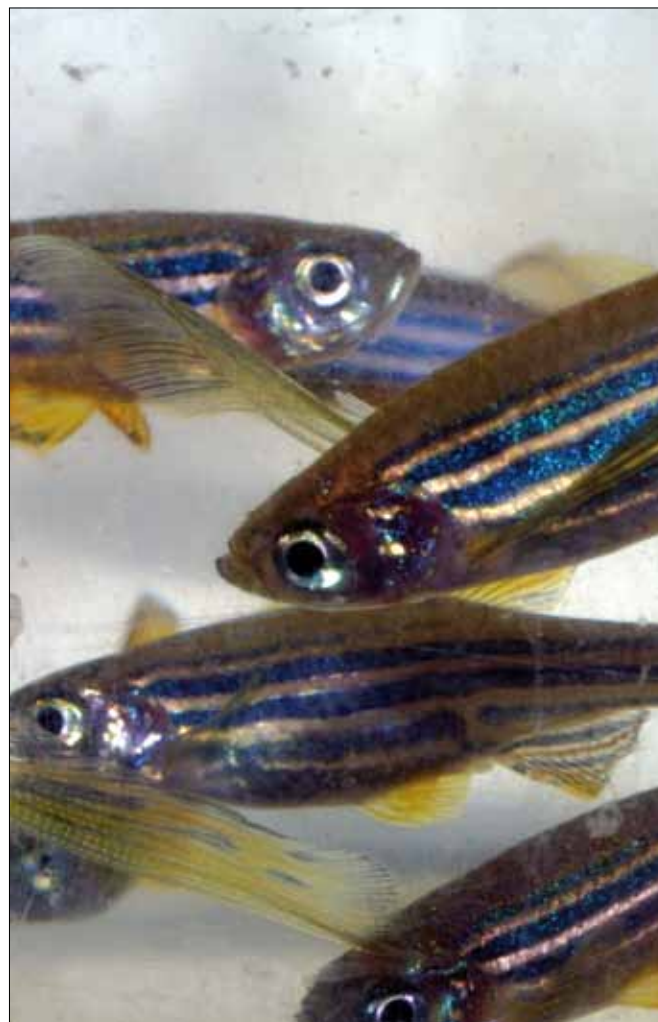
“In this study, we will focus on the parkin gene that is associated with an inherited form of Parkinson's that strikes at an early age. However, it can also result in some cases of Parkinson's that occur in older people. It is estimated that one in

20 people with Parkinson's is under the age of 40 when diagnosed, although only a small number of these will have a directly inherited form due to changes in their parkin gene.

“Specific changes or mutations in the parkin gene are the most common identifiable cause for the inherited form of early-onset Parkinson's. However, we don't yet know how these changes lead to the death of the dopamine-producing nerve cells. There is evidence to suggest that parkin may interfere with the working of mitochondria, which produce energy to power the cells to work normally.

“In this study, we will use the tropical zebrafish. They are a new animal model for Parkinson's and are frequently used for the study of other conditions. Zebrafish are useful in studies of Parkinson's because their parkin gene is very similar to the human parkin (see Fact box 5). We plan on removing the parkin gene from the zebrafish so that we can look at the difference that this makes to the nerve cells and how they work. Mutations have the effect of turning the genes off.

Therefore, these fish will have similarities to cells with the mutant parkin. It will help us to understand how defects in the human parkin gene result in the death of nerve cells that occurs in Parkinson's.



Adult zebrafish

“Ultimately, we may be able to use the zebrafish that lack the parkin gene to screen for new drugs that could slow down the progression of Parkinson's.

“This zebrafish model is also being used in another PDS-funded project (read about this project on pages 13–14 of the summer 2008 issue of *Progress*).”

Fact box 5: Why do scientists use zebrafish?

- Humans and zebrafish share many genes with similar functions.
- Scientists can easily add or remove genes in zebrafish.
- They live for a short period of about three months, so they can be studied over several generations.
- They can breed quite quickly and produce lots of offspring (hundreds of offspring per female per week).
- Their embryos are transparent, and it is relatively easy to change them genetically.
- The system that generates dopamine-producing nerve cells is well characterised in both embryos and the adult zebrafish and is comparable to that in humans.
- Dopamine-producing nerve cells are first detected at approximately 19 hours after fertilisation.

What role does the DJ-1 gene play in Parkinson's?

Lead researcher: **Dr Flaviano Giorgini, University of Leicester**

Cost: **£242,759 over 36 months**



“Mutations in the DJ-1 gene also cause early onset Parkinson's. Although the precise function of DJ-1 is unknown, it is thought to be important in protecting the brain from oxidative stress (see Fact box 6).

“Oxidative stress is a biochemical process that leads to the build up of toxic chemicals, known as free radicals, inside cells. These toxins damage the cells, making them sick and eventually causing them to die. A better understanding of how this happens will be essential to allow us to develop new treatments for Parkinson's.

Fact box 6: Oxidative stress

Free radicals are toxic molecules produced by normal chemical reactions in the body.

Oxidative stress occurs when there is a build up of free radicals within cells. This can also be due to a decrease in the levels of chemicals within the cells, called antioxidants, that normally overcome the effects of free radical levels.

“The purpose of this study is to find out how mutations in the DJ-1 gene affect how it works. The research will be done in collaboration with Dr Tiago Outeiro, who is based at the Institute of Molecular Medicine, Portugal. We will use baker's yeast in this study because it has been shown to be extremely useful in the study of neurodegenerative diseases and particularly the genes that are involved. Once we discover what the gene does and how it malfunctions in Parkinson's, then we can investigate this in greater detail using mammalian cells grown in the laboratory.

“As well as learning about the role of DJ-1 in the development of Parkinson's, the results may also uncover new ways in which drugs could be used to halt or even reverse the progression of Parkinson's.”

How does the DJ-1 gene protect cells against oxidative stress?

Lead researcher: **Dr Gyorgy Szabadkai**,
University College London
Cost: **£262,892 over 36 months**



“We will investigate how the DJ-1 gene interacts with other genes and proteins in the cell and how this may influence its ability to deal with oxidative stress. In particular, we will focus on how it

influences the amount of energy generated within the cell by the mitochondria (these are like the cell’s batteries).

“We will also find out what other factors are altered within the cell when there are changes in DJ-1. Our research will help us understand better what causes the nerve cells to die and will complement the research by Dr Giorgini which is also being funded by the PDS (see page 9). It may also help us to screen for effective new Parkinson’s drugs.”



Investigating changes in dopamine release from nerve cells in Parkinson’s

Lead researcher: **Dr Bazbek Davletov**,
University of Cambridge
Cost: **£99,946 over 24 months**



“In this project, we will be finding out how a protein called alpha-synuclein, dopamine and lipids (fat-like molecules) influence each other’s levels inside nerve cells. Changes in the levels of these three factors may cause nerve cells to

die and we would like to know how to prevent the death of dopamine-containing nerve cells. Dopamine is an important chemical which allows messages to travel between the parts of the brain that control movement.

“Mutations in the gene that produces the protein alpha-synuclein have been linked to an inherited form of Parkinson’s that occurs in younger people. Alpha-synuclein protein is also found in Lewy bodies (see pages 2–6), which are a characteristic of Parkinson’s.

“Despite playing an important role in Parkinson’s, we are still not sure of alpha-synuclein’s actual role within the cell. There is some evidence that it is involved in moving lipids within the nerve cells and also the release of dopamine. Our study will examine these ideas and look at how alpha-synuclein may behave inside the nerve cells during stress. We hope to explain why cells with a mutant form of the protein do not work properly. By understanding what happens at the early stage of the condition when Lewy bodies are formed will help us to develop drugs that can prevent cells from dying.”

The role of inflammation in the development of Parkinson's

Lead researcher: **Dr Matthew Wood, University of Oxford**

Cost: **£116,958 over 24 months**



“One important mechanism that may cause nerve cell death is called neuroinflammation. It occurs because of damage to a cell. Neuroinflammation results in the activation of specific cells and subsequent

release of harmful factors that may cause nerve cell death. This process causes the formation of damaging molecules, known as free radicals, by a process called oxidative stress (see Fact box 6). Nitric oxide is one of the free radicals and it has been suggested that an increase in the levels of this chemical can be harmful to nerve cells. However, it is still unclear as to how it actually prevents the dopamine-producing nerve cells from working correctly and causes them to die.

“In this study, we will investigate the role nitric oxide plays in the development of Parkinson's. In particular, we will look at two genes that are thought to be involved. New techniques that have been recently developed will allow us to switch these genes on or off and to examine what role they play in inflammation and the death of nerve cells. Ultimately, these genes could be used to develop new drugs that would slow down or halve the rate of death of the nerve cells.”

Why are dopamine-producing nerve cells vulnerable in Parkinson's?

Lead researcher: **Dr Siew-Lan Ang, National Institute of Medical Research, London**

Cost: **£189,017 over 36 months**



“There are three main areas of the brain in which dopamine-producing nerve cells are located. However, it is only the cells in a specific area of the brain called the substantia nigra that die in Parkinson's. It appears that the

cells in this part of the brain are much more sensitive or fragile than dopamine-producing nerve cells in other parts of the brain.

“The purpose of this study is to investigate how dopamine-producing nerve cells are produced. We will also look at why these cells are so susceptible to damage and why this is different in specific parts of the brain.

“We will look at the early stages of development of dopamine-producing cells in the embryo to see if there are novel molecules that stimulate the formation of dopamine-producing nerve cells. Our results may also tell us how we could convert stem cells into dopamine-producing nerve cells that resemble those found in the substantia nigra. This knowledge would then be applied to therapies that involve replacing the nerve cells lost in people with Parkinson's with new healthy ones. This research project may also unravel some of the reasons why nerve cells from the substantia nigra region of the brain are more susceptible to damage than those located in other areas of the brain. These new insights may lead to the design of novel treatments for Parkinson's.”

Themed research

Parkinson's disease dementia

What problems does Parkinson's disease dementia cause?

Dementia is a major non-motor symptom of Parkinson's (see Fact box 7) and people with the condition have a greater potential of developing it than those without Parkinson's. This increases the longer someone has had Parkinson's.

Fact box 7: What is dementia

At least one in three people with Parkinson's will get dementia. While each person is unique, symptoms typically include problems with planning, memory, speech and perception.

Parkinson's disease dementia is associated with specific symptoms, including visual hallucinations, delusions, apathy and depression. These symptoms can severely affect a person with Parkinson's quality of life and can cause a range of problems. It also places a greater strain on their carer and family. It is important to identify individuals at high risk of developing dementia so that appropriate therapy and management decisions can be made. This may include the early use of drugs to treat the dementia, and the more effective use of new treatments designed specifically to modify the progression of the dementia symptoms, as and when they become available.

How does Parkinson's disease dementia differ from dementia with Lewy bodies?



JOHN COLE/SCIENCE PHOTO LIBRARY

The diagnosis of Parkinson's disease dementia or dementia with Lewy bodies (to learn more about dementia with Lewy bodies, see pages 4–5) is based on a distinction between the time of onset of motor symptoms and when the memory problems started. Currently, dementia with Lewy bodies is diagnosed if the symptoms of dementia develop before or within one year after onset of motor symptoms and signs (i.e. parkinsonism), whereas Parkinson's disease dementia is diagnosed if dementia develops more than one year after the onset of motor symptoms of Parkinson's.

PDS funding the research gap

The PDS has awarded Professor David Burn, at Newcastle University, a grant of £1.18million to undertake a five-year research programme. Three research groups will be involved – Newcastle University, Cambridge University and Imperial College London.

Based on earlier studies at their clinics, the researchers will test the idea that it may be possible to identify people with Parkinson's that are at 'high risk' of developing dementia, based upon a series of clinical, brain imaging and genetic tests (see Fact box 8).

The investigators hope that this research programme will provide the evidence required to carry out future clinical trials that will lead to better and more effective treatments for people at higher risk of developing dementia.

Why is this study so important?

It is vital that we have a greater understanding of the symptoms of Parkinson's disease dementia to enable us to provide earlier and more effective treatments that can deal with the symptoms. The ultimate aim is to slow down or even halt the dementia.

How is the research being done?



Professor Burn gives us an account on how the research will be carried out: "We will study people who come to the clinic with newly diagnosed Parkinson's who do not have memory problems but who may subsequently develop symptoms of dementia. To confirm the presence of dementia, we will use a range of

Fact box 8: Brain scans, genetics tests and cerebrospinal fluid

Brain scanning studies

Using scans, structural and functional changes in different parts of the brain which have been shown to be associated with dementia will be looked for.

Genetic studies

The main aim of this part of the study is to generate a bank of DNA samples (extracted from each participant's blood cells) for future research studies. However, the focus for this study is to look for genetic factors that increase the risk of a person developing dementia.

Other blood and cerebrospinal fluid studies

Blood This study will look to see if raised levels of an amino acid (called homocysteine) is a factor that increases the risk of developing dementia. Other research groups have looked at this but the results have been inconsistent with some, but not all, studies finding a link.

Cerebrospinal fluid Cerebrospinal fluid is the fluid in which the brain 'floats'. It is also found in the spinal column. The investigators will obtain a sample of this fluid from the spinal column to see if certain proteins found within this fluid can indicate whether people are more likely to develop dementia.

investigations, including brain scanning, genetic tests and assessing cerebrospinal fluid for the presence of specific factors (see Fact box 8). This is a powerful way to identify markers or a 'signature' that may directly reflect ongoing changes in the person's brain. By understanding more about these biochemical changes, we may be in a better position to be more accurate in our diagnosis of dementia. We can then develop more appropriate treatments that can be given at an earlier stage when they are more effective."

How will people with Parkinson's benefit from this study?

"This research will benefit people with Parkinson's by investigating possible predictors of dementia. By identifying people

who are at higher risk, it means that when disease modifying treatments become available for dementia, they can be targeted to the right people, and used at an earlier stage. The earlier such drugs are used, the more likely they are to be effective."

Gill is a carer for her husband Alan, who has Parkinson's and dementia. She talks about her experiences.

"As headmaster of a large school, Alan (now 76) has always been an incredibly organised and energetic person. When he was about 55, Alan's personality began to change. I would find him sitting, just staring into space for long periods. Our GP wasn't sure, but thought Alan might be depressed, and put him on anti-depressants. I felt deep down that there was more going on, and when the depression didn't seem to be lifting I asked what else it could be.

"Alan eventually saw a neurologist, and we were told "it's Parkinson's disease". Within ten days of being put on anti-Parkinson's medication, Alan was his old self, smiling and talking. It was wonderful, and for five years my husband's Parkinson's was reasonably stable and we coped very well.

"About 18 months ago, I noticed that Alan was becoming forgetful. I put it down to advancing years, but then he began to suffer from frightening hallucinations.

"The psychologist that we saw thought Alan now had dementia. However, we were told Alan was not a suitable candidate for the drug Azilect, which

is used to treat dementia, for health reasons. I was devastated. It had taken four months to find this out.

"Alan currently goes to a day centre three days a week and has carers at home two mornings a week.

"It's like looking after a three year old when he's at home; I can't leave him for a minute. I look forward to the times when Alan goes into respite care. It might sound selfish, but 'me time' is very important. Alan still knows who I am, and I want to keep him at home for as long as possible. I try to stay positive and thinking about the future is very painful. My sons think he should be in residential care, but for the moment I can cope.

"It is fantastic that the PDS is funding research into dementia. We found it very difficult initially to get a diagnosis for what was wrong with Alan, and it is very frustrating not knowing what drugs might be out there to help people with Parkinson's and dementia, even if it only improves quality of life for a few months.

"I lost my husband once to Parkinson's and then to dementia. To lose him twice is devastating."

Research funding career development awards

The PDS is supporting the research careers of a further three young researchers. At the May 2009 meeting, the Board of Trustees approved two senior and one training fellowship that covers a range of Parkinson's research – from characterising the clinical changes seen in Parkinson's to ultimately finding a cure for Parkinson's using innovative stem cell technology.

It is crucial to support researchers as they develop their careers. If researchers did not study Parkinson's, many of the breakthroughs made by PDS-supported researchers, such as identifying two of the genes involved in Parkinson's, would not have been possible. Some of these key breakthroughs have been highlighted in our achievements booklet *Four Decades of Discovery*.



A cartoon of DNA in a double helix

In addition to funding specific high-quality research projects, the PDS is committed to supporting individuals who wish to specialise in Parkinson's research. One way in which we can do this is through the career development award scheme. The first two of these were awarded back in 2006. We catch up with Dr Leonora Wilkinson, one of the original researchers to receive an award, later in this article to learn about her achievements.

We are currently funding eight researchers who are studying a range of topics in Parkinson's. This includes identifying the areas of the brain that are responsible for problems with motivation and reward seen in people with Parkinson's, developing a mouse model that will be used to study nerve cell death in Parkinson's and also looking at the involvement of the PINK1 gene in Parkinson's.

The programme supports individuals who wish to specialise in Parkinson's research in the future, either by establishing their own research group (Senior Research Fellowship) or by undertaking relevant research training (Training Fellowship). This means we not only fund high-quality innovative research today, but also the best young researchers who will continue to carry out research in the future towards developing a cure for Parkinson's.

Understanding the effects of Parkinson's in learning

Dr Leonora Wilkinson received one of the first career development awards back in 2006. She gives an account of her discoveries so far (the project is due to end November 2009) and how this will help people with Parkinson's.



"I joined the Institute of Neurology, London, in 2003, where I am currently working as a researcher in the Cognitive-Motor Neuroscience Group with Professor Marjan Jahanshahi (also a PDS grant holder). One of

the major aims of this group is to investigate how Parkinson's affects the non-motor symptoms of Parkinson's, including learning and memory. In the course of the project, I also collaborated with Professor David Brooks (who works at Imperial College London) on studies involving imaging of the brain."

What is the aim of the study?

"The focus of my research is to study a specific type of learning, called implicit learning, which is considered to be involved in learning routine tasks such as riding a bicycle or playing golf. With this type of learning we reach the stage where we don't really have to think about an action when we carry it out. However, a second type of learning, called explicit learning, is responsible for learning specific tasks such as remembering a shopping list. Previous research has suggested that these two distinct learning systems, implicit (unconscious) and explicit (conscious) depend on different parts of the brain. "The Fellowship award from the PDS, has enabled me to further explore whether a

specific region of the brain, called the basal ganglia, controls implicit learning. The basal ganglia are important because the normal functioning of this part of the brain is affected in Parkinson's. Therefore the aims of the fellowship were:

- to study the effect of Parkinson's on implicit learning using tasks that require people to learn complex information, like a sequence of locations on the screen (see Figure 4) or the underlying rules of a complex card game.
- to investigate whether implicit learning, which is altered in Parkinson's, is influenced by medical and surgical treatments for Parkinson's. The two types of treatment studied were the drug levodopa or surgery (deep brain stimulation). Both of these treatments are used to alleviate some of the symptoms of Parkinson's, particularly tremor, slowness of movement and rigidity, and they can lead to remarkable improvements in the symptoms."

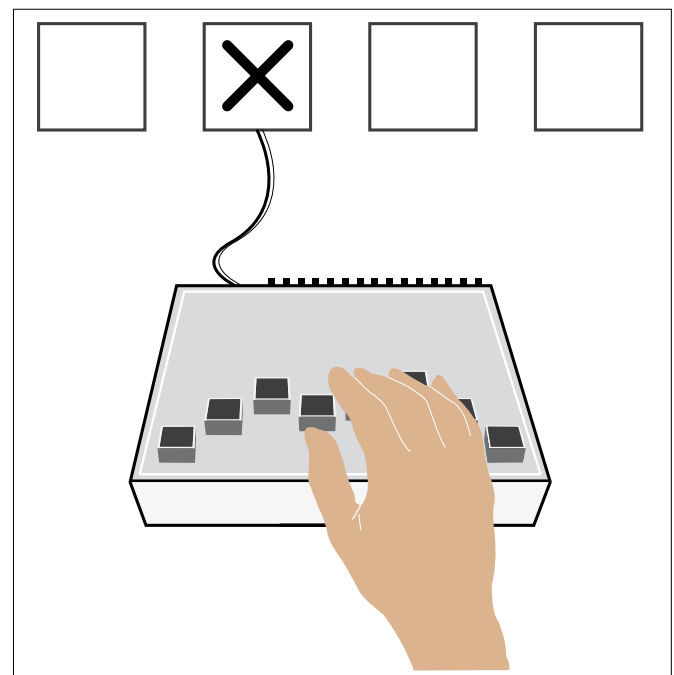


Figure 4 An implicit task in which people learn a sequence of screen locations

What we discovered

“People with Parkinson’s have problems with some forms of implicit learning, including learning a sequence of locations or objects on a computer screen which is called ‘motor sequence learning’. A second form of implicit learning involves being taught the rules of a card game. Deep brain stimulation improves both types of implicit learning described above. While levodopa impairs learning the complex rules of a card game, it has no effect on motor sequence learning.”

How will people with Parkinson's benefit from this study?

“The findings of this project have important implications for our understanding of how Parkinson’s has an impact on some forms of implicit learning in everyday life, including driving, typing or playing golf.

“We have identified that one of the current treatments of choice (levodopa) has adverse effects on some forms of implicit learning. This is important because the drug may give rise to memory problems and will therefore affect the ability of people with Parkinson’s to carry out everyday tasks. Furthermore, the problems associated with levodopa medication may affect the effectiveness of some forms of non-drug therapy in which routine learning plays a part e.g. physiotherapy or speech therapy. This may therefore be less effective when provided to people who are prescribed levodopa as their learning may be worse than if they were not taking the medication.”

Future research plans and how the PDS fellowship has played a role in this

“At the end of the PDS fellowship, I will work as a senior postdoctoral research fellow for two years with Dr Eric Wassermann, a neurologist at the National Institute of Neurological Disorders and Stroke, in Bethesda, USA. This exciting position arose as a direct result of the research findings of the PDS Fellowship. The post will enable me to continue my research on the effect of Parkinson’s on learning and memory and to identify any procedures that may help improve implicit learning in people with Parkinson’s. In a study such as this, we need to know what the problems are, i.e. the effects of levodopa medication on learning. The next stage, which I will carry out in the USA, will identify ways in which we can overcome these problems and so improve the lives of people with Parkinson’s.

“I plan on returning to the UK after two years and will apply the new skills I have learned while in the US to future research in the UK.”

For more information about surgery, you can obtain a copy of our *Surgery and Parkinson’s Disease* booklet by downloading it from www.parkinsons.org.uk or by ordering a copy, free of charge, from Sharward Services (see page 5 for contact details).

Recently awarded fellowships

This year, a total of 13 applications for career development awards were assessed and three were awarded. On the next page, two of the new fellows tell us about their work and give us an insight into what motivated them to get involved in Parkinson’s research. You can find out about the third award recipient, Dr Tilo Kunath, as he gets involved in the stem cell debate on pages 24–29.

Promoting activity and preventing falls in Parkinson's

Lead researcher: **Dr Emma Stack,**
University of Southampton

Cost: **£182,799 over 36 months**



"I am really excited and pleased about receiving a senior research fellowship to look at what causes falls in people with Parkinson's outside the home.

"I have a special interest in the activities that are associated with falls in people with Parkinson's, in particular turning round, which seems to be very difficult for people with the condition.

"My interest in Parkinson's started when, working as a physiotherapist, I met people with balance and movement problems that were difficult to assess, understand and manage. You can read about my other PDS-funded study looking at developing and evaluating a physiotherapy programme designed to help people to be able to stand up without any help, on page 4 of the spring 2009 issue of *Progress*.

"Falls are common among people with Parkinson's and it is estimated that around two-thirds of people with the condition will have fallen within the last 12 months. Most falls occur when a person carries out a specific activity. For example, falls can occur when a person turns round, which is actually one of the most challenging movement problems.

"As Parkinson's progresses, people generally tend to become less active. While there are

physical, psychological and social benefits of keeping fit, a fear of falling may lead to a reduction in the kinds of exercise and outdoor leisure activities that a person formerly enjoyed.

"In previous studies (also funded by the PDS), I found that some people with Parkinson's had "reluctantly given up" certain activities due to problems with their balance. These included a badminton player who felt less able to move backwards at speed; a swimmer who could no longer keep their legs, head and arms above the water simultaneously; and a cyclist worried that her balance was no longer good enough to allow her to ride safely.

"Some research into falls related to activity within the home has already been done, but we need to find out more about what happens in other settings e.g. outside the home. We will conduct a postal survey of a sample of people with Parkinson's around Solent (Dorset, Hampshire and the Isle of Wight) who have recently fallen, in order to learn more about the circumstances surrounding falls that have occurred in unfamiliar settings. We will then go on to assess tripping, stepping backwards and misjudging distances, which are commonly associated with falls in Parkinson's, by comparing people with Parkinson's and people who do not have Parkinson's. In another study, we will interview people about when and why they gave up activities that they previously enjoyed and whether this was related to their increased potential to fall.

"We will try to find new ways of communicating information about creating safer environments and making beneficial active leisure more accessible to people with Parkinson's and their carers, healthcare professionals, local authorities and leisure providers."

How will people with Parkinson's benefit from this study?

“We believe that people with the condition could stay mobile and avoid falls if the environment was more Parkinson’s-friendly and if we identified movement techniques that helped people make the most of their abilities.”

Can we personalise treatment for Parkinson's?

Lead researcher: **Dr Ashwani Jha,**
Institute of Neurology, London
 Cost: **£173,953 over 36 months**



“I am really grateful to the PDS for awarding me a trainee fellowship award. In this study, I will explore the potential for developing treatments tailored to tackle the individual symptoms experienced by people

with Parkinson’s. I have a special interest in Parkinson’s and in particular the surgical procedure known as deep brain stimulation.

“My interest in the condition started as a junior doctor when I was struck by the impact of memory problems in people with Parkinson’s. I have been fortunate enough to work with some inspirational doctors, nurses and people with Parkinson’s who taught me how specialist knowledge can improve the potential for people with Parkinson’s to carry out everyday activities. I have since begun to specialise in the treatment of movement disorders. During 2009, I moved to the Institute of Neurology, London to start a PhD under the supervision of Professor Peter Brown who, through

PDS funding, is looking at how deep brain stimulation works.”

You can learn more about Professor Peter Brown’s project by reading page 8 of the spring 2009 issue of *Progress*.

“Parkinson’s is a complex condition and no two people with the condition have the exact same symptoms. The problem is that we do not know the reason for this variation and the best way to optimise the treatment. It is well known that the electrical impulses that individual nerve cells use to communicate become abnormal in Parkinson’s. Successful treatments, including drug and surgical therapies, try to overcome this abnormal activity and help reduce the symptoms. It is unclear, however, how this altered electrical activity in the brain is related to specific symptoms of the condition.

“Our research will focus on a group of 25 people with advanced Parkinson’s. We will measure the electrical activity within specific parts of the brain by using electrodes that have been introduced into the brain during deep brain stimulation. We will then investigate how the electrical signals vary within the group and how this may relate to their individual symptoms.

“Once we have worked out which parts of the brain are involved in the development of specific symptoms, we will test our findings by actually changing how these particular parts of the brain work. Creating disruptions in specific brain regions should mimic some of the symptoms and will help us to understand what parts of the brain are responsible for them.”

Site visit

How the fruit fly can help to understand the causes of Parkinson's

Dr Frank Hirth hosted an interesting site visit to his research facilities at the MRC Centre for Neurodegeneration Research, Institute of Psychiatry, King's College London. He shared some exciting initial findings from his project involving the fruit fly (see Figure below). His research is looking at factors that are responsible for nerve cell death. Members of the Research Network were present and keen to talk with the researchers and discuss the work that is being funded by the Society.



A adult fruit fly on the lead of a pencil

Dr Hirth started the visit by introducing his team and then giving a clear and enlightening presentation on the background to the project, what it hoped to achieve and the findings so far. The meeting was very informal, so there was plenty of opportunity for the participants to ask questions and discuss the research.

What is the research about?

Symptoms of Parkinson's emerge when around 70% of the nerve cells die in the part of the brain that is involved in movement control. These cells produce the important chemical dopamine, which plays a key role in controlling people's ability to carry out smooth co-ordinated movements. The death of these cells results in a decrease in the amount of dopamine in this part of the brain. This eventually leads to the movement problems that are associated with Parkinson's.

Although it is not known what causes Parkinson's, there is some evidence that problems with the mitochondria, the batteries of a cell, in addition to a process called oxidative stress (see Fact box 6 on page 9) may be responsible for the death of the nerve cells in the brain. However, conclusive evidence for this is lacking.

Dr Hirth gives an account of the progress so far

What is the aim of the study?

"I was pleased to receive a grant of £184,696 from the PDS so that my team could embark on a three-year study that looks at the role of the mitochondria and oxidative stress in the development of Parkinson's. The research is being carried out using fruit flies. They provide an excellent model system with which

to study Parkinson's because of their very specialised genetic make-up (see Fact box 9). Importantly, by making changes (mutations) in specific genes, these flies can be made to exhibit some of the symptoms of Parkinson's, including an age-related loss of dopamine-producing nerve cells that gives rise to them having problems controlling movement."

Fact box 9: What is the link between fruit flies and Parkinson's?

- Each fly has only around 100 dopamine-producing nerve cells in the brain. By contrast, a person has hundreds of thousands of cells. This means flies are easier to study than humans.
- Since people and flies share many genes, they are a great tool for understanding why nerve cells die, as they are easy to study.
- By making changes (mutations) in specific genes, fruit flies can be created that have some Parkinson's-like symptoms such as problems in controlling movement.

What we did

"We exposed the brain of the flies to factors such as chemicals that prevent the mitochondria from working properly. This led to the onset of oxidative stress. We then monitored whether the dopamine-producing nerve cells in the fly brains lived or died (see Figure 5). Each experiment took up to three months to complete."

Results so far

"In the 12 months since we started the project, we have had some very promising results. Importantly, we have identified defects in the mitochondria that result in them not functioning properly. These defects become worse with age and eventually lead to the

death of dopamine-producing nerve cells. Fruit flies, therefore, provide an excellent model of Parkinson's as they allow us to study in detail what actually happens when the nerve cell is dying."

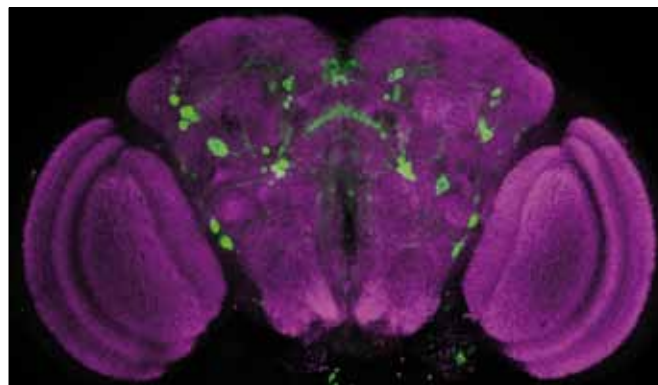


Figure 5 Dopamine-producing nerve cells (in green) in the brain of a fruit fly (coloured magenta).

What happens next...

"The results allow us to use this model to carry out further studies. The questions we aim to answer include:

- Why are dopamine-producing nerve cells specifically vulnerable to cell death in Parkinson's?
- Can we use this information to develop ways in which we can protect the cells from dying?

"Ultimately, we want to use this model to test small molecules for their potential to slow or stop Parkinson's from progressing. These molecules can then be tested in larger animals and if they show that they can protect nerve cells, they can then be tested in the clinic."

George, a member of the Research Network said:

"I think that there is a good chance that the research may indeed discover new mechanisms to protect cells from dying in people with Parkinson's."

Completed research

Helping people with Parkinson's feel more positive

Changes in emotions and mood experienced by people with Parkinson's

Lead researcher: **Professor Richard Brown, Institute of Psychiatry, London**
Cost: **£122,780 over 36 months**



What the research is all about

“Parkinson's is a complex condition and people can have many different symptoms. Problems with movement have long

been the focus of attention and remain the main target of the development of treatments. However, people with Parkinson's can experience a wide range of other problems that we are only slowly coming to understand. The presence and severity of these non-movement problems vary greatly from person to person. For example, some people experience troublesome hallucinations or memory difficulty, while others report feeling anxious or depressed. Some find it difficult to feel enthusiastic, motivated, or excited about new things. However, there are also many

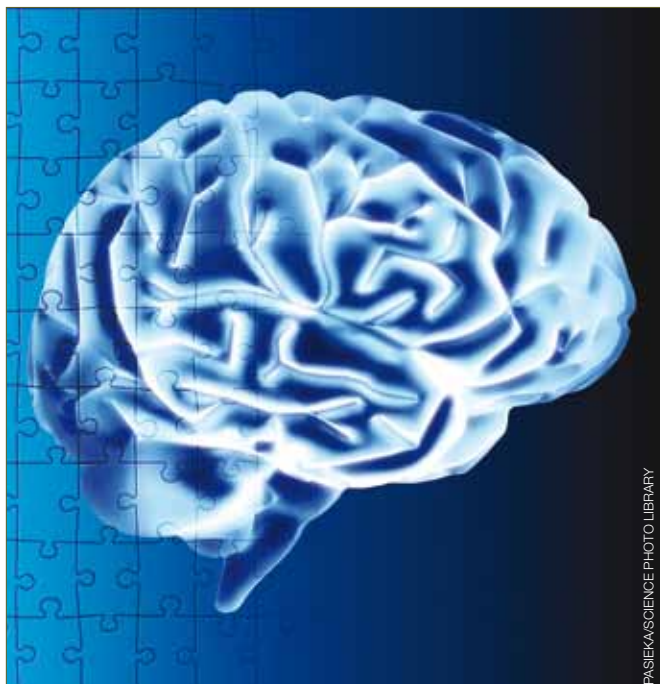
people with Parkinson's who are not affected by any of these symptoms. Understanding the nature of such problems and why there are such differences between individuals is essential if we are going to find better ways to help treat or support these people.

What was the aim of the study?

“Despite these being important problems, we know little about how mood, motivation and cognition (which is the term used to describe how we process thought) interact in Parkinson's. This study was designed to explore this question.

What we did

“Seventy-two people with Parkinson's (who were recruited from a local movement disorders clinic) and 54 people of the same age who did not have Parkinson's (the control group) took part in the study. We used a variety of psychological tests to examine how members of each group process and remember different types of material. We showed them pictures and words, some of which had emotional content (either positive or negative) and some of which were emotionally neutral. Specifically, we wanted to see whether the emotional content of the material either helped cognition (memory and attention) or interfered with it.



PASIEKA/SCIENCE PHOTO LIBRARY

What we discovered

“As expected from previous research, people with Parkinson showed higher levels of depression than the control group.

“There were not enough people in the group of people without Parkinson’s who were suffering from depression so we could not directly compare results from people with Parkinson’s. Depression certainly caused people with Parkinson’s to be more negative. When they were shown unpleasant images (e.g. a rubbish strewn street) they tended to rate them as more unpleasant than people who were not depressed. They were also more likely to describe themselves in negative terms. More importantly perhaps, their memory was also biased in favour of remembering more negative material. This may mean that people with Parkinson’s with low mood may have a more negative view of their life and things that have happened to them in the recent past. This will affect their general morale and view of the future. There is a danger that this can lead to a vicious-circle of negative memory and low mood feeding on each other.

Fact box 10: What is cognitive behavioural therapy (CBT):

CBT is a form of psychological therapy designed to help solve problems in people’s lives, such as anxiety and depression.

CBT can help you to change how you think (‘cognitive’) and what you do (‘behaviour’). These changes can help you to feel better. Unlike some of the other talking treatments, it focuses on ‘here and now’ problems and difficulties. Instead of focusing on the causes of your distress or symptoms in the past, it looks for ways to improve your state of mind now.

What happens next...

“Where depression is not severe, current guidance suggests that psychological treatment called cognitive behaviour therapy (CBT – see Fact box 10) may be beneficial and sometimes preferable to antidepressant tablets in the first instance. However, any treatment has to be shown to work, so the next stage is to prove that CBT is effective in Parkinson’s depression. A recently published pilot study produced encouraging results, and there are currently three clinical trials underway in the USA that are looking at CBT as a treatment option for depression in people with Parkinson’s. Hopefully, once these have produced their results, CBT may become more widely available for people with Parkinson’s.

How this helps people with Parkinson’s

“Even when people do not feel depressed, their mood can be negative – they may be sad, irritable, anxious or worried. All of these can be distressing and interfere with life. Learning to recognise how our thoughts, feelings and actions relate to each other is the first stage to improving things with help. People should be encouraged to talk to their GP to see if referral to a psychologist for CBT may be helpful.”

Stem cells

A cure for Parkinson's?

The PDS has awarded a senior research fellowship, worth nearly £380,000, to Dr Tilo Kunath, at the University of Edinburgh. He will carry out exciting new research to create induced Pluripotent Stem (iPS) cells from people with Parkinson's. iPS cells are special because they have the ability to be transformed into any cell of the body, including nerve cells. They can be used to help us to understand why nerve cells die and can be used to screen new drug molecules (see Figure 6 and Fact box 11).



Dr Kunath gives us an insight into what drew him to Parkinson's research and his views on the future of stem cell research.

What drew you to Parkinson's research?

"I believe that Parkinson's is the most interesting of the neurological conditions to study, and the one most likely to benefit from research using stem cells. I carried out research on embryonic stem cells in Canada, and when I came to Edinburgh I focused on learning how to make nerve cells from stem cells. I decided that this area of Parkinson's research is where I want to be."

What part has the PDS played in helping you develop a career in Parkinson's research?

"The PDS has been hugely important to my career to date, and without their support it would have been extremely difficult to do the kind of research I am interested in. They funded my initial studies as a post-doctoral scientist, and I have just been awarded a prestigious senior research fellowship for very new research that focuses on generating iPS cells from people with Parkinson's. We can use iPS cells to help us understand how Parkinson's develops and create a resource to screen for new drugs. This research will be my focus for the next three to five years."

Getting to know you

Who is your all-time movie hero? I'm a big fan of Mike Myers who is also from Scarborough, Ontario.

If you were stranded on a desert island what would you take? A satellite phone with built in GPS.

What is your favourite dessert? I'm not a big pudding person, but it would have to be crème brûlée.

“I also have very close links with the PDS Edinburgh Branch. They have raised funds to sponsor research equipment for my lab, and will also be helping to recruit people with Parkinson’s for the project described. The branch takes an active interest in research, and I’ve given tours around the labs to several members.”

You can read more about how the PDS Edinburgh Branch has supported Dr Kunath’s research on pages 23–24 of the summer 2008 issue of *Progress*.

How will your research benefit people with Parkinson’s?

“A good model of Parkinson’s does not currently exist and this makes it difficult to examine why human nerve cells die in people with Parkinson’s. My research will investigate whether iPS cells can provide a system with which we can mimic Parkinson’s in the lab (see Figure 6). Establishing such systems will be critical for understanding exactly what happens with the nerve cell of a person with Parkinson’s that causes it to die and also create an invaluable tool for drug discovery. Both of these will be essential to finding an ultimate cure for Parkinson’s.”

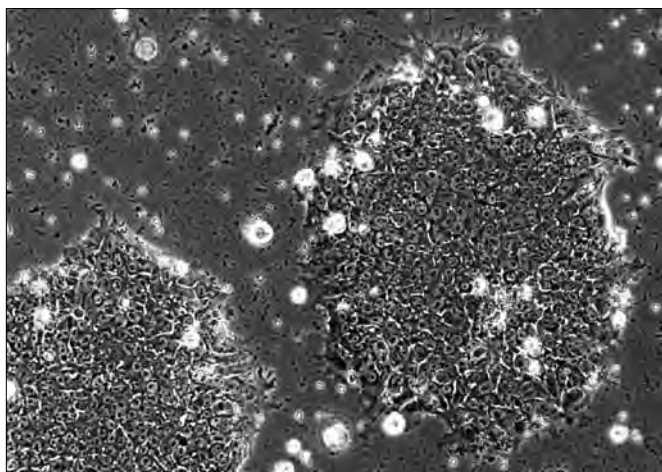


Figure 6 Human induced Pluripotent Stem (iPS) cells derived from skin cells

Where do see your career developing?

“I am at the early stages of setting up my lab in the MRC Centre for Regenerative Medicine in Edinburgh. I plan to establish a research lab at this centre that focuses on using stem cells to study Parkinson’s. I also plan to build up a collaborative research programme for Parkinson’s with neurologists in our centre and in Edinburgh. This has in fact already begun – consultant neurologist, Dr Siddharthan Chandran and I will be supervising a joint project with a PhD student. I believe that close interactions between basic and clinical researchers will be vital to make significant progress towards a cure, and the MRC Centre where I am based is fostering such relationships.”

How will the PDS benefit from the award?

“The PDS will benefit from this award in several ways. The two most obvious and direct benefits, beyond the publications that arise from my work, are that:

- the PDS will be involved in creating Parkinson’s-specific stem cell lines that will be used as research tools within the UK and abroad
- the PDS will have helped to establish a new Parkinson’s research programme in Edinburgh

“The full potential of Parkinson’s-specific stem cells to study the condition are yet to be fully understood, but they are likely to provide a key link to finding a cure. The long-term benefits of establishing a new lab and research programme focused on Parkinson’s is very significant. The fight against Parkinson’s is an international effort, and increasing the critical mass of scientists addressing this problem will have a very positive effect in stimulating this research.”

What does the end of restrictions on embryonic stem cells research mean for the future of Parkinson's stem cell research?

In early March, President Obama announced that restrictions put in place on the US Government funding for embryonic stem cell research have been lifted. Former President George W Bush had blocked the use of any Government money to fund research on embryonic stem cell lines created after 9 August 2001.

While still a Senator, Barack Obama said in 2007 that Bush's obstruction of stem cell research was "deferring the hopes of millions of Americans who do not have the time to keep waiting for the cure that may save or extend their lives".

Dr Kunath says:

"In effect, eight valuable years of potential stem cell research have been wasted. During the time of the ban, scientists had to concentrate on finding other types of cells for research, or were limited to the few embryonic stem cell lines available. Now that US Government funding is available for human embryonic stem cell research, we have also developed iPS cells, which are proving to be a promising alternative for several reasons. The properties of embryonic stem cells and iPS cells are very similar. If the US science machine had not lost eight years of valuable research on human embryonic stem cells, we would all be in a better position to understand how iPS cells can be used. But we can't get those lost years back. It's a huge shame."

What are iPS cells?

"Previous research has shown that many cells in the body, such as those in the skin, can be reprogrammed to become stem cells. These cells, called iPS cells, then have the ability to be transformed into any cell in the body, including nerve cells. They could then be used to model Parkinson's in the lab, screen for new drug molecules, and may even be used to replace the cells lost in Parkinson's by transplantation into the brain (see Figure 7 and Fact box 11)."

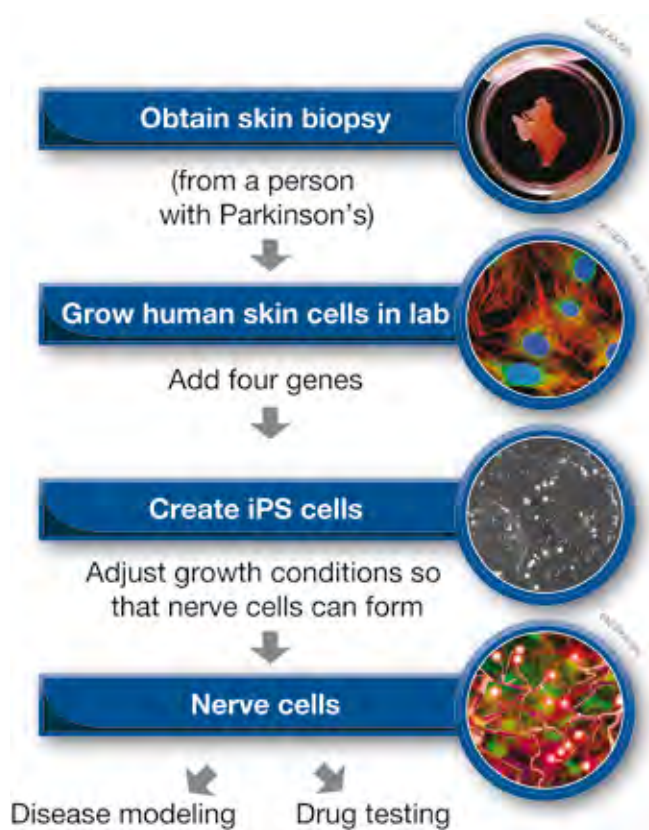


Figure 7 A diagram showing how iPS cells are created. Skin cells are isolated from a skin biopsy and grown in the lab. Four critical genes are inserted into these cells and they are grown in special conditions – this step takes about one month. Once the iPS cells have been established and confirmed, they can be grown in conditions that promote their transformation into nerve cells. These cells can then be used for a large variety of studies, including the investigation of Parkinson's progression and drug testing.

What are iPS cells used for?

“Parkinson’s occurs because of the death of nerve cells in a specific area of the brain involved in co-ordinating movement. By the time Parkinson’s symptoms develop, around 70% of the specific nerve cells have already died.

“Understanding why and how these particular nerve cells die and finding ways to protect them will go a long way towards finding a cure. iPS cells derived from people with the condition could create an ideal cell model of Parkinson’s to both investigate the mechanisms of cell death and to screen for protective drug molecules. Furthermore, cells obtained from people might also be used to replace the nerve cells lost in the brain with new, healthy cells as a future treatment for some people with Parkinson’s. Using nerve cells that have been made from a person’s own cells has great advantages as there is virtually no risk of immune rejection of the transplanted cells (see Fact box 11). However, if the individual had a genetic form of Parkinson’s, a different source of donor cells would be preferred.”

What can iPS cells do?

“Most scientists believe iPS cells will be able to do everything that embryonic stem cells can – this means they can produce every type of cell in the body, including the specific type of nerve cells lost in Parkinson’s. It follows then that if iPS cells can make the exact nerve cells lost in Parkinson’s, we should be able to create a model of the condition in the lab. This is also why scientists think that the transplantation of iPS cell-derived nerve cells might be possible for the treatment of Parkinson’s.”

Fact box 11: Stem cells and immune rejection

Embryonic stem cells are derived from embryos that have been created in the test tube by *in vitro* fertilisation and are no longer required for fertility treatment. Some couples, therefore, decide to donate them to medical research. Research in the UK involving human embryos is carried out under strict guidelines set by the Human Fertilisation and Embryology Authority (HFEA).

Induced Pluripotent Stem cells (iPS) are established from adult cells by a new method (see Figure 7). This involves increasing the levels of four key genes that results in an adult cell, such as a skin cell, being transformed into a stem cell. These exhibit all of the properties of embryonic stem cells, but are not derived from embryos.

Immune rejection – the body generally recognises cells transplanted into the brain as ‘foreign’ unless they come from another part of that person (so called autografts) or an identical twin. In most cases though, the tissue used in transplants comes from another of the same species and when placed into the body this triggers an immune attack that can cause the transplant to fail as the immune system removes the foreign cells. This is especially true when the transplant is an organ or tissue that is placed outside of the brain and in the body; although, even when the tissue is placed in the brain a rejection response can be generated. To reduce the likelihood of this happening, patients who receive cell transplants to the brain should probably take drugs to suppress their body’s natural defences. However, these drugs have side effects and can leave the patients vulnerable to catching a dangerous infection.

For more information about transplantation and studies that the PDS is supporting in this area, see pages 5–6.

What about the critics who say that embryonic stem cells are no longer necessary because we have other kinds of stem cells (including adult stem cells and iPS cells)?

“Adult stem cells are not as versatile as embryonic stem cells, but we shouldn’t disregard them altogether. For example, if an adult stem cell, which is capable of being transformed into dopamine-producing nerve cells, were identified, this would be useful for Parkinson’s research. We know that embryonic stem cells are capable of making all types of nerve cells and are, therefore, considered more versatile. It appears that iPS cells may be as versatile and powerful as embryonic stem cells. However, the standard methods to make iPS cells need genetic modifications and this can make the cells more prone to tumours. The good thing about iPS cells is that they can be obtained directly from people who have a genetic predisposition to conditions like Parkinson’s, and it would be nearly impossible to do this with a donated embryo.”

How do you respond to people who are opposed to the destruction of embryos for medical research?

“All of the human embryos I’ve used were surplus embryos that had been obtained by informed consent from couples undergoing fertility treatment. They didn’t need them anymore, and the embryos would have been eventually destroyed. I do understand that some people have strong ethical and moral objections. A major positive ethical outcome of using iPS cells is that embryos are not used, and no human embryos will be used in my current research.”

Some people with Parkinson’s believe there will be stem cell treatments in their life time. Is this realistic?

“It’s very difficult to put a time scale on when a new drug might be discovered using stem cells or when stem cell transplantation may be available.

“Sudden and unpredictable advances in research do happen, for example the discovery of how to make iPS cells was a very significant, but an unpredictable development.

“I believe that we will come closer to a cure and learn more about how Parkinson’s progresses by following all avenues of research, including the study of stem cells from people who have the condition. As I have mentioned, these cell lines can be transformed into nerve cells and used to identify new drug molecules that can protect nerve cells. This could be done by exposing the nerve cells to different types of chemical stress which may cause them to die, and screening for drugs that protect against the stress. Such protective drugs could then be further tested in animal models of Parkinson’s.”

What research are you currently focusing on?

“A potential drawback in iPS cell research is the fact that we have needed specific genes delivered by viruses to make the iPS cells. This causes permanent genetic changes within the cells and we know that this results in an increased risk of the cells forming tumours. However, researchers have developed new ways of temporarily inserting these genes that does not result in permanent

genetic modification of the cells. During my research, we will use cutting-edge technology that does not rely on viruses to generate the iPS cells.

“I’m now focusing on generating iPS cells from people with Parkinson’s, to see if we can produce cell lines that would be an accurate cellular model to study Parkinson’s. This will be a valuable resource for researchers in the UK and abroad. It would be wonderful

to be able to share our results and valuable cell lines with the Parkinson’s scientific community.”

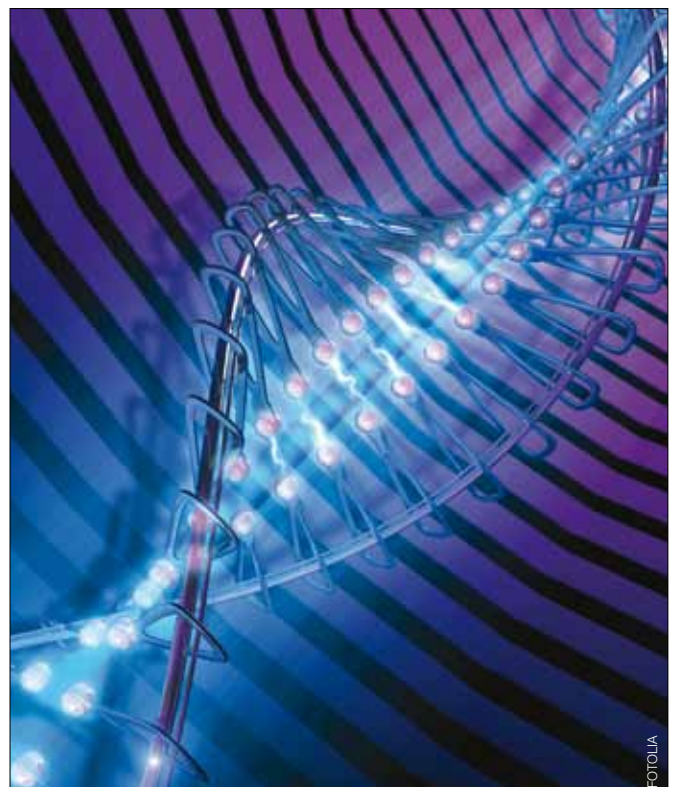
For more information on stem cells, you can read ‘Spotlight on stem cells’ in the summer 2008 issue of *Progress* or our information sheet *Stem cells*. Both are available to download from www.parkinsons.org.uk or are available, free of charge, from Sharwards Services (see page 5 for contact details).

Frequently asked questions

Is Parkinson’s inherited?

The causes of Parkinson’s are currently unknown, but scientists believe that both genetic and environmental factors (such as lifestyle or exposure to chemicals) play a role in its development. For the vast majority of people – around 95% – Parkinson’s is not directly inherited. However, for a small proportion of people (no more than 5%) their Parkinson’s is directly caused by defects in specific genes which can be passed down through generations.

There is an increased risk of more than one person in a family having the condition and this is due to the susceptibility genes being passed on. However, environmental or external factors are the key agents that will spark off the death of nerve cells in these people and trigger the onset of Parkinson’s.



A computer generated image of double helix DNA. DNA contains sections called genes that hold the body's genetic information.

What is the effectiveness of acupuncture therapy?

There have not been enough research studies to build evidence for the effectiveness of acupuncture for treating Parkinson's. Acupuncture is very individual and treats the person rather than the specific condition. The number and quality of trials, as well as the total number of participants included, are too small to draw any firm conclusion. More, carefully planned research studies, are therefore needed to establish any benefits.



The PDS has a *Complementary Therapies* booklet that is available to download from our website or order. It contains information on acupuncture among other popular complementary therapies.

Why does the PDS only fund UK researchers?

The PDS Board of Trustees has made the decision to only fund researchers based in the UK because the majority of the funds are raised within the UK. One of the Society's key roles is to develop and strengthen Parkinson's research within the UK. An example of how we are achieving this is the investment in tomorrow's generation of researchers through the Career Development Award scheme (see pages 15–19 for more information).

The PDS is the largest funder of Parkinson's research in the UK. The PDS does not, however, work in isolation and has been building strong links with other key medical research funding bodies, other neurological charities, government funding agencies and professional bodies both within and outside the UK. Dr Kieran Breen, the PDS Director of Research and Development, is also in regular contact with non-UK funders, such as the Michael J Fox Foundation, to work towards developing better collaborations to ensure that we gain the maximum value for our investment in research.

The Parkinson's Disease Society is the leading charitable funder of Parkinson's research in the UK.

Our research programme is completely dependent on voluntary donations.

So if you would like to invest in our exciting research and contribute towards a cure it would be gratefully received.

To make a donation, please call **020 7931 1303**. To discuss supporting a specific project please call **020 7932 1309**

visit: www.parkinsons.org.uk/donate

write: **Parkinson's Disease Society**

**215 Vauxhall Bridge Road
London SW1V 1EJ**



Making a difference

How PDS research is made possible

Our research achievements

2009 is a very special year for the Parkinson's Disease Society – it marks our 40th anniversary. As part of the celebrations, we looked back at some of the Society's key research achievements that have improved the treatments available and made significant steps towards finding a cure for people with Parkinson's.

Fact box 12: 40 years of difference

Our supporters have enabled us to make discoveries in five key areas:

- 1 Unravelling the causes of Parkinson's – research has uncovered vital clues to what goes wrong deep inside the Parkinson's brain.
- 2 Understanding that Parkinson's is more than a movement disorder – we have improved our knowledge of the non-motor symptoms of Parkinson's.
- 3 Changing clinical practice – results from our research have helped improve the diagnosis and care of people with Parkinson's.
- 4 Better drugs treatment – our research has pioneered new drugs that, taken alongside levodopa can provide greater relief from Parkinson's symptoms.
- 5 New hopes for a cure – we are playing a vital role in finding a cure.

Since the Society was founded, we have spent over £40million on cutting edge research. To promote our achievements, we published a booklet *Four Decades of Discovery*. This highlights the discoveries that we have made in five main areas (see Fact box 12).

Brain Donor Appeal update

Our supporters have also enabled us to continue the valuable work of the Parkinson's Brain Bank, which is owned and funded by the PDS. During Parkinson's Awareness Week in April 2009, the Society launched a nationwide Brain Donor Appeal to encourage more people – with and without Parkinson's – to register to donate their brains following their death. The Appeal has already exceeded all expectations with nearly 5,000 new donors registered so far. This is in addition to the 1,000 people who had already registered prior to the appeal. Over 6,500 information packs have been sent out to date and more enquiries are being received every day.

In fact, the Brain Donor Appeal has won two awards including the Third Sector Excellence Award 2009 for best communications campaign and also the best not-for-profit campaign in the corporate and public category at the PRWeek Awards. This is fantastic news, as it recognises the success of the integrated communications campaign

that was helped by well-known celebrities who agreed to sign up as brain donors. We used a mix of press, broadcast, online and social media to launch the campaigns. This generated over 700 pieces of publicity in five days and we had such a great response from the media coverage that we smashed our target within weeks of the campaign launch.

The Brain Donor Appeal featured in the spring 2009 issue of *Progress* on pages 21–24.

To join the Brain Donor Register please email pdbank@imperial.ac.uk or visit www.parkinsons.org.uk/brainbank

Raising essential research funds

It is important not to overlook the fact that a large number of people play key roles in ensuring that PDS research gives rise to outcomes that will benefit all people affected by Parkinson’s. These include the researchers who devote their time to researching into Parkinson’s, as well as our voluntary fundraisers who spend a vast amount of their time raising money so that this valuable research is made possible.

Almost a quarter of the Society’s annual budget gets spent on research (see Figure 8). Thanks to our supporters, the PDS remains the UK’s leading charitable funder of Parkinson’s research. The Society would not be able to continue to support research without voluntary contributions. We are dependent on fundraisers, individual donors, Trusts and other grant makers and those who have left us money in their will.

Here are just a few ways in which the PDS raises the essential funds necessary to make major breakthroughs in research that may one day lead to finding a cure.

Society’s spend

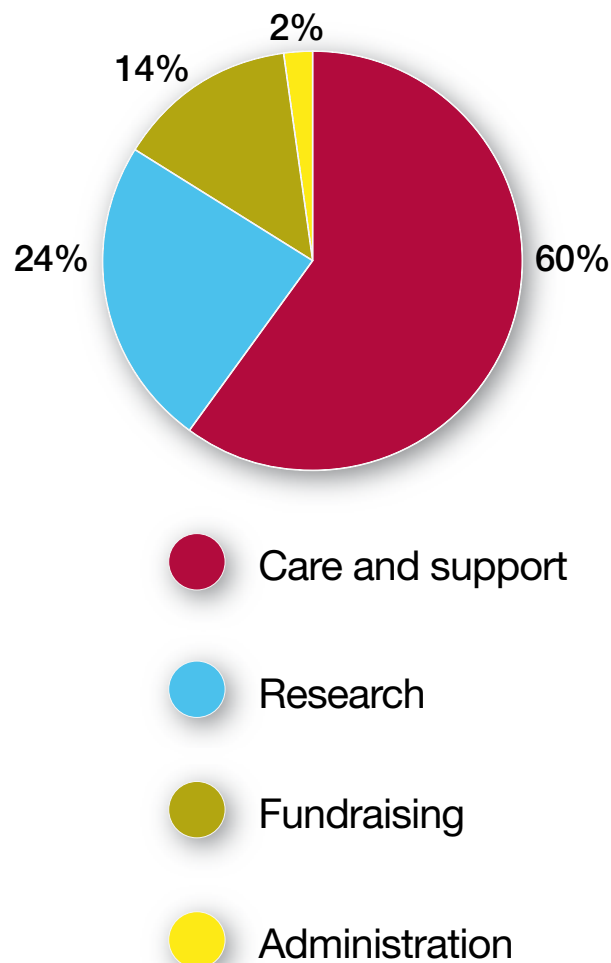


Figure 8 A diagram showing how the Society’s money is spent

Events – Albert Weir completes two treks in one year

The PDS runs events that supporters can take part in to help raise funds. We have a variety of different activities, ranging from holding a cake sale to trekking the Great Wall of China. During these activities, we promote the work of our research programme and explain to our supporters how the vital funds they raised support our work. Our overseas treks have been very successful over the last five years and the PDS has so far raised over £747,000.

Albert Weir (pictured below), who has a personal connection with Parkinson's, wanted to make a difference, so set himself the challenge of completing two treks in one year! Albert started his challenge in June 2008, when he and 40 others trekked 50km through the Alpujarras region of southern Spain. His adventure continued in October 2008 when he travelled to the Sacred Valley of the Incas, in Peru. With 31 other trekkers, Albert, successfully completed a gruelling eight days of trekking, covering 12–15km per day to reach an amazing 4,445 metres above sea level! So far, Albert has raised almost £7,000 for research.



Albert Weir trekking Southern Spain

He said: "My first trek with the PDS in Spain was one of the most rewarding overseas trips I have ever made. It brought together a wonderful group of people, all determined to achieve their own personal goal in

different ways and at varying speeds. All had stories to tell along the way, some tragic, some inspiring. I returned home emotional, inspired but above all more positive to continue to raise funds for such a worthwhile cause."

Trusts – capturing a portion of the £9.2billion given to charitable causes

Currently there are over 60,000 charitable Trusts in the UK that give more than £9.2billion to charitable causes annually. Of these, many Trusts support medical research into conditions such as Parkinson's. We submit applications to Trusts to ask for support towards our research programme in order to achieve a future free of Parkinson's.

Depending on the size of the Trust, we may ask for small donations that can be put towards our general research programme or we ask for much larger donations to fund specific research projects. One such example is the Big Lottery Fund award of £399,448 that was used to help fund Dr Roger Barker's project to study sleep disturbances in people with Parkinson's (read more about this on pages 12–13 of the spring 2009 issue of *Progress*).

Regional fundraisers – branches and support groups take on the challenge

The Society's branches and support groups have taken on the challenge of raising money specifically for research during our 40th anniversary year. Unique regional events have been taking place to capture the imagination of local communities in the quest to fundraise for a cure for Parkinson's.

In April, the Harlow and District Branch organised a tea dance. This was an event with a difference, with money being raised through cake sales and an antiques valuation stand in the style of the *Antiques Roadshow!* Guests were charged £1 to have an item valued, and the organisers got everyone on their feet dancing (picture below). The event was attended by 100 people, including the local Mayor, and raised £840 for research!



Harlow and District Branch

In Herefordshire, recently retired GP Dr Nick Ovenden, who has himself been diagnosed with Parkinson's, is now dedicating his time to raising money for Parkinson's research. Nick has thought of many innovative ways to get the word out about the work of the PDS while raising money. These include organising an event at Shobdon Airfield where his pilot friends even flew in to join the party! So far Nick has managed to raise over £4,000 through his events and isn't stopping there as he has more planned for the future. Good luck Nick...

Individual giving – The Time is Now

The Individual Giving team work hard to generate donations from individuals. This can be achieved in a variety of ways including regular monthly giving, one-off gifts, payroll giving, Christmas card trading, prize draw participation and legacies. Without our supporters, we would not be able to continue our vital work.

During Parkinson's Awareness Week (in April 2009), the Individual Giving team mailed an information pack to people who had previously supported us. The pack focused on the 40th anniversary year and was based on our research achievements booklet *Four Decades of Discovery*.



It highlighted the fact that scientific research into the condition was entering a critical stage. 'The Time is Now' appeal greatly surpassed its target. Paul Jackson-Clark, Director of Fundraising, said: "The original income target for the direct mail appeal was £54,000. To date the appeal has made over £86,000. This is our best appeal yet, particularly in terms of speed and the value of responses."

Find out how you can support us

We have made a tremendous impact in the field of Parkinson's research in the last ten years alone. We are closer than ever to finding a cure for Parkinson's that enables people to live a life free of the debilitating symptoms of the condition.

The Time is Now to help us keep the momentum going – to find out how visit www.parkinsons.org.uk/support or call 020 7932 1303.

Our new handy A5 leaflet version of *Four Decades of Discovery* will help us to:

- raise money that is crucial to help us in our search for a cure
- raise awareness about the vital research the Society supports

A copy can be requested, free of charge, from **Sharward Services** (see page 5 for contact details).

Help us make *Progress* magazine better! please complete this form

How interesting did you find this issue? (tick the appropriate box: 1 = not very interesting, 5 = very interesting)

	1	2	3	4	5
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Site visit	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
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Which article did you like most and why? _____

Which article did you like least and why? _____

Which research topics would you like to hear more about? _____

Is there a research-related question you would like to ask us? _____



***Progress* is produced by the PDS Research & Development team in collaboration with the Information Resources and Communications teams**

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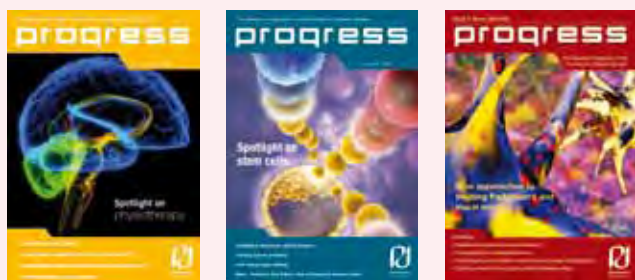
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The research magazine of the Parkinson's Disease Society

progress

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"Thank you for the magazine, I find it most interesting"

"I especially liked reading about the new research projects"

"It is a very interesting magazine and very helpful"

"I enjoyed the whole magazine very much"

If you are not on our mailing list and would like to sign up to receive future issues of *Progress* contact the Research and Development team:

Tel: 020 7931 8080

Email: research@parkinsons.org.uk

Visit: www.parkinsons.org.uk/progress

Trek China

18-26 September 2010



Parkinson's
Disease Society

Join this unique challenge and experience rural China in its most unspoilt state.

Call 020 7932 1328
events@parkinsons.org.uk

www.parkinsons.org.uk/events

This trek is promoted by P.D.S. (Sales) Limited, registered company number 1575175 which covenants its taxable profits to the Parkinson's Disease Society a registered Charity in England and Wales No. 258187 and in Scotland No. SC037554.

Help us to improve our information resources

Our Information Advisory Panel is made up of people with Parkinson's, their family members and health and social care professionals. By providing feedback on new and existing booklets, information sheets and DVDs, they play an important role in helping us ensure they contain the information people want and need, and are easy to understand.

To join the Information Advisory Panel, or to find out more, contact Katie Moss, Information Resources Manager.

Email: publications@parkinsons.org.uk

Tel: 020 7932 1311

Write: Parkinson's Disease Society, 215 Vauxhall Bridge Road,
London SW1V 1EJ





Trek Spain

10-14 June 2010

Explore the beauty of the Sierra Nevada on our new trekking route and raise funds for Parkinson's research.

Contact us for a brochure
020 7963 9309
events@parkinsons.org.uk
www.parkinsons.org.uk/events

Parkinson's Disease Society

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visit: www.parkinsons.org.uk/donate

write: **Parkinson's Disease Society**
 215 Vauxhall Bridge Road
 London SW1V 1EJ



Helpline

Do you need advice or information on Parkinson's disease?

The Parkinson's Disease Society Helpline provides confidential advice, information and support from qualified nurses and advisers

0808 800 0303

The Helpline is a confidential service. Calls are free from UK landlines and some mobile networks

Monday to Friday 9am to 8pm (except bank holidays) Saturdays 10am to 2pm
 email: enquiries@parkinsons.org.uk

The Parkinson's Disease Society (PDS) works with people with Parkinson's, their carers, families and friends, and health and social care professionals to provide support, information and advice. We are committed to investing in research, education and campaigning to improve the lives of people affected by the condition. The PDS has over 31,000 members, and more than 330 branches, support groups and special interest groups throughout the UK.

Parkinson's Disease Society of the United Kingdom
 215 Vauxhall Bridge Road, London SW1V 1EJ

Tel: **020 7931 8080** Fax: **020 7233 9908**

Free Phone Helpline: **0808 800 0303**

(available Monday to Friday, 9am to 8pm (except bank holidays) Saturday, 10am to 2pm)

Email: enquiries@parkinsons.org.uk

There are local PDS branches throughout the UK.

Please call **0808 800 0303** for details.

www.parkinsons.org.uk