PARKINSON'S UK CHANGE ATTITUDES. FIND A CURE. JOIN US.

Cambridge Branch Newsletter – July-August 2022

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BRANCH ACTIVITIES

PAUL MAYHEW-ARCHER SHOW SET FOR AUGUST 23 AT FITZWILLIAM COLLEGE

If you haven't already done so, now is the time to buy tickets for the Paul Mayhew-Archer show that will celebrate our 40th anniversary – in just a few weeks' time.

On Tuesday, August 23, Paul will be entertaining us at Fitzwilliam College, with a one-man show that has been a huge success nationwide. Entitled Incurable Optimist, the show, which changes all the time, was first performed at the Edinburgh Festival in 2018.

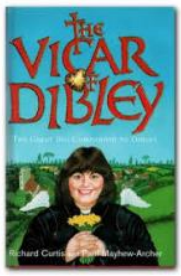
Paul's writing credits include: The Vicar of Dibley, Mrs Brown's Boys and the screen version of Roald Dahl's Esio Trot, which starred Judi Dench and Dustin Hoffman. He also produced the much loved Radio 4 shows I'm Sorry I haven't A Clue and Old Harry's Game, and as a script editor has worked on Spitting Image and Miranda.

Comedy writer Paul Mayhew-Archer: an Incurable Optimist

In 2011 he was diagnosed with Parkinson's, which as we all know, gets progressively worse and features over 50 symptoms. But it is also – as Paul quickly found out – capable of being funny. Since his diagnosis, he's had some of the best times of his life.

In 2016 he made a documentary, Parkinson's: The Funny Side, for which he won the Grierson Award for Best Documentary Presenter. In 2017 he started doing stand-up about Parkinson's, first at the Royal Albert Hall then at The Comedy Store. In 2018 he took part in his first podcast, and performed the Incurable Optimist for the first time in Edinburgh.

In 2019 he took his show on the road, across the UK. Now, post-Covid, he is bringing an updated and extended version for us to celebrate our 40 years as a Parkinson's Branch. The show epitomises the therapeutic power of comedy and laughter – from a man who, as his own description puts it, "is not contagious but well worth catching."



Tickets for the show cost £20 each (this event is also raising funds for the Branch). Paul will be performing in Fitzwilliam College's auditorium, which some members will know as it has staged the Gretschen-Amphlet memorial lectures in the past. A ticket includes a celebratory glass of wine at a reception in the auditorium foyer, starting at 6pm. The show kicks off at 7pm.

So spread the word and come with friends and family to support Paul, Parkinson's and the Branch – as it embarks on its next 40 years! Get tickets via the Eventbrite page at https://parkinsonscambridge-incurableoptimist.eventbrite.co.uk. Or buy them at our next Branch Meeting on July 22.

CAMBRIDGE FAMOUS FIVE MEANT STALIN KNEW ABOUT THE ATOMIC BOMB

Our May Branch Meeting featured a talk from a historian, Dr Andrew Lacey, whose subject was the five notorious Cambridge spies: Philby, Burgess, Maclean, Blunt and Cairncross.

They could be known as the Famous Five, but they were a lot more sinister than Enid Blyton's version. As Dr Lacey said, there has always been a tendency to romanticise the world of espionage, but these people were responsible for probably hundreds of deaths of agents who they betrayed to the Soviet Union.

Dr Lacey revealed some interesting facts which I suspect few of us knew, even if we have watched dramas and read books about the spies.

For example, when Harry Truman, newly president of the USA after Roosevelt's death, told Stalin that the US had acquired a weapon of huge destructive power, Stalin's reaction was noticeably nonchalant. That was because he already knew about the atomic bomb as the programme that built it, the Manhattan Project, “had leaked like a sieve”, Dr. Lacey said.

From left: Cairncross, Blunt, Burgess, Philby, Maclean.

He asked how they got away with their treachery for so long, and suggested that at least a factor in this was that they were all upper middle-class, public school educated, extremely intelligent Cambridge graduates.

Cairncross, for example, probably the least known of the five whose identity as a traitor was not confirmed until 1990, came first in the demanding civil service exams, both for the Home and Foreign Office and Diplomatic Service. He went on to work as a code breaker at the famous Bletchley Park.

And Anthony Blunt was a positive pillar of the establishment, having been made Purveyor of the King's Pictures in 1945, and occupying the position for many years, advising our present Queen about art, in which he was an expert. He was also not revealed as a traitor for decades, until the then Prime Minister, Margaret Thatcher, announced it in the House of Commons in 1979.

It simply didn't occur to their colleagues that such "English gentlemen" from the "right" sort of background, as far as they were concerned, could possibly be traitors. In the end, they were both given immunity from prosecution.

Dr Lacey also offered some suggestions as to why they did it. This was an era of huge inequality in the UK, with mainstream industries failing and unemployment, particularly in the north of the country, being appalling.

Anthony Blunt advising HM the Queen on art.

The five looked at the regime in the USSR and felt it had some definitely superior aspects to it. They saw events such as the General Strike and the depression as clear evidence that capitalism was finished, and that the USSR’s communism was the way forward. Famous “fellow travellers” such as George Bernard Shaw and Barbara Castle, visited the USSR and came back praising it.

Another fact that was particularly revealing was that the writer and political commentator for the Manchester Guardian newspaper, Malcolm Muggeridge, also visited the country and wrote reports about areas where famine was killing thousands if not millions of people, notably in the Ukraine. The paper published only bits of his reports, and not under his name, because many newspapers then were reluctant to criticise the USSR!

FRAUD TALK CONCLUDES: IF IT SOUNDS TOO GOOD TO BE TRUE, IT ALMOST CERTAINLY IS!

Our most recent Branch Meeting near the end of July featured the Cambridgeshire Constabulary Cybercrime and Fraud Prevention Team, who gave a talk based on a booklet called The Little Book of Big Scams.

The frauds people are experiencing today range from what you might call conventional face-to-face frauds to those carried out online. Advances in technology that enable us to perform day to day tasks are frequently exploited by fraudsters looking to steal our personal information or money, she says.

The launch of the first edition goes back to 2012, since when more than 25 constabularies and agencies have adopted it to give the public the best possible advice on how to combat fraud. The Cambridgeshire Police recently launched a crime prevention strategy that it calls One More Step, and the booklet will help support this.

"With the internet enabling fraudsters to target us from abroad, it is becoming increasingly complicated for the police to investigate fraud and very difficult to recover any stolen funds," says assistant Chief Constable Vicki Evans.

On the booklet's contents page are listed no fewer than 17 different types of frauds ranging from those involving

banking and cards, to computer software services, door-to-door, holidays, investments, online shopping and auctions, recruitment, romance and dating, and ticketing.

If you do get scammed, you should report it online to www.actionfraud.police.uk or telephone 0300-123-2040. That is, unless a crime is actually in progress or about to be committed, or involves a vulnerable victim, in which case dial 999 and ask for the police.

For more information visit the Cambridgeshire Constabulary website at www.cambs.police.uk/information-and- services/fraud. Perhaps most of all, remember these two things: if you have initiated something yourself, fraud is less likely than if you have been approached by someone unknown to you. In which case beware! And secondly: if it sounds too good to be true, it almost certainly is!

BAD DREAMS AN EARLY WARNING SIGN?

Probably all of us have had bad dreams. But recent studies have shown that PwP suffer from them more often than normal. A study in 2021 found that newly diagnosed people who have recurring dreams with 'aggressive or action-packed' content experience more rapid disease progression in the years following their diagnosis, than those without aggressive dreams.

The question arises, could the dreams of people without Parkinson's predict future health outcomes? A new study at Birmingham University has shown that increasing occurrence of bad dreams when you are older could be an early warning sign of Parkinson's.

Participants who reported bad dreams at least once a week were followed for around seven years to see if they were more likely to be diagnosed with Parkinson's. During this period, 91 people were diagnosed, and those with frequent bad dreams at the beginning of the study were twice as likely to develop Parkinson's compared with those having them less than weekly.

A significant proportion of diagnoses happened during the study's first five years, when those experiencing bad dreams were three times as likely to develop Parkinson's.

The study also shows that our dreams can reveal important information about our brain structure and function and may prove to be an important target for neuroscience research. However, there is a caveat: only 16 of the 368 men with frequent bad dreams in the study developed Parkinson's. So it is still a relatively rare condition, and most people with frequent bad dreams are unlikely to develop it.

But for those with other Parkinson's indicators, like daytime sleepiness or constipation, the finding could be important. Frequent bad dreams – particularly if they start suddenly in later life – could be an early indicator, potentially leading to earlier diagnoses and treatment. The Birmingham team is now using electroencephalography (brain imaging) to try to find the reasons for these dream changes in PwP.

POWERFUL BRAIN SCANNERS IN CAMBRIDGE MAY HELP TREAT COGNITIVE SYMPTOMS

Ultra-powerful MRI scanners could help identify PwP and determine which are most likely to benefit from new treatments for previously untreatable symptoms, say scientists at Cambridge University.

They are considering in particular the damage to motivation and cognition that can affect PwP, as well as those with a related condition called progressive supranuclear palsy (PSP). These symptoms frequently have a major impact on a patient's outcome, affecting their survival and general well-being.

To understand the causes of cognitive symptoms, the Cambridge researchers used a new ultra-high strength scanner at the Wolfson Brain Imaging Centre, on the Addenbrooke's Hospital site, to measure changes in the brains of PwP, as well as controls in good health. The scanner, made by Siemens, is rated as '7T', which refers to the strength of the magnetic field – most MRI scanners tend to be 3T or below. It is the first in a new generation of 7T MRI scanners in the UK (and only the third globally). It will form part of a UK 7T network together with others in Nottingham, Oxford, Cardiff and Glasgow.

The standard treatment of Parkinson's using L-DOPA does little for many of the condition's non-motor symptoms. That is why more attention is focusing on noradrenaline, a chemical that plays a critical role in brain functions like attention and arousal, thinking and motivation.

Noradrenaline is created in the brain by a tiny region at the back called the locus coeruleus, which means 'the blue spot.' It is located at the very base of the brain, in the brain stem. A study last year that examined brains donated to the Cambridge Brain Bank found that some people with PSP had lost as much as 90% of their locus coeruleus.

The question the team wanted to answer was: how could this tiny region be studied in patients who are still alive? Previous MRI scanners have not had the resolution to do this in living patients.

"Even good hospital scanners can't see the locus coeruleus very well," a researcher explained. "And if you can't measure it, you can't work out how two people differ: who's got more, who's got less? We've wanted MRI scanners to be good enough to do this for some time."

While most scanners can show structures with the level of detail of a grain of rice, 7T scanners with their ultra-strong magnetic fields can provide resolution at the size of a grain of sand. The scanners allowed the team to examine patients' locus coeruleus and confirm that the more damage there was, the more severe the symptoms of apathy and the worse they performed at cognitive tests.

The findings offer the hope of new treatments for these symptoms. A number of drugs that boost noradrenaline have already been through clinical trials for other conditions, and thus shown to be safe and well-tolerated. A clinical trial is now underway at Cambridge University Hospitals NHS Foundation Trust to see if these drugs can alleviate symptoms.

Not every patient with Parkinson's or PSP is going to benefit from noradrenaline-boosting drugs. Those with a damaged locus coeruleus are more likely to benefit, and the greater the damage, the more benefit they are likely to see.

The 7T scanner should help identify those who the team thinks will benefit most. This will be important for the success of the clinical trial, and if the drugs are effective, will identify which patients should receive the treatment. In the long term, this will prove more cost-effective than giving noradrenaline boosters to patients who would see no benefit.

It is thought that in PSP, damage to the locus coeruleus is caused by a build-up of the junk protein tau. When noradrenaline breaks down, it appears to trigger changes in the tau protein that causes the build-up. This then damages the same cells that produce noradrenaline, leading to a vicious circle. A similar situation may occur in Parkinson's.

VIEWPOINT

One of the most mysterious phenomena in medicine is the placebo effect.

A huge pile of evidence proves that if people are treated by someone they believe is a doctor, in an appropriate medical environment like a hospital, many will show a significant improvement in their condition. This happens even if the “treatment” they have been given is totally ineffective, like a saline or sugar solution, which had no capacity to affect their condition in any way, good or bad.

Placebo is clearly an example of “mind over matter”. Indeed, it is probably the best example there is. The relationship between the two – known as the mind-body problem – has been a favourite subject for philosophers for millennia. But when you are conducting a clinical trial to test a new drug, for example, it is a serious obstacle. That is because participants in the trial may improve as a result of the placebo effect, and not because the treatment being tested actually does any good.

This problem can be solved relatively easily: give some participants a placebo. Then if there is a significant difference between their outcomes and those who had the real thing, we know the treatment is having an effect. This can be done in a double-blind way, meaning both those managing the trial and the patients do not know who is getting a placebo.

For Parkinson's, this happens not only in drug trials, but also with surgery. “Sham surgery” is now part of increasing numbers of clinical trials for Parkinson's but it is controversial. Is it ethical? One paper said some scientists consider it “an expensive, potentially dangerous and possibly unethical bit of biomedical theatrics.”

Patients are told they are taking part in a trial featuring sham surgery, and here "sham" means “not the full operation”. But it isn’t as risk-free as a placebo pill, as it usually involves drilling small holes into the skull. Sometimes, these penetrate the dura, the membrane surrounding the brain. Perhaps not surprisingly, in one study about half the subjects had a negative reaction when told sham surgery would take place. ***Even so, they accepted the rationale underlying it***. The study also revealed it was important for participants that they could have the “real” operation after the trial, if they had had the sham version originally (assuming of course it was safe and effective).

In the end, it is the acceptance of the rationale of sham surgery that is crucial. And even if it seems a surprising process, ultimately the purpose behind it is its justification: namely, that it helps us discover if a therapy has a real, beneficial effect, and is not just the mind affecting the body. Perhaps in future, we will understand more about the placebo effect. For now, it remains a mystery we have to accept and work with – or around!

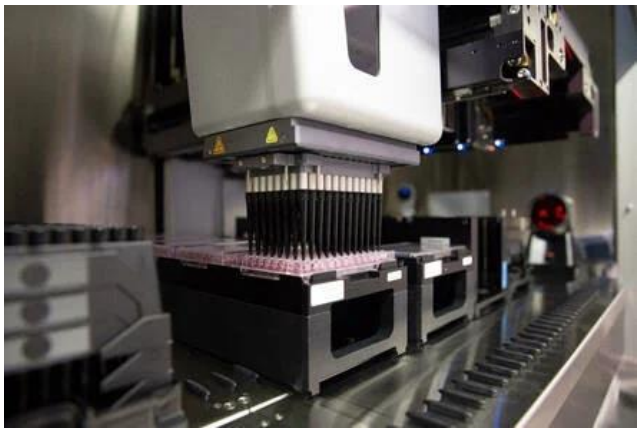
ARTIFICIAL INTELLIGENCE AND ROBOTICS REVEAL HIDDEN SIGNATURES

Combining artificial intelligence image analysis with robotics is helping to discover what is happening at the cellular level in various conditions, particularly Parkinson's.

Scientists at the New York Stem Cell Foundation (NYSCF) have worked with Google Research to identify new cellular hallmarks of Parkinson's, by creating and profiling over a million images of skin cells taken from around 90 patients and healthy controls.

“Traditional drug discovery isn't working very well, particularly for complex diseases like Parkinson's,” said NYSCF CEO, Susan Solomon. “The robotic technology NYSCF has built allows us to generate vast amounts of data from large populations of patients, and discover new signatures of disease as an entirely new basis for finding drugs that actually work.”

“This is an ideal demonstration of the power of AI for disease research,” added Google’s software engineer Marc Berndl. “And the advanced robotic systems at NYSCF (pictured) create reproducible data that can yield reliable insights."



The study used NYSCF's vast repository of patient cells and its state-of-the-art robotic system, called the Global Stem Cell Array (pictured), to profile the millions of cell images from patients and controls. The Array isolated and expanded skin cells called fibroblasts, labelled different parts of these cells with a technique called Cell Painting, and created thousands of high-content optical microscopy images. These were then fed to the AI image analysis system, which identified features specific to patients’ cells that could be distinguished from ones from healthy controls.

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AI can determine what patient cells have in common that might otherwise be unobservable, Google says. And it is important that the algorithms are unbiased. They do not rely on any prior knowledge or preconceptions about Parkinson's, making it possible to discover entirely new signatures of disease.

One reason these new signatures of Parkinson's could be important is the high failure rates of recent clinical trials for drugs based on specific disease targets and pathways believed to be drivers of the condition. The signatures make it possible to distinguish between images of patient cells and healthy controls, and between different subtypes of the disease. Researchers can even predict fairly accurately which donor a sample of cells comes from.

The signatures can now be used as a basis for conducting drug screens on patient cells, and it has created the largest known Cell Painting dataset (48 terabytes) as a community resource, which is available to the research community.

The system is 'disease-agnostic', only requiring easily accessible skin cells from patients and can be applied to other cell types, including derivatives of induced pluripotent stem cells that NYSCF creates to model various diseases. The researchers are hopeful that their platform can open new therapeutic avenues for many diseases where traditional drug discovery has been unsuccessful.

NYSCF says this is the first tool to successfully identify disease features with this level of precision and sensitivity. Its ability to identify patient subgroups could be important for precision medicine and drug development, especially in conditions like Parkinson's that vary so much.

CRANBERRY JUICE HAS NEUROPROTECTIVE EFFECTS – AT LEAST IN RATS

Cranberry juice is believed to contribute to various health benefits. But our knowledge of any neuroprotective potential it may have is limited, even though we know it controls oxidative stress in several organs, most clearly the brain.

Now a new study has examined whether cranberry juice can provide protection against Parkinson's, using a rat model. The experiment lasted 45 days, and looked at the accumulation of alpha-synuclein and apoptosis (cell death) markers in the midbrain. Researchers also performed microscopic examination, and assessed postural instability.

The results indicate that cranberry juice treatment does indeed provide neuroprotection, as α-synuclein accumulation declined, and this was accompanied by enhanced neuronal activity survival and reduced postural instability.

There are thought to be several mechanisms underlying Parkinson's, including oxidative stress, mitochondrial dysfunction, and protein (alpha-synuclein) aggregation. These are seen as important routes for developing new therapies.

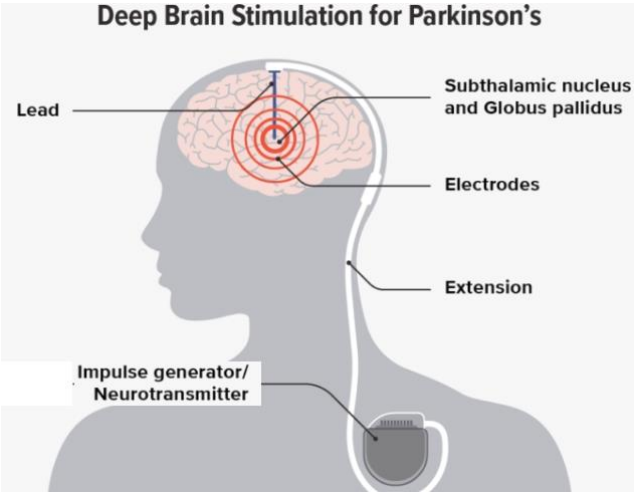
Mitochondria are cellular energy producers and maintain homeostasis in cells, and if they don't work as they should, the result is oxidative stress and neurodegeneration. Cranberries contain high levels of substances called flavan-3-ols (F3O), and studies have shown that taking F3O-rich foods can help slow cognitive decline and even improve cognitive functioning. Other foods with a similar effect include cocoa, grapes, apples, strawberries, green tea, and last but by no means least, red wine – make mine a large one!

A DEEP MODEL OF HOW DBS MAY WORK

PwP – and their doctors – confront many unknowns, including the answer to exactly how Deep Brain Stimulation (DBS) relieves some of the motor symptoms patients experience. Now, US researchers have produced a detailed model explaining the underlying circuit dynamics, providing a theoretical explanation that, if experimentally confirmed, could improve the therapy further.

One thing we do know about Parkinson's is that it involves the lack of dopamine, and this is associated with abnormally high brain waves (beta rhythms) at a frequency of about 20Hz. DBS delivers electrical stimulation to a region called the subthalamic

nucleus (STN), and in doing so, apparently suppresses these elevated beta rhythms (known as 'runaway beta'). This restores a healthier balance with other rhythm frequencies and results in better movement control for the patient.



The new study suggests that the beneficial effect of DBS stems from the fact that it interrupts a vicious cycle of runaway beta rhythms created between the STN and the striatum. This echoes theoretical work done a decade ago in which mathematical models showed how, in the absence of dopamine, runaway beta might happen in the striatum.

In healthy people who have adequate dopamine, cells in the striatum called fast-spiking interneurons (FSIs) regulate beta activity. But as dopamine levels fall, the FSIs fail to do this and beta comes to dominate a whole circuit loop. Indeed, the FSIs become conduits for beta themselves, leading to its amplification. DBS stops the beta from propagating towards FSIs so it is no longer amplified. Also, by exciting the FSIs, DBS restores their ability to control beta at its source.

By providing a deep physiology-based explanation of how DBS works, the study may also offer clinicians clues to how to make it work even better for patients. The key is finding the optimal rhythms of the FSIs, which may vary somewhat from patient to patient. If that can be accurately determined, the DBS frequency can be set precisely to achieve the best results. However, before that can be tested, the model's fundamental findings need to be validated experimentally. The model makes predictions that are needed to do such testing.

TWO PARKINSON'S CAFES OPENING

Two new Parkinson's 'cafes' are opening in our region, both based at care homes – Cambridge Manor and Arlington Manor. Each café will organise a monthly afternoon meeting, one in the first week of the month, the other during the third week.

Representing the care homes will be George Bacon from Cambridge Manor, and Martin Hickson from Arlington. Both are joining Parkinson's UK and will become Parkinson's Volunteers. Our membership secretary, Keith, has agreed to be the 'host'.

Both cafés will operate under the auspices of the Cambridge Branch, with the venues funding the room and refreshments. The cafés will be open to the wider community and will be featured in our publicity materials, emails, and so on. PwP residents and family members will of course be invited.

Set up as an informal way for people to meet, socialise and chat, Parkinson's cafés are popping up all over the UK and are run by volunteers and Parkinson's UK staff. Originally, they were a Dutch initiative, created by the Netherlands' national Parkinson's organisation, to help overcome the sense of isolation that often affects PwP.

While plenty of coffee and cake is consumed, the cafés are far from being just about espresso machines and frothy milk. Venues range from local libraries to nursing homes, and the cafés aim to create a sense of community for PwP, their families, and the professionals who treat them.

Today, there are scores of Parkinson's Cafés operating in the Netherlands, and each one arranges regular meetings featuring a varied programme of speakers and performances. Most of those involved give their time for free, or in return for a small amount of travel expenses. The format, say the organisers, has proved a runaway success.

The two homes have agreed to develop Parkinson's training for their care teams. The plan is to have the cafés start operating in September.

T-CELL GENES NEW TARGETS FOR THERAPIES

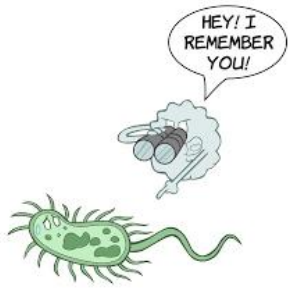
Scientists at La Jolla Institute for Immunology (LJI) have found that PwP have a clear 'genetic signature' of the condition in their memory T-cells, which are a critical part of our immune system. The scientists hope that targeting these genes could lead to new treatments and diagnostics.

Parkinson's is not usually seen as an autoimmune disease, but their work suggests T-cells have a role in the condition. The hope is that as we can see what T-cells are doing, using antibody therapies could affect disease progression, especially early on.

LJI's research has shown that PwP have T-cells that target alpha-synuclein early on. Called 'self-reactive', these T-cells can damage the body's own cells, including neurons. In fact, self-reactive T-cells are behind many autoimmune diseases. The new study offers a way to stop these T-cells in their tracks.

The LJI's key finding is that Parkinson's patients have memory T-cells with a very specific gene signature, which appear to be responsible for targeting alpha-synuclein and potentially causing ongoing inflammation. Identifying these genes will make it possible to see which patients have T-cells that respond to alpha-synuclein and which do not.

One important gene expressed in these T-cells is LRRK2, which is associated with the genetic, or familial, form of Parkinson's. Neurons in many PwP express LRRK2, but the new study is the first to show this gene expressed in T-cells. But many of the genes in the T-cells were completely unexpected and not previously linked to Parkinson's. The finding suggests these could be new targets for potential therapies.



The next step is to study post-mortem brain samples, which will reveal whether or not the same self-reactive T-cells found in blood also target neurons in PwP. To develop new therapies, it will be important to study how different genes can be activated or inhibited at various stages of Parkinson's progression.

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Help Line 0808-800-0303 (free phone call) Specialist advisers can answer questions on any aspect of Parkinson's
Parkinson's Nurses in our area: for help and information contact the Parkinson's Nurse Team on 0330-726-0077
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