

## THE SHAKING PALSY – ADVANCES IN OUR UNDERSTANDING OF PARKINSON’S DISEASE

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Parkinson’s disease (PD) is a debilitating movement disorder that affects over 100,000 people in the United Kingdom. Using a combination of genetic analysis, epidemiology and molecular biology, our knowledge of how this disease occurs and of the mechanisms that lead to cell death in the brain, has increased greatly over the last two decades. In spite of this knowledge, a cure for the disease remains out of our reach. Here, we review the advances that have aided the quest for a cure and the role that UCL has played in this research - whilst looking forward to what the future holds for patients with PD.

The profile of Parkinson’s disease in the public eye has been raised significantly over the last twenty years, with several highly visible figures such as Michael J Fox, Janet Reno and Pope John Paul II being diagnosed with the disorder (Figure 1).



*Figure 1. High-profile Parkinson’s patients such as Pope John Paul II have raised the awareness of the disease in the public consciousness (photograph courtesy of José Cruz, Agência Brazil).*

Parkinson’s disease was first described almost 200 years ago, but despite the large amount of time and money that has been spent researching the disease, the causes remain an enigma. PD was first dubbed ‘the shaking palsy’ by James Parkinson in 1817, and was based upon 6 cases, 2 of whom Parkinson had actually met and 3 of whom he saw ‘casually in the street’ (Parkinson, 2002). We now know Parkinson’s disease to be the most common neurodegenerative movement disorder, with a prevalence of 0.3% in the industrialized world (de Lau and Breteler, 2006). The disease is a progressive and irreversible degeneration of neurons involved in motor relays, resulting in an inability to initiate and maintain voluntary movement. It is predominantly a disease of old age - with an average age of onset between 55 and 60 - although there are also rare cases, often inherited,

where people develop PD at a much younger age, occasionally as young as 8 (Gasser, 2007).

UCL’s Institute of Neurology and the National Hospital for Neurology and Neurosurgery – part of UCLH – have long been one of the leading international centres for research into PD, and the diagnosis of PD is partly based upon criteria that were established by neurologists and pathologists working with the Institute of Neurology Queen Square brain bank. Symptoms that need to be presented for a diagnosis are a slowing of movement (bradykinesia) accompanied by either muscle rigidity, a resting tremor at between measuring 5-7Hz, and/or postural instability. Additional symptoms presented by many people with PD can include speech problems, micrographia (tiny handwriting), depression or confusion (Hughes, 1992). The onset of this disease is insidious, and slowly progresses over the course of a decade or more until sufferers are totally incapacitated and bed-bound.

### What happens in the brains of patients with Parkinson’s disease?

Looking at the brain of someone who has died of PD, it is evident that there are several obvious macroscopic pathological features. The most striking pathology is seen in the brain stem, the *substantia nigra*. This region gets its name from the dark, pigmented neurons that are contained there - *substantia nigra* is Latin for ‘black substance’ - and is visibly decreased in the brains of patients with PD compared to someone without the disease. This pathology is caused by the widespread death of neurons in this region of the brain (Braak and Braak, 2000). Neurons in the *substantia nigra* relay signals to and from the area of the brain that controls voluntary movement, the basal ganglia. Communication occurs at the synapse – the interface between neurons of the *substantia nigra* and basal ganglia – where the neurotransmitter dopamine is released from the neurons of the *substantia nigra* into the synapse. When these cells die, the amount of available dopamine is vastly reduced and communication with the basal ganglia is decreased, resulting in a lack of control of voluntary movement (Hughes, 1992). This is manifested in PD patients as cessation in the middle of an action or problems with starting a movement, for example, getting up out of a chair or walking.

### Treatments for Parkinson’s disease

The currently available drug treatments for PD are aimed at increasing the amount of dopamine

available for transmission within the brain. The first treatment introduced for PD in 1969 was a compound known as Levodopa, a precursor for dopamine, based upon work by Arvid Carlsson at the University of Goteborg (work for which he subsequently won the Nobel prize) (Carlsson, 1987). Levodopa (L-dopa) is taken up into the brain and converted to dopamine, compensating for the decrease of this chemical in patients with PD. The impact of this is remarkable: In patients suffering from the early symptoms of PD, L-dopa essentially reverses the symptoms. A dramatic example of the power of L-dopa is given by the treatment of patients with post-encephalitic Parkinsonism, a variant of PD thought to be caused by exposure to the 1918 influenza virus. This was first described by a group working at UCLH, where L-dopa treatment rescued these patients from a state of akinetic mutism (inability to speak or move) and essentially brought them back to life - a tale subsequently eloquently recorded by Oliver Sacks, who trained at the Middlesex hospital, and popularized in the film *Awakenings* (Calne et al., 1969; Sacks et al., 1970). Paradoxically, in the face of new drug discoveries and the rapid advancements that are being made in the pharmaceutical industry, L-dopa remains the most important treatment of PD and is nearly always the first drug that is given. Due to the progressive degeneration of dopaminergic neurons, however, L-Dopa alone is not sufficient for the long-term management of PD (Fischer, 1995). As the condition deteriorates, the dosage of L-Dopa can be increased, but this is associated with side effects such as hallucinations and unwanted involuntary movements known as dyskinesias. Additionally, treatment of PD with L-Dopa is associated with 'on and off phases' where patients switch between phases of increased and decreased ability to move freely.

To try and modify this, other drugs are usually co-prescribed with L-dopa. Dopamine agonists such as Pramipexole are compounds similar to dopamine that mimic the effects of this neurotransmitter. Monoamine oxidase (MAO-B) inhibitors are also often co-prescribed with L-Dopa. Selegiline and rasagiline are two drugs which belong to this class, and act by stopping the breakdown of dopamine - both naturally occurring, and as a result of L-Dopa metabolism - after it has been released into the synapse (Koller, 1996). These drugs act to prolong the effects of L-dopa. Lastly, a new entry in the field of PD therapies is Catechol O-methyltransferase (COMT) inhibitors such as entacapone, which act to channel more L-Dopa towards the dopamine pathway, increasing its bioavailability in the brain (Schrag, 2005)

## Why we study PD

Life expectancy after a diagnosis of PD is, on average, 17 years, so effective long-term management of the disease is crucial (Fischer, 1995). In the absence of a cure for PD, the symptomatic drug therapies that exist for PD are beset with side effects, which limit their efficiency due to the necessity of lower doses. Compared to many other disorders such as cancer, our understanding of the biological events underlying this disease is somewhat limited. Approximately ten percent of Parkinson's disease is thought to be inherited, and is caused by mutations in certain genes; however, the trigger for the remaining ninety percent is unknown (de Lau and Breteler, 2006). As will be discussed later in more detail, studying the genetic causes of PD has given us valuable insights into the molecular mechanisms behind Parkinson's disease; however, a cure is still a distant goal. This leaves the available therapies that alleviate the symptoms of PD as the only weapons we have against the disease. The medical and social impacts of this problem are daunting and increasing. In Britain, one in 500 people are estimated to have PD and as average life expectancy is increasing in the general population, so the prevalence of PD is also increasing - bringing with it suffering for the patients and their families, and a burgeoning burden on the NHS (Schrag, 2000). It is, therefore, of paramount importance that a cure be developed for this disease.

## Development of the first models of Parkinson's disease

In 1982, seven people in Santa Clara County, California, were found in a 'frozen' state, unable to move. After much investigation, it was discovered that each of these seven were heroin users and had all been injecting the synthetic opioid 1-methyl-4-phenyl-4-propionoxypiperidine (MPPP) (Langston et al., 1983). MPPP was first synthesised in 1976, by a chemistry student called Barry Kidson in Maryland. Unfortunately, if the reaction is performed above -30°C, then a by-product of the reaction, 1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine (MPTP), is formed. Kidson injected his drug, having synthesised it at room temperature, and over the next three days, he developed Parkinsonian symptoms. A post-mortem examination of his brain showed neuronal death in the *substantia nigra*, and further studies on this drug concluded that its toxic effects are selective for neurons in the *substantia nigra*, resulting in Parkinsonian symptoms (Langston and Ballard, 1983). It was later discovered that the seven people in Santa Clara county had all repeatedly injected

themselves with drugs containing MPTP-contaminated MPPP, and that this frozen state was an extreme form of Parkinson's disease (Langston et al., 1983). Subsequent use of this drug in research led to the first animal and cell models of PD, and a more accessible way of testing drugs to try and reverse the symptoms of Parkinson's at a cellular level (Burns, 1983). Use of these cell models led to the understanding of how oxidative stress -damage to cells caused by the oxidation of molecules - can contribute to neurodegeneration. It was discovered that mitochondria – organelles within cells that are involved in energy production - are also involved in the breakdown of MPPP to its toxic product MPP+, and that the enzyme MAO-B is chemically involved in this reaction . By developing inhibitors of MAO-B using the new models of Parkinson's, the scientific

community was able to provide better defence against neurodegeneration (Kopin, 1993). As mentioned, modern management of PD often includes use of the MAO-B inhibitors selegiline and rasagiline. Mitochondria were further linked to PD, and importantly to the common sporadic form of the disease, by Professor Tony Schapira working at the Royal Free Hospital (now part of UCL medical school). He showed that the complex I electron chain within the mitochondria, involved in energy generation, is impaired in sporadic PD (Schapira, 1989).

The development of rapid onset PD in the seven cases from Santa Clara county also provided neurosurgeons with an opportunity to develop new surgical techniques. The fact that the onset of the disease was rapid and that all seven were young

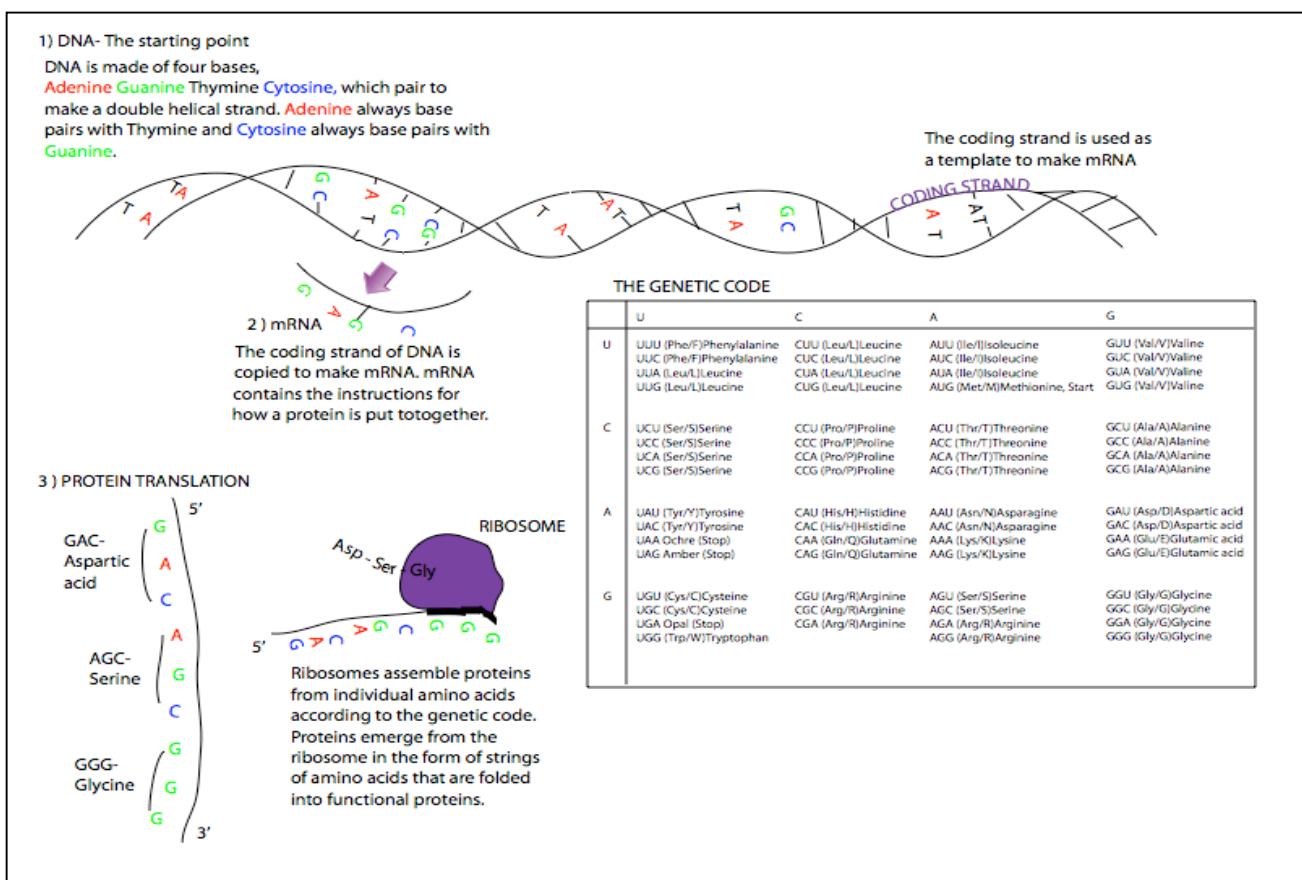


Figure 2. How protein is synthesised from DNA. When genetic mutations occur in the form of a base substitution or deletion, the end result can be a change in the amino acid composition of the protein, or in premature termination. This results in a shorter protein that may be missing important functional domains. Each amino acid has individual biochemical properties, such as a positive or a negative charge. Depending on the position of the amino acid, and the substitution that has been made, a mutation can have severe effects in the overall functionality of a protein.

meant that contributory factors found in the older brains were not present. Collaborations between American neurologist J William Langston, working at the National Institutes of Health, and a Swedish group in Lund, led to two of the seven being selected to undergo neuronal grafts using human foetal tissue. In Sweden, unlike in America, the law permits surgery involving stem cell transplantation. Examination at intervals following surgery indicated that after the neural tissue had been grafted, it successfully formed dopaminergic neurons, and a visible rescue of some normal functioning occurred (Widner, 1992). Unfortunately, similar surgeries on naturally-occurring PD patients did not show the same results, possibly due to the fact that the factors causing progressive death were still present, thus killing the grafted neurons as well. This technique, however, has gone on to pave the way for current studies looking to adapt neuronal cell grafting and has supported the case for research into stem cell therapies for PD patients (Lindvall and Kokaia, 2006).

### Mechanistic insights gained from genetic studies

Perhaps the single largest contribution to our understanding of PD has been the identification of genetic mutations in individuals with familial and sporadic forms of the disease - discoveries in which the Institute of Neurology has played a key role. In 1997, a single base pair mutation in the DNA of the  $\alpha$ -synuclein gene was found in a Greek and Italian family (for a description of how these mutations can disrupt cells and cause disease, see Figure 2). This causes a change in the structure of the  $\alpha$ -synuclein protein that is thought to increase the propensity of  $\alpha$ -synuclein to aggregate (Conway, 1998). The importance of  $\alpha$ -synuclein was further underlined by the discovery in the laboratory of John Hardy, now a professor at the Institute of Neurology, of a triplication of the gene in the genome, which is thought to result in a doubling of the normal amount of protein being made (Singleton, 2003). When viewed under a microscope, the *substantia nigra* and areas of the cortex show insoluble lumps of this protein in inclusion bodies, which are thought to sequester aggregated proteins in the cell, possibly in an attempt to reduce the toxic effects of this aggregation. These inclusions are referred to as Lewy bodies, after Frederick Lewy who was the first to describe them in 1912 (Figure 3) (Lewy, 1913).



Figure 3. *Lewy bodies in the midbrain. A lewy body in a melanised neuron from the substantia nigra. The lewy body is the spherical body indicated by an arrow. Image courtesy of Dr Susan Daniel.*

Although the role that  $\alpha$ -synuclein plays in the cell has not been definitively proven, the phenomenon of proteins misfolding and aggregating is an important one and is seen in many other neurodegenerative diseases such as Alzheimer's disease, Huntingtons chorea and Creutzfeldt-Jakob disease (CJD). When a protein is degraded, it is usually transported to the proteasome - a barrel-like structure containing enzymes within the barrel. Proteins unfold in order to fit into the barrel, where they are degraded. Degradation of aggregated proteins via the proteasome is problematic due to their larger size. An alternate pathway, via a degradation machinery called the lysosome, is used instead. Studies have shown, however, that mutant  $\alpha$ -synuclein has the ability to inhibit the activity of the lysosome by binding to receptors on the outside of the lysosome (Cuervo, 2004).

When we see Lewy bodies, it may well be that we are in fact seeing an adaptive cell mechanism trying to reduce the damage done by these protein aggregates. Cells maintain their structure because of a so-called 'cytoskeleton.' This network of structural fibres is also used as a railroad along which proteins are transported to and from the cell nucleus. There are three types of these fibres, which have different properties depending on their function, and are able to grow and retract. The microtubules, one such 'fibre,' are arranged around a microtubule organising centre (MTOC), from which they extend outwards. The Lewy body is thought to be the final product of a cellular phenomenon called the aggresome, which involves rearrangement of the microtubules around the MTOC into a cage-like structure which sequesters the aggregated  $\alpha$ -synuclein protein (Olanow, 2004).



## The other 'PARK' genes

Genetic analysis of PD patients has revealed five more genes that are thought to cause, or act as risk factors for, Parkinson's disease when inherited. Due to their association with Parkinson's, they have been named the PARK genes. At least two of these are involved in mitochondrial function and have been linked to oxidative stress with multiple mutations associated with PD. In the PARK genes as a whole, the range of effects of the mutations is varied and ranges from single amino acid substitutions such as those seen in LRRK2, the product of PARK8, to the truncation of large segments of the PARK9 product ATP13A2. Somehow, all of these different mutations and pathways lead to the death of cells in the *substantia nigra* and thence to Parkinson's disease. Genetic engineering aimed to recreate these familial mutations in proteins and cells used in the lab has allowed us to study this in detail. In this way, molecular genetics have provided us with an effective way of elucidating the pathways that underlie the progressive degeneration of neurons as seen in PD.

A second gene (PARK2) was found to cause Parkinson's codes for the protein Parkin (Kitada, 1998). Mutations in this protein were identified in a number of young onset PD patients.

Targeting of proteins to the proteasome for degradation involves tagging the proteins with a small molecular marker, ubiquitin, which instructs chaperone proteins to traffic them to the proteasome for degradation. Parkin is involved in this proteasomal pathway as part of a complex of proteins that attach ubiquitin to proteins for degradation (Dawson, 2006). Over a hundred different mutations in the parkin gene have been discovered, and the general consensus is that the mutations found in PD patients cause a loss of function of the parkin protein, which could result in the accumulation of proteins that should have been degraded (Gasser, 2007).

The protein encoded by the PARK6 gene, PINK1, has been implicated in signalling cascades with parkin in a number of recent publications, and it is thought that they are part of a common pathway linked to the structure and dynamics of the mitochondria. PINK1 mutations, which were first described by a group at the Institute of Neurology led by Professor Nick Wood, are known to cause swelling and fragmentation of the mitochondria (Valente, 2004). Exactly how these proteins, PINK1 and Parkin, contribute to PD is currently uncertain; however, the thesis that the two act in the same signalling pathway is one that is becoming widely accepted.

The seventh Parkinson's locus to be described was in the gene for DJ-1 in 2001, a gene that had previously been implicated in cancer (Bonifati, 2003). DJ-1 is expressed predominantly in glial cells within the brain. Its loss of function has been implicated in the communication of mitochondrial stress, and was found to cause Parkinson's disease with early onset. DJ-1 mutations contribute to the smallest number of familial PD cases. However the next locus to be linked to Parkinson's has proved to be the most prevalent and has also been found in many apparent sporadic cases of PD.

LRRK2, the product of PARK8, is an extremely large protein with many different functional regions, and was first described by researchers here at the Institute of Neurology in collaboration with groups in Spain and at the National Institutes of Health (Paisan-Ruiz, 2004). Its exact function in the brain is unknown, however certain mutations have been shown to cause changes in neuron branching and outgrowth, and so a role in this kind of pathway has been proposed. Because of the large number of functional domains in LRRK2, mutations manifest themselves in different ways, in terms of their impact on the protein: amino acid changes as a result of genetic mutations have been shown to increase enzymatic activity of certain parts of the protein and reduce the activity of others (Jaleel, 2007; West, 2007). Although LRRK2 has proven to be technically challenging to study, the similarity between the patient cases associated with mutations in this protein and the more common sporadic form of the disease suggests that the protein may be of great importance with regard to the pathological causes of this disease.

## What does the future hold?

The past decade has seen an explosion in our knowledge of what causes cells to die in the brains of patients with Parkinson's disease and, if anything, the pace at which research is progressing is speeding up. The discovery of genetic forms of PD, and the subsequent identification of the causative genes behind these cases, has provided us with important signposts towards research areas that we need to focus on in this disease. Recently, a putative thirteenth region of the genome has been identified, which is known to code for the protein TNRC15 (Lautier, 2008). It is likely that other such genes will be identified in the future.

In terms of patient therapy, we are unfortunately still a long way from tackling the root cause of PD, and much work remains to be done before we have a full picture of the molecular basis

of this disorder. Here at the Institute of Neurology, we have several multidisciplinary groups looking at different aspects of PD, ranging from the neuropathology of the disease with the Reta Lila Weston Institute and the Queen Square brain bank, to clinical care at the National hospital for Neurology and Neurosurgery, to the structural, molecular and cellular basis of the disease in the department of Molecular Neuroscience. The aim of our research, and research by groups like ours across the world, is to refine our knowledge of the molecular mechanisms that lead to cell death in PD, to the point where we can identify specific molecular targets for therapy. These targets can then be evaluated in cell and animal models of disease before finally being taken into clinical trials and thence to patients. As yet, treatment of PD patients with rationally designed therapeutics remains a relatively distant goal, but given the progress that has revolutionized our understanding of this disease in such a short amount of time, there is certainly hope for the future.

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