Can we cure PD?

More than $100 million is spent on research into Parkinson's disease each year. Where is this research leading us? Can we expect a cure or prevention of the disease in the foreseeable future? Are new developments in research likely to change contemporary practice? Are there biomarkers for the disease and will these help us to diagnose the condition before symptoms are established? What of neuro-transplantation? These questions are addressed in the following article.

Dr Jeremy Player **retired consultant Geriatrician, Liverpool**
email **jrplayfer@doctors.org.uk**

There is a strong perception within the medical profession that neurodegenerative diseases such as Parkinson's disease (PD) and Alzheimer's disease are incurable yet the charitable societies that support groups of patients with these conditions invest heavily in research aimed at finding cures for these illnesses. The Parkinson's Disease Society UK (PDS) puts at the centre of its new strategy finding a "cure for all" backing this up with record levels of investment in research, making the society the largest non commercial supporter of PD research in the UK. In my role as a trustee of the PDS and chairman of their research strategy group I have had to evaluate current research programmes in PD. This exercise has led me to some surprising conclusions that highlight the importance of current research into PD.

What is a "cure for all"?

What do we mean by "a cure for all"? Chronic diseases are an awkward reminder to the medical profession that we eradicate very few diseases, smallpox being the only disease that has been removed from the list of human afflictions by medical intervention. As doctors we are most comfortable dealing with acute illnesses that are self-limiting. Members of the PDS certainly have the ambition to remove PD from medical textbooks in the future; as one patient put it: "I hope science will be able to remove the risk of my grandchildren ever having the same experience as me." Is such ambition realistic?

To answer this question we need to review the history of the progress of our understanding and treatment of the condition so far. Since the publication of James Parkinson's Shaking Palsy in 1817, progress and improvements in our understanding and treatment of the condition have occurred in fits and starts. Parkinson's work was largely ignored until rediscovered by Charcot in 1871. Charcot introduced belladonna as a treatment that attenuated tremor although at that stage the rationale for its use (anti-cholinergic activity) was not understood. Almost 90 years lapsed before Hornykiewitz established dopamine deficiency in the basal ganglia as the crucial deficit in PD with Cotzias demonstrating the effectiveness of levodopa in the treatment of PD in 1968. Arvid Carrlson elucidated the role of dopamine as a neurotransmitter around the same time, winning the Nobel Prize for Medicine in 2000 for his achievements. These discoveries changed forever the perception that neurodegenerative disorders were untreatable and subsequently patients with PD have received increasingly effective treatment based on dopaminergic therapy.

Basic scientific research over the past three decades has begun to unravel the puzzle of PD at the fundamental levels of cell biology and molecular pathways. The investment in such research is colossal with over $100 million a year being spent in the USA alone. There is an increasing optimism in the field that we are on the threshold of a breakthrough that will move thus from remedy to prevention and cure, hence the urgency of the PDS to be ambitious in its future research strategy.

The selective death of neurones that produce dopamine is the key to understanding PD. Translating the insights we are gaining of the pathways that result in cell death into new therapeutic approaches is the challenge that it is hoped will bring us closer to a cure than our present symptom relieving medications. There are a number of lines of attack: diseased cells could be protected from the progression of pathology (neuroprotection); damaged cells could by the use of growth factors be replaced by healthy cells (neurorestoration); lost cells could be replaced using

stem cells implanted surgically (neuro transplantation); potential PD patients could be recognised in the early preclinical phase of their illness and intervention targeted to identifiable deficits and prevent the emergence of symptoms.[1] This may appear science fiction but in fact considerable progress is being made along these lines.

Neural transplantation

Neural transplantation has captured the media's attention more than any other development in research in this area. President Obama's recent moves to facilitate stem cell research in the USA has increased speculation with PD always being top of the list of conditions that are likely to benefit, yet progress so far has been frustrating. It is now over 30 years ago that animal experiments transplanting nerve cells began to show signs of success and this encouraged Bjorklund and others to initiate work using human foetal cells in the first experimental transplants in PD patients.[2] This work needed to overcome ethical objections for using material obtained from human foetuses derived from therapeutic abortions. While the Scandinavian team in particular had some long-term successes and were able to demonstrate survival of tissue, the overall project of neural transplantation has resulted in disappointing results. Transplantation has been beset with unexpected problems. Two major trials of foetal neural transplant failed to meet their primary endpoints and were complicated by severe dyskinesias that failed to respond to the withdrawal of medication.[3] These findings led to a moratorium on further foetal transplants.

The ineffectiveness of this approach has resulted in radical rethinking in this field. The use of foetal tissue is limited by the low yield of functional cells and raises problems as to how transplanted cells integrate within the complex circuitry of the basal ganglia and how their growth is controlled to stop the possibility of tumour formation. The recent and important finding that transplanted foetal cells become affected by PD pathology (Lewy bodies and accumulation of alpha-synuclein) casts serious doubt about whether cell replacement can ever cure the condition in the long term.[4] There is a realisation that a lot of preliminary basic research needs to be undertaken before significant progress can be made. Nevertheless the rapid development of stem cell research is opening up exciting possibilities. Adult stems cells avoid the difficulties of using foetal tissue. The increasing ability to manipulate and reprogramme adult cells means that a plentiful supply of specific dopaminergic cells should become available for future trials.[5] It is still, however, very much in doubt whether this approach will ever provide a solution to the problems of PD as it is always going have surgical hazards, be expensive and unlikely to be applicable to more than a small minority of patients. Older patients in particular are unlikely to benefit and most patients with PD are over 70 years.

Development of PD

Other approaches depend on our improved understanding of the pathophysiology of PD. The pathways which lead to the death of dopaminergic cells in the pars compacta of the substantia nigra are increasingly understood. Attention is focused on three factors which seem to play a part in the development of PD; the effects of environmental factors, failure to eliminate harmful proteins and dysfunction of mitochondria.[6] As more is known more possible targets for intervention become apparent.

Two common environmental factors that are known to influence the development of PD are smoking and coffee drinking—both habits reduce the risk of developing the disease.[7] How these apparently neuro-protective effects are mediated remains unknown. Caffeine is an adenosine A2 antagonist and this has led to research into using this class of compound to treat PD. The possibility of nicotine having neuro-protective properties is also being investigated. The clearest examples of environmental toxins inducing Parkinsonism are MPTP and Rotenone both of which are used to produce animal models of PD that are helping develop a greater understanding of how free radicals and oxidative stress are important in the death of neurones.

Familial PD

Neurones are highly differentiated cells, which generally do not undergo mitosis. The highly evolved mechanisms to rid cells of aberrant and misfolded proteins are particularly important for this type of cell. The discovery of kindreds of familial PD from 1990 onwards has resulted in the recognition of mutations in genes affecting the ubiquitin-proteosome system (UPS), an important mechanism for degradation of proteins within cells.[8] Such defects seem to selectively cause pathology in the dopaminergic cells of the substantia nigra and

cause aggregation of proteins within these neurones that manifest themselves as inclusion bodies called Lewy bodies. The synaptic protein alpha synuclein is an important component of Lewy bodies in sporadic PD and mutations in the alpha synuclein gene were the first to be recognised as a cause of familial PD. PD associated genes are called PARK genes and at least seven different genes are now known to be implicated. While none of these genetic mutations are common in sporadic PD, they offer important clues to the molecular mechanisms that are implicated in the pathology of PD. Although there are 11 Park genes the nomenclature is confusing as there is some duplication in the naming of genes. The first five PARK genes all produce proteins, which are implicated in the UPS mechanism. PARK6 and PARK7 code for the proteins PINK1 and DJ-1 respectively, which combat oxidative stress and mutations are linked with mitochondrial dysfunction. PARK8 codes for LRRK2—a kinase essential for mitochondrial function.[9]

The present state of knowledge of these intricate molecular pathways is exciting because the different components are coming together to make a more coherent picture of what happens in PD. The picture is however no where near complete but we begin to see that common pathophysiological pathways in dopaminergic neurones result in cell death by apoptosis (programmed cell death). Cells producing dopamine are subject to higher levels of free radicals resulting in oxidative stress which damages both macro molecular complexes such as the UPS and mitochondria. Damaged mitochondria lose membrane potential and trigger apoptosis by releasing a caspase cascade.

The future

What are the consequences of PD research and where do we go from here? We need to be able to use current advances for the benefit of patients. In order to slow down or reverse the pathology of PD we need to be able to find ways of manipulating the biochemical pathways that lead to cell death. To do this we need models appropriate to the disease as we see in humans. Current animal models need to be improved to take this into account. Age is the greatest risk factor for PD yet most experiments use young animals. What ever is acting on neurones to cause their death acts over a long time yet today's models use acute chemical insults. What is needed is a simple organism such as a fruit fly or nematode or a culture of cells in which to test interventions.

If we are going to slow the disease down we need to recognise patients either at risk of the disease or at the very early stages so that intervention to protect cells from damage can have maximum effect. To do this we need biomarkers that can select such individuals. Great progress is being made in this direction; one of the most promising techniques being trans-cranial sonography, which detects hyperechogenicity in the substantia nigra early in the disease.[10]

I hope we can envisage a time when early recognition of individuals with a risk of the disease will be followed by appropriate interventions that prevent the emergence of symptoms. This is an exciting prospect and justifies the expensive research investment that will be needed to achieve this goal.

Conflict of interest: none declared

References

1. Swanson CR, Sesso SL, Embourg ME. Can we prevent Parkinson's disease? *Front Biosci* 2009;**14**: 1642–60
2. Freed CR, Greene CG, Breeze RE ,et al Transplantation of embryonic dopamine neurones for severe Parkinson's disease. *N Eng J Med* 2001; **344**: 710–19
3. Lindvall O, Kokain Z. Prospects of Stem cell therapy for replacing dopamine neurones in Parkinson's disease. *Trends Pharmacol Sci* 2009; **30**(5): 260–7
4. Laguna Goya R, Tyers B, Barker RA. The search for curative cell therapy in Parkinson's disease. *J Neurol Sci* 2008; **265**: 32–47
5. Harrower TP, Barker RA. Is there a future for neural transplantation? *Biodrugs* 2004; **18**(3): 141–53
6. Lees A, Hardy J, Revesz T. Parkinson's disease. *Lancet* 2009 ; **373**: 265–87
7. Olanow CW. The Scientific basis of the current treatment of Parkinson's disease. *Annu Rev Med* 2004; **55**: 41–60
8. Li H, Guo M. Protein degradation in Parkinson's disease revisited; it's complex. *J Clin Invest* 2009; **119**(3); 442–5
9. Gasser T. Molecular pathogenesis of Parkinson's disease: insights from genetic studies. *Expert Rev Mol Med* 2009; **11:** e22
10. Poewe W. Treatments for Parkinson's disease-past achievements and current clinical needs *Neurology* 2009 17; **72**(7 Suppl): S65–73.