Could you provide an insight into your background; explaining what led you to study neurology and, more specifically, Parkinson’s disease (PD)?

I was fortunate to study at the University of Western Ontario where there was an outstanding Department of Clinical Neurological Sciences comprising many leaders in the field. During my residency, I was looking for a topic to present for a seminar and came across a book on Huntington’s disease (HD). I was fascinated by the connections of the basal ganglia and the profound effect of neurotransmitters on brain function. That led naturally to an interest in PD. Later, I went to the University of British Columbia (UBC) for fellowship training. A programme in positron emission tomography (PET), which was just opening up, then offered an opportunity to study neurotransmitter function in vivo, so I was hooked.

You have held numerous positions during your career. How did you come to occupy these roles and what do they entail?

The various roles are, to a large extent, complementary. I am a clinician interested in research. I devote approximately 20 per cent of my time to patient care, but I only see patients with movement disorders, mostly PD and related conditions. I work in a multidisciplinary clinic where we see a significant volume of patients, many of whom are interested in participating in research and contributing to furthering knowledge about PD. It is our capacity to integrate clinical care and research, particularly with imaging and genetics, which has led to our success. I would not be able to do this in isolation, and the work depends upon a very talented and committed team.

My role as Head of Neurology obviously takes me into territory substantially removed from PD. It is, however, rewarding in that I care passionately about academic neurology and combining excellence in clinical care with research and teaching. My experience in running the Parkinson’s programme has allowed me to assist other programmes in neurology that have required further development. It is extremely gratifying to witness their success.

With whom do you partner and how are these collaborations beneficial to your work?

The partnership with the Mayo Clinic in Jacksonville goes back many years. My colleague Dr Zbigniew Wszolek worked in Vancouver at one point and was tenacious in his efforts to pursue families with PD and other movement disorders at a time when it was not trendy to do so, and when people suggested genetics played a very small role in PD. Zbigniew has been a major player in the identification and characterisation of many families with parkinsonism. Because of the close relationship, and our access to detailed characterisation of these families using PET, we have imaged many of the families that Zbigniew has studied and continue to do so.

The relationship with Canada’s National Laboratory for Particle and Nuclear Physics, TRIUMF, is also critical to the imaging programme and dates back approximately three decades. The development of new tracers is tricky and time-consuming and decisions on new radiotracer development are taken together, to ensure we select optimal targets and ligands and that any new tracer will be put to good use.

As past Chair of the Scientific Advisory Board (SAB), can you provide a window into your close work with Parkinson Society Canada (PSC)?

I have had a longstanding relationship with PSC and first joined their SAB in 1992. After two three-year terms as Chair, I felt it was time to step aside as every organisation needs to have turnover and a fresh perspective. Although I am no longer on their SAB, I maintain close working relations with the Society and do serve on their Medical Advisory panel. As Chair, I worked very closely with the manager of the National Research Programme.

Finally, do you think there is enough awareness of PD?

Awareness has improved substantially over the past 10-15 years, in part because Michael J Fox has encouraged people to realise that PD is not just a disease of old people, and that it is much more than a nuisance and can have a profound impact on people’s lives. On the other hand, Fox has done extremely well and continues to be active and productive. Sadly, although many people do remain active for many years, not everyone does so well.
The Parkinson’s Disease Foundation (PDF) estimates that as many as 10 million people worldwide are affected by this neurodegenerative illness. Characterised by dysfunctional dopamine projection in the brain, the symptoms of Parkinson’s disease (PD) are generally observed in adults aged over 50 experiencing an 80 per cent loss of their striatal dopamine and a 50 per cent loss of their nigral cells. PD is not exclusively an illness of middle-aged and older adults, however, and individuals are subject to varying rates of disease progression. As the reasons for the onset of neuronal loss are currently unknown, a comprehensive understanding of the pathology of PD remains elusive and anything resembling a cure is a distant goal. Today’s treatments are familiar, longstanding strategies designed to help manage the disease, mostly through the pharmacological replacement of dopamine.

Advances are being made, however, in understanding PD’s pathogenesis. Developments over the last 25 years have seen significant improvements in imaging approaches and it is hoped that biological markers for the underlying processes of the disease may soon be identified. With the diagnosis of sporadic PD currently relying on neurological examinations and a patient’s medical history, suitable biomarkers could eventually lead to the development of tools for a much earlier diagnosis of the disease.

Treatments and Testing

Professor of Neurology at the University of British Columbia (UBC), Dr Jon Stoessl, MD, serves as Head of the Division of Neurology. In addition to holding the Canada Research Chair (Tier 1) in Parkinson’s Disease, Stoessl is the Director of the Pacific Parkinson’s Research Centre (PPRC) and the National Parkinson Foundation Centre of Excellence. With funding from the Canadian Institutes of Health Research (CIHR), the Pacific Alzheimer Research Foundation and the Michael J Fox Foundation, UBC’s PPRC has been critical in advancing research towards a greater understanding of PD. Stoessl’s focus is on finding out what causes PD; unravelling the mechanisms that lead to disease complications and create treatment challenges. Finally, he investigates how PD can be used as a model for elucidating the function of dopamine in the unaffected brain.

The programme’s research objectives encompass a wide variety of disciplines, and so, a broad range of expertise is essential for maintaining both its clinical and research functions. “All of the skills are critical to the Centre and excellent management of PD really requires a team approach,” Stoessl states. Though primarily employed on a clinical basis, nurses who specialise in PD, a physiotherapist and a social worker also use their skills to contribute toward meeting the research aims. As a research facility, the programme employs systems support staff, research technicians, coordinators, radiochemists, behavioural and preclinical neuroscientists, a physicist, a statistician and, alongside Stoessl, three academic neurologists.

Causes Unknown

Loss of dopamine neurons corresponds to lowered dopamine levels in the brain’s putamen. It has therefore been hypothesised that the pathology of PD might originate in the dopamine terminal, though the exact position remains unknown. In a study comprising the largest longitudinal positron emission tomography (PET) data available on the progression of PD, Stoessl has uncovered important insights into the impacts of age on dopamine dysfunction. He and his colleagues have demonstrated that the loss of dopamine
Developments over the last 25 years have seen significant improvements in imaging approaches and it is hoped that biological markers for the underlying processes of the disease may soon be identified.

function in PD differentially affects subregions of the striatum; that the differences are maintained throughout the course of the illness; and that the progression is non-linear and best described by an exponential decline whose rate is similar across different striatal subregions. This illustrates the dissimilarity between mechanisms contributing to initiation and progression of disease. While factors that cause disease initiation affect the subregions of the striatum to different degrees, those that determine progression affect all subregions to a similar extent. Though the cause of cell death in PD remains unknown, studies like these are providing vital clues for understanding the natural history of disease progression. If neuroprotective interventions are realised in the future, studies continuing in this vein will be invaluable in concluding when treatment should commence and what is being targeted.

Stoessl and his colleagues have demonstrated that the degree of dopamine dysfunction is actually greater in patients with younger age of onset, suggesting that they are better able to compensate for the loss of dopamine through a combination of pre- and post-synaptic factors.

RECOVERY REWARD

The placebo effect has been shown to have a powerful effect in PD, previously demonstrated by Stoessl and his colleagues to be related to dopamine release in the striatum. The fact that dopamine is released in response to anticipation of benefit has led to suggestions that the placebo effect is analogous to the expectation of reward. An illuminating study conducted at UBC Hospital in Vancouver studied dopamine release in 35 patients who thought they were about to receive a dose of levodopa, but instead received a placebo. The only independent variable between the subjects was the perceived expectation of benefit; they were told they had either a 25, 50, 75 or 100 per cent chance of receiving active medication. Strikingly, Stoessl and his colleagues found that the dopaminergic response related to expectation is maximal when a factor of uncertainty remains. Only at 75 per cent apparent probability of receiving an active treatment was there a significant instance of dopamine release, which in all striatal regions was heavily associated with dopaminergic response to active medication openly administered. These trials illustrate the large extent to which the weight of expectation can modulate placebo-induced release of dopamine. Stoessl is unwaveringly clear on recognising the importance of taking such consideration into account in the future: “This has substantial implications for the design and interpretation of clinical trials,” he explains.

MARKING MALADIES

Biomarkers are essential for the detection of disease expression, yet currently there are none available that are fully validated. Though imperfect, functional imaging with markers of dopamine function represents the best choice. By measuring the regional presynaptic activity and biochemical maintenance processes that characterise the unaffected brain, these methods can distinguish effectively between patients with and without loss of dopamine; can detect early, and even preclinical, disease; and serve as an independent measure of disease progression. It is likely, however, that instead of being used in isolation, a combination of biomarkers will be the preferred option. Indeed, the Parkinson’s Progression Markers Initiative is already searching for the most complementary mix. Though a great deal remains unknown about the underlying causes of PD, Stoessl’s investigations have helped and continue to help science characterise all aspects of the disease, making earlier and more accurate diagnoses, monitoring PD progression and developing therapeutic interventions an increasingly imaginable reality.

INTELLIGENCE

CANADA RESEARCH CHAIR IN PARKINSON’S DISEASE

OBJECTIVES

This multi- and interdisciplinary programme is focused on three overarching questions about Parkinson’s disease (PD):

1) What causes PD?
2) What mechanisms contribute to the complications of longstanding PD and its treatment?
3) How can we use PD as a model to better understand the role of dopamine in the normal brain?

KEY COLLABORATORS

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JON STOESSL is Professor and Head of Neurology and directs the Pacific Parkinson’s Research Centre and National Parkinson Foundation Centre of Excellence at the University of British Columbia & Vancouver Coastal Health. He holds a Tier 1 Canada Research Chair in Parkinson’s and has directed a CIHR Team in Parkinson’s, a Pacific Alzheimer Research Foundation Centre grant on ‘Overlap Syndromes Resulting in Dementia’ and a Michael Smith Foundation Research Unit. He co-chairs the Steering Committee for the World Parkinson Congress which was held in Montreal in October 2013. Stoessl is a Member of the Order of Canada. His research involves the use of positron emission tomography to study PD and related disorders, including the use of imaging as a biomarker, the basis for complications of treatment and mechanisms of the placebo effect. He has published more than 250 papers and book chapters.