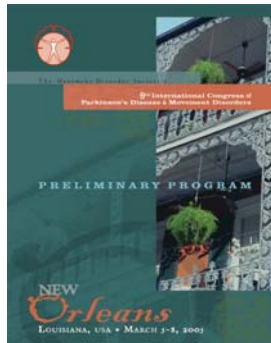


# 9th International Congress of Parkinson's Disease and Movement Disorders

5-8 March, 2005; New Orleans, US

The 9th International Congress of Parkinson's disease and Movement Disorders was located on the banks of the Mississippi in New Orleans in Louisiana. Several members of the ACNR team were to be found in the French Quarter after the sun had set exchanging notes on the day whilst sipping a Hurricane cocktail and listening to jazz! The main findings from this hugely popular event are perhaps best presented as a series of points:

- PD pathogenesis:** One recurring theme in both the plenary and parallel sessions was the key issue of the pathogenesis of Parkinson's disease, and in particular the likely importance of an interaction between genetic and environmental influences. The final common pathway probably involves three major areas of biochemical abnormality in the PD brain: mitochondrial dysfunction, oxidative free radical damage and proteosomal inhibition. Both the known environmental risk factors for PD and known genetic mutations act via these biochemical pathways to cause cell death, perhaps as follows: Mitochondrial complex 1, the activity of which has been shown to be reduced in the substantia nigra in PD brains, is inhibited by environmental toxins associated with PD risk, including annonacin (a toxin found in the tropical fruit soursop) and MPTP. PD patients with Parkin mutations are also known to have a specific reduction in peripheral complex 1 activity, and Parkin deficient mice have a striatal respiratory chain defect. Complex 1 deficiency appears to mediate cell death via reduced cell respiration, increased superoxide generation, proteosomal inhibition and a reduced threshold for apoptosis. Both annonacin and MPTP, as well as pesticides such as rotenone and paraquat, also cause direct free radical mediated oxidative damage to the cell. Furthermore, there is increasing evidence that Park gene products have a role to play in this pathway: oxidative stress increases  $\alpha$ -synuclein expression and promotes the interaction of DJ-1 and Parkin. Other environmental toxins known to be associated with PD risk are naturally occurring proteosomal inhibitors. Dysfunction of the ubiquitin-proteasome system is a good candidate for a pathogenic pathway in PD, given that the Lewy body, a protein aggregate containing ubiquitin, is central to the pathology of PD. At least some of the park genetic mutations may feed into this pathway: parkin encodes a ubiquitin ligase, and  $\alpha$ -synuclein is, of course a key component of the Lewy body. Indeed the recent proteasome inhibitor model of PD, created by systemically administering proteasome inhibitors to rodents for a two



week period, was discussed with respect to providing a better model of the clinical condition. This model, particularly if replicated by other groups, may provide a very useful tool for investigating the biochemical basis of PD and for testing putative neuroprotective agents.

- PD genetics:** This featured heavily at this meeting with an emerging consensus on pathogenic pathways that may link

the autosomal dominant forms of PD (PARK 1,5 and 8 =  $\alpha$ -synuclein, UCHL1 and LRRK2) and autosomal recessive forms of PD (PARK 2,6 and 7 = parkin, PINK-1 and DJ-1). Furthermore the potential role for heterozygous mutations in recessively inherited forms of PD increasing the risk of developing PD was explored. There was also much discussion about the clinical features and pathology in the latest genetic form of PD, as well as the molecular pathogenesis of the LRRK2 mutations in the PARK 8 families reported in *Neuron* in the autumn of last year (ACNR 4(6)). This 144kilobase gene, contains 51 exons and is a member of the ROCO gene family, and appears to be ubiquitously expressed in the brain. There is speculation that its effects lie through a cascade of kinase activity, perhaps ultimately influencing the phosphorylation of  $\alpha$ -synuclein.

- PD drug therapies:** The new MAOI, rasagiline, appears to improve the control of moderately advanced PD (LARGO study recently reported in the *Lancet*) as well as having a possible neuroprotective role in early PD. Furthermore there was much discussion about the future of GDNF in PD. Although shown to be safe in an open label trial in Bristol (*Nature Medicine* 2003 and *Annals of Neurology* 2005) in five patients, the efficacy has not been replicated in a double blind placebo controlled trial sponsored by Amgen, the company that make the drug. This negative clinical outcome at 6 months, coupled to reports of cerebellar pathology in monkeys treated with high levels of this drug and the presence of anti-GDNF antibodies in some patients has led to the trial being abandoned. This has dashed the hopes of many for the use of growth factors in PD, but it was emphasised that the trial used different parameters (catheter size, dose of GDNF infused etc) to the open label study which has reported post-mortem evidence of GDNF efficacy in one of their patients. In particular they have shown that in one of their patients there was dopaminergic fibre sprouting around the site of GDNF infusion, which correlated well with the F-dopa PET findings in this patient. Undaunted, other groups are continuing to explore this therapeutic avenue using viral vector delivery systems, an

approach that is currently being explored clinically in PD using virally delivered GAD to the subthalamic nucleus.

- A pilot study of six patients showed impressive improvements in their UPDRS following implantation of retinal pigment epithelial cells on the surface of gelatin microcarriers (spheramines) into the striatum. A sham control study is underway.
  - PD surgical therapies:** Deep brain stimulation continues to be a very active area in the treatment of PD as well as a range of other movement disorders, most notably essential tremor and primary generalised dystonia. However there is also an emerging story on side effects with this treatment, especially speech as well as some unpredictable psychiatric complications.
  - PD clinical features:** Another major development in PD discussed at this meeting was the new UPDRS, which takes into account the non-motor features of PD to a much greater extent. This often-neglected aspect of PD is now emerging as a major research theme with much work looking at the cognitive, autonomic and psychiatric features of PD and how they are best recognised and treated.
  - PD pathology:** Braak presented his thorough, but controversial work on the staging of pathology in this condition. This painstaking work involving many dozens of brains defines six stages of PD, with the earliest abnormalities being seen in the medulla and olfactory bulb, and disease then spreading rostrally up the brainstem such that the nigra is only involved in stage 3 disease. Thereafter the disease focus switches to the transitional and then neocortex. This beautiful work raises many questions, not least what constitutes the first clinical features of PD, and perhaps even more fundamentally how PD is actually defined.
  - Other movement disorders:** Mark Hallett presented an interesting account on apraxia (see also ACNR 5(1)) whilst Stan Fahn discussed dystonia, and a workshop on HD was presented by Flint Beal and Kathleen Shannon. In the session on MSA, Wenning discussed the existence of neuronal inclusions (that stain positively for  $\alpha$ -synuclein and ubiquitin) in addition to the well described glial cell inclusions. Electron microscopy of these neuronal inclusions reveal subtle differences from the Lewy bodies seen in PD.
- Concerns that, coming so soon after the meeting in Rome, there might not be much new data presented in New Orleans proved to be largely unfounded. The new style of the meeting brought a freshness to the format and conference fatigue was not a major issue. There are already plans afoot to stick to a similar format for the next conference in Kyoto, 2006.

Roger Barker, Caroline Williams-Gray, Tom Foltynie, Andy Michell and David Burn.

# SPRING Meeting 2005

7 February, 2005; London, UK.

An audience of scientists, clinicians, patients and their carers gathered to hear an exceptional day of lectures and discussion at this year's SPRING conference (the research-promoting arm of the UK Parkinson's disease Society). Professor Nicholas Wood presented work examining the role of single gene mutations in familial cases of PD, in particular two recently identified genes; PARK6 and PARK 8, and discussed the role of common variation in such genes in the commoner idiopathic form of PD.

Neuronal death in PD is thought to be characterised by such mechanisms as oxidative stress, excitotoxicity and mitochondrial dysfunction – mechanisms which are undeniably interlinked. Professor Peter Jenner presented work examining proteasomal dysfunction in PD as a way of identifying a single event upstream of the cycle of oxidative stress and cellular dysfunction in order to discover novel therapeutic targets with the potential to halt the progression of neuronal death and clinical impairment in PD. Data from brain tissue of PD patients showed a remarkable 40-50% downregulation of the  $\alpha$  subunit of the proteasome in the substantia nigra pars compacta compared to controls; a finding specific to this brain region. Other components of the proteasome such as the PA700 regulatory cap were also downregulated in the PD SNc, but were also upregulated throughout other brain regions, suggesting a change in the protein handling of the whole CNS in PD.

Professor Moussa Youdim argued that since neurodegenerative diseases such as PD and Alzheimer's disease have complex and distributed pathology with alterations in several neurotransmitter systems, multifunctional drugs which can target several of these pathways at once will prove superior to monofunctional drugs both in symptomatic relief and slowing disease progression. Dr Philip Robinson discussed the merits of a proteomics approach to identify the interacting partners of the protein products of genes associated with PD such as  $\alpha$ -synuclein and Parkin. Overexpression of  $\alpha$ -synuclein leads to a decreased expression of the proteasome  $\alpha$ -subunit and lactate dehydrogenase and an increased expression of mitochondrial transport protein, hinting at roles of  $\alpha$ -synuclein in the proteasome pathway and in mitochondrial function.

Michel Goedert discussed the role of  $\alpha$ -synuclein in PD and current efforts towards the generation of a transgenic mouse expressing the human form of this protein as a model of PD progression. Lewy bodies, the pathological hallmark of idiopathic PD, are constructed mainly from abnormal filamentous protein aggregates consisting of  $\alpha$ -synuclein. It seems that some pathological pathway exists in which the natively soluble unfolded  $\alpha$ -synuclein is converted to these insoluble filamentous aggregates. Mutations leading to familial PD have been identified in the  $\alpha$ -synuclein gene and are essentially of two types; missense mutations which render the gene product more liable to form filaments, or gene duplications/triplications. Thus even a single gene dosage effect, i.e. expressing more of

the wild-type  $\alpha$ -synuclein, is sufficient to lead to aggregate formation and clinical disease.

The use of cell line models to manipulate the expression of PD associated genes, with a view to providing a better understanding of the mechanisms leading to their damaging effects on cells and ultimately ways in which to minimise this damage, was discussed by Professor David Latchman. Using this approach Prof. Latchman has analysed the effects of overexpression of  $\alpha$ -synuclein (WT and mutant forms) and PINK1, as well as reducing the expression of Parkin, on cell death when exposed to a variety of exogenous stressors such as dopamine, staurosporine and hydrogen peroxide. Whilst mutant forms of  $\alpha$ -synuclein are damaging regardless of which stress the cells encounter the wild-type form can be either protective or damaging in different circumstances. Of particular interest is a protective effect of WT  $\alpha$ -synuclein (and a damaging effect of mutant forms) when cells are exposed to dopamine. The introduction of a Parkin antisense plasmid into cells in order to reduce Parkin expression levels resulted in increased cell death in response to stress, an effect which was reversed by caspase inhibitors, thus suggesting that the death seen in the absence of Parkin is mediated through the apoptotic pathway. Recent work in collaboration with Professor Nick Wood lead to the identification of the protein kinase PINK1 as having a protective function against collapse of the mitochondrial membrane potential in response to proteasome inhibitors. Further characterisation of the mechanisms through which these single gene mutations lead to cellular dysfunction, death, and ultimately clinically apparent disease is likely to identify novel therapeutic targets which may be more broadly applicable to sporadic cases of the disease.

Transcriptome analysis, the establishment of a microarray-based expression profile of the parkinsonian substantia nigra as a method of providing a novel molecular pathology based set of diagnostic criteria for PD, was presented by Professor Maneul Graeber of Imperial College, London. The sophisticated mathematical analyses employed in these studies are providing a picture of the different molecular pathways disturbed in PD, with the ubiquitin-proteasome pathway and mitochondrial dysfunction featuring prominently.

Work leading to the first clinical trial of gene transfer therapy in Parkinson's disease using adeno-associated viral vectors to transfer the glutamic acid decarboxylase (GAD) gene into subthalamic nucleus (STN) neurons, was presented by Professor Matthew Durrin of Cornell University. The results of the initial phase one safety trial of this novel gene therapy approach to PD are due to be published later this year.

Another novel therapeutic approach to PD was presented by Professor Steven Gill, who, having



heard of preclinical trials using GDNF in animal models of PD at a SPRING meeting some 5 years ago, went on to use this neurotrophic factor in human PD patients in small scale phase 1 trials (see report from the 9th International Congress of Parkinson's Disease and Movement Disorders in this issue). Dr David Dexter presented results of experiments using antioxidant flavonoids found in fruit, vegetables, tea and wine as neuroprotective agents in the 6-

OHDA rat model of PD. He demonstrated a significant reduction in TH+ cell death following 6-OHDA lesioning in animals treated with orally administered antioxidant tangeretin. Professor David Goldstein provided a discussion of the potential role of pharmacogenetics in optimising pharmacological therapies for PD based on patients' genotypes. The potential benefits would be able to predict particular groups of patients who would respond well or adversely to a given drug treatment and also to minimise the time spent trying to achieve optimal dosing through the traditional trial and error approach. This was illustrated with data from Prof. Goldstein's work on single nucleotide polymorphisms (SNPs) in genes known to influence the metabolism, and therefore required dose, of anti-epileptic drugs such as carbamazepine and phenytoin. There is as yet no systematic analysis of the effects of single gene polymorphisms on response to anti-parkinsonian drugs. The final speaker of the day, Dr Matthew Wood, discussed the potential of therapeutic gene silencing for Parkinson's disease using the relatively new technology of (short interfering RNA) siRNA. This highly conserved cellular pathway whereby short double stranded RNA leads to the destruction of homologous mRNA (i.e. post-transcriptional gene silencing) will be one possible future approach to PD therapy. As with all experimental forms of therapy there are problems to overcome; the major one here being the delivery of siRNA to specific target cells in the adult brain. The use of viral delivery systems may allow sufficient targeting, however, it may be possible through chemical modifications of the siRNA molecules to enhance stability of the naked RNA and to apply a certain degree of target specificity, thus avoiding the need for a viral delivery system. An alternative would be to use an ex-vivo technique, introducing the si-RNA into neural stem cells before transplanting them into the PD patient.

Any major advance in therapy is likely to involve a synthesis of several current major strands of research including genetic and cellular approaches, with the development of each of these individual strands driven by our ever-advancing understanding of the pathogenesis of this complex heterogeneous disease.

Mark Sayles,  
Cambridge Centre for Brain Repair,  
Cambridge.

# Association of British Neurologists Spring Meeting

30th March-1st April 2005; Belfast

The Spring meeting of the ABN at the Queen's University campus in Belfast was a feast of 29 research presentations, 49 posters (the organisers clearly like odd numbers), four guest lectures, a clinicopathological conference and an educational symposium on stroke. The meeting was held a few yards from a library dedicated to Seamus Heaney, Nobel Prize winning poet who studied at Queen's; Philip Larkin was a former sub-librarian here, though seemingly not commemorated. Would these literary associations prompt the ABN to new poetic heights? As always it was a mixed bag, although the neurogossip was as good as ever.

A recurrent theme was 'the structure of neurological care', overviewed by Dr Victor Patterson, a pioneer of teleneurology in Northern Ireland, also demonstrating the "added value" of specialist opinions for distant patients with neurological problems. Future developments may include e-mail triage of new outpatient referrals which seems safe, effective, cost-effective and sustainable, as well as being acceptable to GPs and, more so, to patients. Loizou suggested that perhaps 50% of referrals may be dealt with through e-mail without the patient needing to attend clinic. A poster showed that e-mail teleneurology could bring neurological resources effectively to the developing world. Patterson had to travel to Brisbane (poor chap!) to show that modern technology (real-time telemedicine) also allows outsourcing of night time cover to a different (daytime) time zone. Worrying for those out-of-hours supplements!

With all the sophisticated techniques now at the disposal of the practising neurologist, what role remains for neurological examination? McNeill's comparison of the 1897 and 2002 editions of Hutchinson's Clinical Methods revealed an increased amount of text devoted to neurological examination over the 105-year period, whereas a reduction was noted in chapters on respiratory medicine and cardiology. Unfortunately, a similar analysis could not be performed for history taking.

The PRCP, Carol Black, spoke in her guest lecture of the modernisation of the Royal College ("Change, adjustment and redefinition") and discussed the challenges of the nascent specialty of "Acute medicine" and the changing pattern of chronic care (towards the community). It was good to hear elsewhere in this and previous meetings that neurologists are taking on the management of acute neurology (a sub-specialty of "Liaison Neurology"?). However it was fortunate that the PRCP didn't hear some of the less than enthusiastic opinions (widely reiterated over coffee) concerning the neurological competence of general physicians. GKT medical school (Ridsdale) showed that five weeks full time neurology teaching could reduce 'neurophobia' in students (and hence future acute medicine specialists?) and improve their interest and confidence in neurology... something for curriculum planners



to consider.

The cannabis story continues. Collin showed in a drug company sponsored trial that Sativex was well tolerated and superior to placebo for the relief of spasticity in multiple sclerosis, using a numerical rating scale as the primary end point (i.e. subjective evaluation by patient). Secondary endpoints were improved but not statistically so, possibly due to the strong placebo effect noted in the trial. Interestingly there was a trend to improvement in muscle strength rather than the anticipated weakness and the benefit seems to be sustained in an extension trial.

Serial volumetric imaging of low grade gliomas may allow prediction of malignant transformation (Rees). Annual tumour growth rate was greater in patients who subsequently transformed as compared to non-transformers. This may offer important opportunities for early intervention in a group of patients with poor prognosis.

The diagnosis of herpes simplex encephalitis is often considered in patients with an acute encephalopathy with seizures, but may be difficult to establish. An audit of all suspected cases seen at Queen Square over a five year period found that only 10 out of 222 had a definite diagnosis; an alternative diagnosis was established in 144. 20% of cases remained undiagnosed. Investigations used included PCR (31%), intrathecal antibodies (11%; relatively unused) and brain biopsy (8%) (Davies).

Two presentations audited the diagnostic use of brain biopsy. At Atkinson Morley Hospital, 186 biopsies performed over a 10-year period (1993-2002) were mostly done to confirm a diagnosis of tumour, with a high diagnostic yield (97%). Yield was lower for "white matter lesions", with cerebral vasculitis confirmed in only one of 13 patients referred for this indication, alternative diagnoses being established in seven (O'Riordan). Biopsies performed at Queen Square, for the investigation of demen-

tia in the period 1989-2003, had a lower yield still (59% diagnostic). The most frequent finding was non-specific gliosis, possibly akin to the syndrome of progressive subcortical gliosis reported by Neumann in 1967. In only 11% of cases did information obtained at biopsy directly influence treatment; very few "reversible" dementias were identified (Schott).

Dementia was considered in three platform presentations (including the above audit of biopsy) and six posters (four concerning CJD). A Liverpool study showed that observing whether a patient, referred to a dementia clinic, followed instructions and brought a relative to the clinic was a test for the presence of dementia with 100% sensitivity but rather low specificity. Referrals to the dementia clinic from Liverpool neurologists were shown to have "added value" compared to those GPs and other clinicians (pew!). Steve Wroe reported that tonsillar biopsy achieved 100% specificity and sensitivity in the diagnosis of nvCJD, whilst a poster from Bristol demonstrated that some find it difficult to distinguish the EEG of CJD from non-convulsive status unresponsive to anticonvulsants.

Movement disorders were the subject of three platform and seven poster presentations. We heard from Gibson (Belfast) that simple non-invasive analysis of ocular fixation might improve the clinical differential diagnosis of parkinsonism. Molloy (Newcastle) showed that l-Dopa improved alertness in patients with Parkinson's disease but at the expense of increasing impulsivity (the speed of responses increased but the accuracy fell) in those with cognitive problems. Meanwhile in the MS section the Oxford group showed that modafinil improved the fatigue of patients with MS especially if they were also drowsy (perhaps when some patients say they are 'tired' they mean sleepy rather than fatigued?).

An impressive presentation from Schaeffer (Newcastle) showed that at the least the physiological parameters of patients with mitochondrial myopathies could be improved with exercise induced activation of muscle stem cells. Mark Wiles confirmed the clinical impression that patients with myotonic dystrophy fall a lot but we still don't know why or what to do about it. Farrugia (Oxford) considered the important point that the problem of muscle atrophy (especially tongue wasting) in MuSK positive myasthenia might be exacerbated by steroid therapy. Brian Lecky in presenting five cases of limb girdle dystrophy type 2I further emphasised the difficult task of identifying genotypes from phenotypes in muscle disease. He concluded that this dystrophy might be a more common cause of a proximal myopathy with a high CK than previously thought. The biopsies of some cases showed inflammatory cells which could be removed by steroids without helping the muscle disease.

Epilepsy problems were considered in four platform presentations and five posters. A

senior member of the ABN rather deflated the usefulness of Hitiris' presentation from Glasgow on the usefulness of investigation in a first seizure clinic by (correctly) pointing that there was "nothing new here". The same could be said of the poster which produced no surprises in showing that structural abnormalities of the brain were more likely to be found in patients referred to neurology outpatients with seizures than in those referred with headache.

There were only two platform presentations on cerebrovascular disease (and six posters), one about the IST-3 trial of outside the licence use of r-tpa in acute stroke which Peter Sandercock largely duplicated in his presentation on the same subject in the Stroke educational session. Rory Collins' data-packed guest lecture on cholesterol, statins and stroke made all of us over 45 feel uncomfortable about not taking a statin for breakfast in order to emulate the health of Chinese peasants. Unfortunately much of this was repeated in Ian Young's more austere talk in the Stroke educational session. Thus, by Friday, after two hotel breakfasts, we were all heartily fed up with cholesterol. In the final educational talk of the meeting, Rothwell, by teasing us with totally atypical presentations



of posterior circulation TIAs, came some distance short of showing that the reliable diagnosis of TIAs requires a neurologist. However, of course, we all know that it does. Fortunately the expression "Brain Attack" was not to be heard in the whole three days.

The local Belfast expertise in Paramyxoviruses was demonstrated in a perhaps over comprehensive review of these interesting beasts and how they enter the brain and cause diseases, possibly via CD46 and SLAM receptors on endothelial surfaces and elsewhere. Those working in rural areas will need to be on

their guard to recognise the human equivalent of the Barking Pig Syndrome, if Nipah viruses are shown, like their relatives the Hendra viruses, to transfer to humans from their animal reservoirs. This talk was followed by a very entertaining performance by Brendan McLean as the discussant in a very difficult CPC. He predicted he would get it wrong and did, as we all would have done, except one member of the audience who told us, after the denouement, that it was a classic example of Enterovirus 71 encephalomyelitis!

Sydney Allison, the great Belfast neurologist who started the systematic study of MS in populations, was commemorated in a brilliant guest lecture by Stephan Waxman. He guided us through the numerical jungle of neuronal sodium channels in a fluent exposition of this area of neuroscience which holds so much promise in our search for effective treatments for axonal disease and degeneration. This, on its own, was worth the trip to a rather grey and damp Belfast.

*Chris Allen, Addenbrooke's Hospital, Cambridge.*

*Andrew Larner, Walton Centre, Liverpool.*