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The Year in
Parkinson's
Disease
2009

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Foreword

The best of Parkinson's disease research in 2009

Welcome to the second ACNR supplement, which concentrates on the recent work that has been done in the field of Parkinson's disease.

As with all things to do with the journal, the "pick and mix" of what is presented is somewhat idiosyncratic and eclectic, but we hope that it does capture most of the major breakthroughs and discoveries of the last year or so. We are very grateful to all those who have contributed to this special edition and particular thanks go (in no particular order) to Michelle Hu, George Tofaris, Nin Bajaj, Tom Foltynie, Huw Morris, Vinod Metta, Alexandra Rizos, Ray Chaudhuri, and John Hardy. We are also extremely grateful to GlaxoSmithKline for their kind sponsorship of this supplement. While they have sponsored the cost of production, the content and views expressed are entirely our own.

So what have we covered in this special supplement?

Michelle Hu and George Tofaris have reviewed the major PD related meetings of the last year and identified the key presentations which include work on aetiology, phenomenology, imaging and therapies. This is complemented by a series of reviews on articles from the major neurological/movement disorder journals by Tom Foltynie and Nin Bajaj – which includes a similar range of topics. Huw Morris reviews trials, I review major scientific breakthroughs and John Hardy updates us on the genetics of PD, especially the emergence of Glucocerebrosidase mutations as an important aetiological factor in PD as well as the results of the GWAS in PD.

These studies all converge onto a number of key issues, not least of which are the extent to which we can better understand PD through genetic cases and causes. This is important as the relevance of rare genetic Mendelian forms to idiopathic PD has, and remains, an issue but seems the only likely route of success, given our inability to know when idiopathic PD truly begins and what triggers it from an environmental perspective. This is where the GWAS may help, and also epidemiological work some of which is pointing towards problems in

calcium channel activity in vulnerable neuronal populations, most notably the nigral dopaminergic neurons. However any theory that only discusses this latter population of cells is unsatisfactory, given the body of work and evidence that PD has as many non-motor features as motor and a significant degree of non-nigral pathology. Ray Chaudhuri and colleagues discuss this further in their article, as they present recent findings from the results of questionnaire responses on the non-motor features of PD.

This is a crucially important aspect of better understanding PD, but sometimes I get the feeling that if you say PD does have motor features and dopaminergic pathology that you are regarded as being rather out of date! This is obviously a problem for those working on new therapies for PD, as most of us would agree that dopaminergic drugs can help the odd patient with PD for some time! Thus whilst having a dopaminergic cell centric view of PD is not the whole story, it is at least a helpful starting point for thinking of better strategies for brain repair which may come through the development of differentiated stem cells – such as iPS and iN (see also ACNR 10.1). This ability to reprogramme cells is, I think, one of the major scientific breakthroughs of this century and directly speaks to PD, which has also been the subject to attack from a new theory of pathogenesis concerning the possibility of alpha-synuclein behaving in a prion like fashion. These are the two themes I develop in my short account on PD Science.

Finally we have some useful pieces on the work of charities most directly involved in PD. The UK Parkinson's Disease Society (which has now been rebranded as Parkinson's UK), the European Parkinson's Disease Association (EPDA), Cure PD and HealthyAlliance have all given us an insight into their work in 2009.

So we hope you enjoy this new ACNR Supplement. If you have any ideas or would like to be involved in similar projects with us in the future, then do just let us know.

Roger Barker .

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Conferences

The Year in Parkinson's Disease - Conference Proceedings

Michele Hu and George K Tofaris

This section will summarise the salient 2009 presentations in Parkinson's disease (PD) covering meetings at the American Academy of Neurology, Movement Disorders Society, European Neurological Society, Association of British Neurologists, European Federation of Neurological Societies and the World

Congress of Neurology. To give you the most interesting updates in a digestible form, we have grouped the presentations, some of which featured in more than one conference in four main themes: Pathogenesis and Phenomenology, Imaging, Therapies and Genetic studies in PD.

Pathogenesis and Phenomenology of PD

L-type Calcium channel blockers neuro-protective for PD

Unlike most neurons in the brain, adult substantia nigra pars compacta dopaminergic neurons are Ca21 calcium channel-dependent autonomous pacemakers that in the absence of synaptic input generate action potentials at a 2-4 Hz rhythm. It has been suggested that reliance on calcium channels might create a special dopaminergic neuron susceptibility to cellular ageing. Cells in which calcium channels drive pacemaking may experience higher levels of basal oxidative stress due to ATP demands for intracellular calcium handling. Dopaminergic neurons can be returned to juvenile ionic mechanisms of pacemaking by the L-type Ca21 channel antagonist isradipine in-vitro and in-vivo. These channel blockers protect animals against cell loss and motor deficits after the administration of MPTP

This Danish study led by Dr B Ritz identified 1,931 patients with a first-time diagnosis and/or treatment for PD via a national hospital and outpatient clinic record system between 2001 to 2006. Patients were matched by birth year and sex to 9,651 controls selected from a Danish population

control register. Employing logistic regression analysis adjusting for age, sex, chronic pulmonary obstructive disorder and comorbidity, cases were prescribed L-type Ca21 calcium channel blockers of the dihydropyridine class (excluding amlodopine, a blocker that acts mainly peripherally rather than centrally) less frequently than controls between 1995 and a two year period prior to PD diagnosis. Risk of receiving a PD diagnosis was 27% lower in the group treated with calcium blockers (odds ratio (OR) 0.73; 95% CI 0.55 to 0.97). The estimated risk reduction did not differ with the intensity or length of treatment, and protective associations for PD were not found with other antihypertensive medications or calcium channel blockers. This elegant study is the first to suggest a potential neuroprotective role for L-type calcium channel blockers in PD, and is unique because it is the first of its kind to evaluate specific L-type dihydropyridine calcium blockers that cross the blood brain barrier, lending increased credence to the calcium hypothesis in PD – Michele Hu

Ritz B, Qian L, Schernhammer E, Olsen J, Friis S. L-type calcium channel blockers and the risk of developing Parkinson's Disease in Denmark. *MOVEMENT DISORDERS* 2009;24(Suppl 1):S130, We-82.

Family history of Melanoma increases PD risk

This study builds on recent work by the same group from Harvard Medical School, recently published in *Annals of Neurology* (Gao X et al, 2009;65:76-82) which trawled the databases of

over 132,000 men and women to find that hair colour, and the distribution and quantity of melanin, influences the risk of developing PD. In essence, PD risk is 1, 1.4, 1.61, and 1.93 for black, brown, blond and red hair respectively. Red heads – watch out! For PD onset before age of 70 years, there was an even greater correlation. This explains why PD patients are at risk of melanomas, because they are more likely to be fair or red-haired. However, how variable expression of melanin is related to the risk of PD is unclear. Melanin, like dopamine is synthesised from the amino acid tyrosine. A major pathological feature of PD is the loss of neuromelanin containing cells within the substantia nigra. Neuromelanin is chemically similar to melanin and may be neuroprotective by scavenging metals and pesticides. The current study prospectively examined the association between a family history of melanoma and PD in 131,995 men and women free of PD at baseline participating in two ongoing US cohorts: the Health Professional Follow-up study and the Nurses's Health study. During 14 to 20 years of follow-up, 543 incident PD cases were identified. A self-reported family history of melanoma in a first-degree relative was associated with an increased risk of developing PD (multivariate RR=1.92; 95% CI: 1.3,2.9; P=0.002), after adjusting for smoking, ethnicity, caffeine and other variants. In contrast, associations between a family history of colorectal, lung, prostate or breast cancer and PD were not seen. These findings support the notion that melanoma and PD share common genetic components, and the authors conclude that the genetic determinants of melanoma could therefore be explored as susceptibility candidates genes for PD. – Michele Hu

Gao X, Simon C, Han H, Schwarzschild M, Ascherio A. Family History of Melanoma and Parkinson's Disease Risk.

AMERICAN ACADEMY OF NEUROLOGY
2009; SC02.004.

See also page 10, Pigment & PD - it's in the genes, by Tom Foltynie

Personality traits do not influence PD risk

This study investigated whether a distinct 'parkinsonian personality' exists, as less novelty seeking, more morally rigid, introverted, punctual, cautious and conventional personality traits have been suggested to precede PD onset. Led by Dr Arabia, researchers established a historical cohort of 7216 subjects who completed the Minnesota Multiphasic Personality Inventory (MMPI) at the Mayo clinic from 1962 to 1965. Of these, 6,822 subjects (94.5%) were followed up over four decades either through phone interviews with the subject or a close relative or by archived records or death certificates. During follow-up, 227 patients developed parkinsonism, of whom 156 were diagnosed with PD. Researchers examined the association of novelty seeking personality traits measured using 5 MMPI scales (sensation seeking, hypomania, positive emotionality, constraint and social inversion scales) with the risk of parkinsonism. The investigators found no association with either low or high degree of novelty seeking personality traits and risk of developing PD. Of great interest would be to investigate the link between premorbid novelty-seeking personality traits and the later development of dopaminergic drug-related impulse control disorders in PD patients such as pathological gambling, compulsive eating, buying and hypersexuality. – Michele Hu

Arabia G, Grossardt BR, Colligan RC, Bower JH, Maraganore DM, Ahlskog JE, Rocca WA. Novelty seeking personality traits do not influence the risk of Parkinson's disease.

MOVEMENT DISORDERS
2009;24(Suppl 1):S233, Mo-160.

Creativity linked to dopamine agonists in PD

PD is characterised by loss of cognitive abilities such as flexibility, conceptualisation and visuospatial function. Creativity results

Importantly, this study also shows that good things, not just bad things, can happen with dopamine agonists!

precisely from such cognitive skills. Case studies however show emergence or enhancement of creativity in the course of PD. This French study set out to determine whether creativity may be part of a spectrum of behavioural changes, most of them not so positive, that are seen with the dopamine agonists. A newly developed behavioural scale for PD was administered to 11 creative and 22 control PD patients before and one year after STN deep brain stimulation (DBS). The two groups were the same in terms of baseline cognitive function. Creativity selection was based on the recent re-emergence of creativity, with artistic creativity starting in 6/11 creative patients while on dopamine replacement therapy. Before DBS, there was no difference in total dopamine replacement therapy between the two groups, but creative patients took significantly more dopamine agonists than controls and had higher scores for mania, hobbyism and 'on'-euphoria. They did not differ from controls in gambling, shopping, hypersexuality, irritability or addiction. Post-operative improvement in UPDRS motor scores, stimulation parameters and mean dopamine replacement therapy reduction (69%) were the same in the two groups. Apathy increased in both groups. Only 1/11 creative patient remained creative after surgery, and patients who lost their creativity said they missed it. This study shows that creativity is linked to dopamine agonist therapy and arises with other modifications of the hyperdopaminergic spectrum, but not impulse control disorders. Creativity disappears after DBS surgery when dopamine replacement therapy is drastically reduced and treating physicians need to be aware of the broad range of effects of dopamine agonists when prescribing these drugs. Importantly, this study also shows that good things, not just bad things, can happen with dopamine agonists! – Michele Hu

Batir A, Lhomme E, Ardouin C, Fraix V, Seigneuret E, Chabardes S, Benabid A-L, Pollak P, Krack P. Creativity induced by dopamine agonists in Parkinson's disease.

MOVEMENT DISORDERS
2009;24(Suppl 1):S234, Mo-163.

Distinguishing dystonic from parkinsonian tremor

Approximately 10% of subjects thought clinically by movement disorder specialists to have early PD have normal dopaminergic functional imaging (SWEDDs – Subjects Without Evidence of Dopaminergic Deficit). Adult-onset tremor may be one of the causes of SWEDDs, and this Queen Square group aimed to delineate clinical and electrophysiological characteristics that might differentiate patients with SWEDDs from PD and to clarify the underlying pathophysiology of SWEDDs. Clinical details of 30 patients referred with a diagnosis of tremor-dominant PD but with normal DaT (Dopamine Transporter) SPECT scans (SWEDDs) were compared to 10 tremor-dominant PD patients with abnormal DaT SPECT scans. Tremor analysis using accelerometry in patients with SWEDDs, PD, and segmental dystonia with limb tremor was performed. Transcranial magnetic stimulation with a facilitatory paired associative stimulation (PAS) paradigm was used to test if sensorimotor plasticity in SWEDDs resembled the pattern seen in PD or dystonia. The presence of dystonia, lack of true bradykinesia, and position and task-specificity of tremor favoured a diagnosis of SWEDDs, whereas re-emergent tremor, true fatiguing or decrement, good response to levodopa and the presence of non-motor symptoms made PD more likely. Basic tremor parameters overlapped between the three

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These findings demonstrate the importance of uncertainty and/or prominence over and above a patient's prior treatment response in regulating the placebo effect

groups, however re-emergent tremor and highest tremor amplitude in the resting condition was characteristic of PD tremor, while SWEDDs and dystonia subjects had the highest tremor amplitude during action. Both SWEDDs and dystonia patients exhibited exaggerated sensorimotor plasticity in response to the PAS paradigm, while PD patients showed no response to PAS. It is therefore likely that adult-onset dystonia is one of the main diagnoses in SWEDDs patients, and uncomfortably that a sizeable proportion of patients currently diagnosed as tremor-dominant PD in fact have dystonic tremor. – Michele Hu

Schwingschuh P, Ruge D, Edwards MJ, Terranova C, Carrillo F, Schneider SA, Silveira-Moriyama L, Kagi G, Katschnig P, Dickson J, Lees A, Quinn N, Mir P, Rothwell J, Bhatia K. Clinical and Electrophysiological Parameters Can Differentiate Patients with SWEDDs from Tremor-Dominant Parkinson's Disease. 61ST AMERICAN ACADEMY OF NEUROLOGY, 2009;P02.073.

Imaging in PD

Placebos mimic the effect of medication in PD

The placebo effect represents a compelling example of the influence of cognition on physiological processes. In PD, placebo effect is associated with endogenous dopamine release in motor and reward circuitry. Midbrain dopaminergic neurons have been shown to encode the expected reward value of an impending reward, as well as the uncertainty associated with reward expectation. This study shows that the likelihood of improvement, as well as the patient's prior medication experience, drive dopamine release in the striatum. Verbal manipulation was used to modulate the

strength of expectation of symptom improvement and resulting dopamine release in dorsal and ventral striatum was measured using 11C raclopride positron emission tomography (PET). Maximal dopamine release occurred when the declared probability of receiving active medication was 75%, but not at lower probabilities, or when administration of active medication was deemed uncertain. Placebo-induced dopamine release in all regions of the striatum was highly correlated to the degree of release in response to open administration of active medication. Whereas prior medication experience was the major determinant of dopamine release in the dorsal striatum in response to placebo, expectation of clinical improvement was additionally required to drive dopamine release in the ventral striatum. These findings demonstrate the importance of uncertainty and/or prominence over and above a patient's prior treatment response in regulating the placebo effect. This result has important implications for the interpretation and design of future clinical trials.

– Michele Hu

Lidstone SC, Schulzer M, Dinelle K, Mak E, Sossi V, Ruth TJ, de la Fuente-Fernandez R, Phillips A, Jon Stoessl A.

Great expectations: placebos mimic the effect of active medication in Parkinson's disease. MOVEMENT DISORDERS, LATE BREAKING ABSTRACTS, LB-09, 2009.

Forced-exercise produces benefits similar to Levodopa in PD treatment

Patients with PD who exercise on a stationary tandem bicycle with a healthy partner during a single session experience a 35% improvement in motor function and increased brain activation similar to that found with levodopa treatment. Previous

studies have shown that lower extremity forced-exercise (FE) intervention resulted in significant improvements in parkinsonian symptoms in upper and lower extremity motor function in mild to moderate PD. Symptomatic motor improvement produced by FE is similar to that seen with standard levodopa (LD) therapy in PD, suggesting that both interventions may produce similar changes in motor pathway network function, translating into motor improvement. In this study performed at the Cleveland Clinic, UPDRS-III and fMRI examinations were completed in 10 mild to moderate PD patients in three conditions: no medication, on medication and no medication with FE. The FE intervention consisted of one 40-minute session in which patients exercised on a stationary tandem cycle with an able-bodied trainer maintaining a rate of 80 to 90 revolutions per minute. Gradient Echo fMRI was performed during performance of a bimanual finger tapping and force-tracking task utilising a standard block design. Both FE and LD therapy produced similar significant reductions in motor UPDRS scores (35 and 38% respectively). Functional MRI demonstrated increased activation in supplementary motor area and M1 region with both FE and LD therapy. Motor performance was improved by 35% following forced exercise compared to no exercise. This study shows that both forced-exercise and levodopa therapy produce a similar pattern of fMRI activation and therapeutic response. They may facilitate the same motor control processes in PD patients producing similar symptomatic relief. Maybe we should be encouraging patients to get out their exercise bikes! – Michele Hu

Ahmed A, Ridgel AL, Phillips MJ, Vitek JL, Lowe ML, Hutson M, Feldman M and Alberts JL. Effect of forced-exercise on motor symptoms and cortical activation in Parkinson's disease. MOVEMENT DISORDERS, LATE BREAKING ABSTRACTS, LB-13, 2009.

Tonic stimulation of the orbitofrontal cortex by dopamine agonists wipes out reward processing and increases risk taking behaviour

This study from Toronto investigated the differential neurobehavioural effects of dopaminergic medication in the context of reward processing and risk-taking in PD patients. Eight non-gambling PD patients on a combination of levodopa and dopamine agonists were studied on three different days following overnight withdrawal. One session OFF medication, one session after 100mg levodopa and one session after levodopa equivalent dose of dopamine agonist. Patients played a roulette game during fMRI and performed a financial risk-taking task offline. Brain maps of synaptic activity change at the time of outcome and correlation with the index of reward processing were calculated. Dopamine agonists specifically changed the activity in the reward system in two ways; both associated with risk-taking. Firstly, plain outcome-induced induced activations in orbito-frontal cortex were higher with dopamine agonists compared to levodopa/off medication state. These activations significantly correlated with risk-taking scores. Secondly, both levodopa and dopamine agonists equally diminished local reward processing compared to off states in the ventral striatum. However, only dopamine agonists completely abolished local reward processing in the orbitofrontal cortex. This is the first study to specifically link synaptic effects of dopamine agonists in PD with impaired reward processing and increased risk-taking behaviour, and provides a possible model as to how dopamine agonists could prime pathological gambling in PD. – Michele Hu

van Eimeren T, Ballanger B, Pellecchia G, Miyasaki J, Chuang R, Steeves T, Lang AE, Strafella AP. Tonic stimulation of the orbitofrontal cortex by dopamine agonists in PD wipes out reward processing and increases risk taking behaviour: Are they at risk for gambling? MOVEMENT DISORDERS 2009;24(Suppl 1):S217, Th-140.

Dopamine transporter imaging to differentiate Parkinson's disease and cerebrovascular parkinsonism

The classical presentation of vascular parkinsonism is characterised by sudden onset, symmetric and rapid progression of motor symptoms, postural instability with shuffling gait, absence of tremor and absent or poor response to dopamine therapy making it a distinct clinical entity from PD. However this presentation is variable in many patients with parkinsonism and vascular lesions, and data on the relationship between PD and stroke have been conflicting. For the clinician, the practical clinical problem is to determine whether a patient's parkinsonism can be related to an identifiable cause other than a neurodegenerative process. 123I-FP-CIT SPECT (DaTSCAN) is a sensitive marker of dopaminergic degeneration and offers a quick, objective method to confirm or exclude presynaptic parkinsonism in difficult cases. Whereas 123I-FP-CIT uptake is significantly reduced in the striatum of PD patients, recent reports claim that dopamine transporters are usually normal in patients with vascular parkinsonism or show only a slight, diffuse putaminal reduction. In this study from Imperial College, 20 patients with a differential diagnosis of vascular parkinsonism versus PD underwent 123I-FP-CIT SPECT. Clinical signs were recorded and correlated with clinical outcome. 8/20 scans

were abnormal, there was no significant relationship between any clinical measures and the DaTSCAN results. A correlation between DaTSCAN outcome and response to levodopa was demonstrated in 20 patients, suggesting that accurate diagnosis aided by DaTSCAN can improve the clinical management of these patients. – Michele Hu

Hensman DJ, Bain PG. Dopamine transporter imaging to differentiate Parkinson's disease and cerebrovascular parkinsonism. EUROPEAN JOURNAL OF NEUROLOGY 2009;16(Suppl 3):335-624.

Therapies in PD

The ADAGIO Study

Slowing disease progression is a major therapeutic aim in PD that is yet to be fulfilled. Rasagiline has neuroprotective properties in several animal models of neurodegeneration, which seems to be independent of MAO-B inhibition. Recent data from the ADAGIO study, which was published in the NEJM and featured in a number of conferences last year, suggest that rasagiline has a disease-modifying effect using a delayed start design. In this double-blind trial, a total of 1176 subjects with untreated PD were randomly assigned to receive rasagiline (1mg or 2mg/day) for 72 weeks or placebo for 36 weeks followed by rasagiline (1mg or 2mg/day) for 36 weeks (the delayed-start group). There were three primary hierarchical endpoints based on total-UPDRS scores. The authors found that early treatment with rasagiline at a dose of 1mg/day met all the end-points in the primary analysis: a smaller increase in the UPDRS score between weeks 12 and 36 in the early vs. in the placebo group and the delayed-start group. However, the primary end-points were not met by rasagiline 2mg/day. Both rasagiline doses significantly improved the UPDRS-Total scores compared to placebo. Moreover, in the 1mg/day group the need for additional anti-PD treatment was about 60% less. Interestingly, in a post hoc analysis using the non-motor aspects of experience of daily living in the new MDS-UPDRS, the authors found that that rasagiline 1mg but not 2mg/day also demonstrated a significant benefit vs. placebo. This study confirmed the

The authors found that early treatment with rasagiline at a dose of 1mg/day met all the end-points in the primary analysis...however, these were not met by rasagiline 2mg/day

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symptomatic efficacy of rasagiline and demonstrated that it delays the introduction of additional treatments. It is currently unclear why the two doses did not provide a similar disease-modifying result. One possibility is that a marked effect of the 2mg dose on symptoms might have masked a benefit associated with early-start treatment in this population of patients with very mild disease. Although post hoc analysis and results from the TEMPO study, in which subjects had a relatively high UPDRS score, might support this hypothesis, it is also possible that the disease-modifying effect of 1mg/day may represent a false positive result and thus this finding must be interpreted with caution. – George K Tofaris

Rascol O. Rasagiline in early Parkinson's disease: results from the ADAGIO study.

EUROPEAN JOURNAL OF NEUROLOGY
2009;16(Suppl 3):655-6.

Also see Poewe W, Hauser R. Rasagiline 1mg/Day Provides Benefits in the Progression of Non-Motor Symptoms in Patients with Early PD.

61ST AMERICAN ACADEMY OF NEUROLOGY
2009, Abstract P06.154 and

Olanow CW, Rascol O, et al. A double-blind, delayed-start trial of rasagiline in PD.
NEW ENGLAND JOURNAL OF MEDICINE.
2009;361:1268.

Memantine may benefit PDD and DLB

Dementia associated with PD (PDD) and Dementia with Lewy bodies are common forms of dementia. Currently only rivastigmine is licensed for PDD and there are no treatments for DLB. Memantine is an NMDA-receptor antagonist, affecting glutamatergic neurotransmission and is already approved for use in moderate to severe Alzheimer's disease. To test the efficacy and safety of memantine (20mg/day) in PDD and DLB, Aarsland and colleagues contacted a parallel-group, 24 week, randomised placebo-controlled pilot study in the UK and Scandinavia. The primary outcome was the Clinical Global Impression of Change (CGIC) scale. Seventy five patients were randomised and 56 (78%) completed the study. All withdrawals were due to adverse events, but the proportion of withdrawals was similar in treatment and placebo groups. At week 24 the patients in the memantine group had significantly better CGIC scores than those taking placebo (mean difference 0.7, 95% CI 0.04-

1.39; p=0.03). With the exception of improved speed on attentional tasks in the memantine group (a quick test of cognition [AQT] form: difference 12.4, 95% CI 6.0-30.9; p=0.004), there were no significant differences between the groups in secondary outcome measures. The difference in MMSE score was 1.9 in favour of memantine (p=0.09). The result of this study is limited by the relatively small patient number for each of the two conditions studied. Whether the authors' findings will translate to a noticeable difference in patients' daily functioning, remains to be seen. In this respect the outcome of a larger randomised-controlled trial including 199 patients with either PDD or DLB is awaited with interest.

– George K Tofaris

Aarsland D, Ballard C, Walker Z, Bostrom F, Alves G, Kossakowski K, Leroi I, Pozo-Rodriguez F, Londons E.

A double-blind multicentre trial of memantine in patients with Parkinson's disease dementia and dementia with Lewy bodies.

MOVEMENT DISORDERS
2009;24(Suppl 1)LB-02.

Also see Aarsland D et al.,
LANCET NEUROLOGY
2009;8:613.

Extended release dopamine agonists in early and advanced PD

The normal physiological state in the substantia nigra is one of relatively constant dopamine levels. Since the recognition that motor complications of L-dopa treatment in PD arise at least partly from pulsatile dopamine delivery, treatment paradigms have shifted towards delivering dopamine replacement with a more constant pharmacokinetic profile. Extended release (ER) formulations of dopamine agonists are taken once daily thus providing continuous delivery of the drug over 24h and increasing compliance.

Studies presented last year have validated the efficacy of recently introduced pramipexole ER in early PD. In a double-blind trial pramipexole ER and immediate release (IR) were assessed in patients with Hoehn-Yahr stage I-III. The patients were assessed using the motor score (part II) and activities of daily living (part III) sections of UPDRS and maintenance of efficacy was predefined as <15% worsening at week 33 compared

with week 18. Of 100 patients treated for 18 weeks, 84 completed 33 weeks. On UPDRS II+III, the mean change from baseline to week 33 was -11.5 for ER, -11.9 for IR and -2.7 for placebo. In a related 9-week double-blind, randomised, parallel-group study conducted in 156 patients with early PD on stable dose of pramipexole IR (2.7 0.9 mg/day), it was assessed whether patients could be successfully switched overnight from pramipexole IR to ER formulation. Patients were randomised overnight to ER or IR (2:1 ratio) at unchanged dosage. Dose adaptation was allowed at week 4 and 5 if UPDRS II+III was >15% worse than baseline. Primary efficacy endpoint was the proportion of patients successfully switched (no worsening of UPDRS II+III >15% from baseline, and no adverse effects leading to withdrawal). 84.5% patients switched successfully from pramipexole IR to ER in early PD without significant change in UPDRS II+III or CGI-I responder rates.

The PREPARED study assessed the effect on symptom control of adjunctive ropinirole ER vs. ropinirole IR in patients with advanced PD not adequately controlled with L-dopa. Patients were randomised to adjunctive ropinirole ER (2-24mg/day) or ropinirole IR (0.75-24mg/day) for 24 weeks. The authors reported that ropinirole ER significantly increased the adjusted percentage of patients maintaining >20% reduction from baseline in "off" time at week 24 vs. ropinirole IR (66% vs. 51%, OR 1.82; p=0.009). The mean UPDRS total motor score was also significantly improved from baseline at week 24 (-10.2 vs. -7.9) with an adjusted mean treatment difference -2.30; p=0.022. A non-significant benefit, was also observed in UPDRS-Activities of daily living, in favour of Ropinirole ER. At week 24, the mean (SD) doses of L-dopa had decreased from baseline by -162 (226)mg and -113(138) in the ropinirole ER and IR respectively. These findings show that symptoms in patients with advanced PD were better controlled by adjunctive treatment with ER, compared to IR ropinirole. – George K Tofaris

Stocchi F, Giorgi L, Hunter B, Schapira A.

The PREPARE Study: An assessment of symptom control in patients with advanced PD receiving treatment with adjunctive Ropinirole prolong release or ropinirole immediate release.

61ST AMERICAN ACADEMY OF NEUROLOGY
2009;Abstract S43.003.

Salin L, Hauser R, Koester J.

Double-Blind evaluation of maintenance of efficacy of pramipexole extended-release in early PD.

61ST AMERICAN ACADEMY OF NEUROLOGY 2009;Abstract P06.150.

Rascol O, Barone P, Debove Debievre C, Hauser R, Mizuno Y, Poewe W, Salin L, Schapira A, Sohr M. Overnight Switching from Immediate - to Extended - Release Pramipexole in Early PD.

61ST AMERICAN ACADEMY OF NEUROLOGY 2009; Abstract P06.152.

Dopamine replacement therapy for non-motor symptoms

Although PD is characterised by motor symptoms, about 90% of patients have at least one non-motor symptom and 10% have five or more. Non-motor symptoms (NMS) include depression, anxiety, dementia, obsessional behaviour, sleep disorders, dysphagia, impaired gut motility and sexual dysfunction. These symptoms become more apparent with disease progression despite medical control of motor symptoms and can lead to marked deterioration in quality of life. While some NMS can be improved by non-dopaminergic agents, three recently presented studies showed that dopamine replacement improves depression and sleep disturbance in PD patients.

Depressive symptoms are common in PD and may be directly related to dopaminergic dysfunction in subcortical-cortical circuits regulating mood and affect. In this multicenter (N=76) international trial, 296 patients received double-blind pramipexole or placebo for 12 weeks, in order to assess prospectively the efficacy of this drug against depressive symptoms in PD. All patients had PD at modified Hoehn-Yahr stage I-III, with stable motor function and stable PD treatment without a dopamine agonist for at least the preceding 4 weeks. Patients also had to be suffering from depressive symptoms. Pramipexole was administered at 0.125-1.0 mg tid, as optimised during the first 5 weeks. Ongoing antidepressant use was permitted at dosage unchanged for at least the prior 6 weeks. Using two validated depression scales, the authors found that low dose pramipexole was significantly superior to placebo for reducing depressive symptoms in PD.

Another study has assessed the benefit of ropinirole on sleep disturbance in patients

with advanced PD not optimally controlled with L-dopa. Patients were randomised to once-daily ropinirole ER (2 24mg/day), placebo, or three-times-daily ropinirole IR (0.75 24mg/day). Sleep disturbance was assessed by mean change from baseline in Parkinson's Disease Sleep Scale (PDSS) total score (range: 0 150; 100=significant sleep dysfunction). Compared with placebo, ropinirole reduced sleep disturbance, as measured by PDSS total score, in patients with PD exhibiting significant sleep dysfunction at baseline. Interestingly, despite the assumption that slow-release formulations might be better for night-time symptoms, a similar improvement was observed in patients treated with ropinirole ER or IR.

Intra-jejunal levodopa infusion has been used successfully in advanced PD for control of motor symptoms and improvement in dyskinesias. A multicentre open-label, prospective study of 22 patients with advanced PD, has now shown evidence that levodopa infusion is also beneficial for NMS. Using an internationally validated PD NMS scale the authors found significant benefit in 6 out of the 9 NMS scale domains: cardiovascular, sleep/fatigue, attention/memory, gastrointestinal, urinary and miscellaneous and in the PDQ-8 (quality of life) score. The highest proportion of improvement was related to an effect on sleep/fatigue (86.4%). Although this is a pilot study, it highlights the dopaminergic basis of some NMS and the correlation between improvement in NMS and quality of life.

– George K Tofaris

Barone P, Poewe W, Massey D, Debove C. Pramipexole Ameliorates Depression in Parkinson's Disease: A Randomized Double-Blind vs Placebo Trial.

61ST AMERICAN ACADEMY OF NEUROLOGY 2009;Abstract S43.004.

Chaudhuri K, Giorgi L, Statham J. Ropinirole Prolonged Release Reduces Significant Sleep Disturbance in Patients with Advanced Parkinson's Disease (PD) Not Optimally Controlled with L-dopa.

61ST AMERICAN ACADEMY OF NEUROLOGY 2009;Abstract S13.005.

Antonini A, Martinez-Martin P, Odin P, Martin A, Chaudhuri K.

Intra-jejunal levodopa infusion in PD: A pilot multicentre study of effects on non-motor symptoms using the PD non-motor scale.

MOVEMENT DISORDERS 2009;24(Suppl 1)S255, Mo-179.

Genetic studies in PD

Genome-wide association studies for sporadic PD

Advances in genotyping technology have made possible rapid genome-wide screening of common variants in large populations.

In 2009 the two largest PD genome-wide association studies (GWAS) were reported. A total of 2,011 cases and 18,381 controls from Japan and 1713 cases and 3978 controls of European ancestry were screened.

The Japanese study identified two new susceptibility loci, on 1q32 designated as PARK16, and BST1 on 4p15 ($P = 3.94 \times 10^{-9}$). By comparing results from the two studies the authors identified PARK16, SNCA (α -synuclein) and LRRK2 as shared risk loci for PD and BST1 and MAPT (tau) as loci showing population differences.

These studies establish a clear role for common genetic variability in loci involved in autosomal dominant parkinsonism (SNCA, MAPT and LRRK2) in the risk of developing sporadic PD and also demonstrate a possible population-specific genetic heterogeneity in this disorder, as the association with MAPT was absent in the Japanese study and BST1 was absent in the study of patients of European ancestry.

The identification of α -synuclein and tau genes as susceptibility loci for sporadic PD lends further support to the idea of shared molecular pathways for PD and Alzheimer's disease. – George K Tofaris

Toda T, Satake W, Nakabayashi Y, Mizuta I, Yoshikawa T, Yamamoto M, Hattori N, Murata N, Nakamura Y.

Genome-wide association study for sporadic PD. MOVEMENT DISORDERS 2009;24(Suppl 1):S155, Th-99.

Also see Satake et al, Nat Genet. 2009;41:1303.

Hardy J. Genetic analysis of sporadic neurodegenerative disease. JOURNAL OF NEUROLOGICAL SCIENCES 2009;285(Suppl 1):S33. Also see Simon-Sanchez et al, Nat Genet. 2009;41:1308.

Key publications - Brain, Neurology, Annals of Neurology

Time to invest in GBA

This paper reinforces our knowledge that the numerically largest genetic risk factor(s) for developing PD (in the UK at least) are mutations in the glucocerebrosidase gene (GBA). Mutations in this gene that lead to a deficiency in the activity of enzyme are responsible for the development of the autosomal recessive lysosomal storage disorder Gaucher's disease. Up to 31% of Ashkenazi Jews are carriers for GBA gene mutations. Since 2004, it has been increasingly noted that patients with Gaucher's disease and their relatives have a high frequency of PD. This series exploits the Queen Square & Imperial college brain banks to examine the DNA of 790 patients and 257 controls, matched for age and ethnicity, who were all screened for mutations within the GBA gene by sequencing the whole gene. This study represents the largest investigation to date of GBA and PD among a non-Ashkenazi Jewish population. The authors found that 33/790 PD patients (4.18%) had GBA mutations compared to 3/257 (1.17%) in the control group. Four /33 patients with GBA mutations had a family history of PD and 29/33 had sporadic PD. The prevalence of GBA mutations in British patients with sporadic PD thus translates to ~3.7%. Clinical features comprised an early onset of the disease (mean age 52.7 years), a good response to L-dopa, the presence of hallucinations in 14/31 (45%) and symptoms of cognitive decline or dementia in 15/31 (48%) of patients. Pathological examination revealed widespread and abundant α -synuclein pathology in all GBA mutation carriers.

Parkinsonism due to GBA mutations is thus clinically and pathologically indistinguishable from sporadic, so-called "idiopathic" PD. Study of GBA in relation to PD is particularly fascinating because it suggests a novel pathway that may be associated with neurodegeneration, possibly due to ineffective lysosomal degradation of α -synuclein. Further elucidation of such a pathway will hopefully uncover new therapeutic avenues. – Tom Foltynie

Neumann et al. Glucocerebrosidase mutations in clinical and pathologically proven Parkinson's disease. *BRAIN* 2009;132;1783–94.

See also page 13, The Glucocerebrosidase gene and Lewy body pathology, by Nin Bajaj/Tim Soane

When the toes go up...

The combination of juvenile onset parkinsonism and pyramidal signs has long been referred to as the "pallido-pyramidal syndrome". Patients with this phenotype have been discovered previously to have mutations in the ATP13A2 gene (the Kufor Rakeb syndrome), or rarely in the context of "parkin" related PD.

A further gene known as FBX07 was linked to an Iranian kindred with young onset spastic paraplegia followed years later by the development of an akinetic-rigid syndrome. As an isolated finding this linkage was of uncertain relevance to other families with this phenotype, but novel pathogenic mutations in this gene have now been implicated in the development of a pallido-pyramidal phenotype in a further two families.

This paper describes these two families, one Dutch and one Italian, with autosomal recessive pattern of inheritance of disease (affected sibling pairs). Patients had juvenile onset parkinsonism together with brisk reflexes, spasticity and extensor plantar responses. Patients exhibited tremor as well as bradykinesia and rigidity, responded well to L-dopa, developed L-dopa induced dyskinesias and had no evidence of cognitive impairment. After excluding the known genes causing autosomal recessive parkinsonism, the FBX07 gene was sequenced and a homozygous stop mutation was identified in one family and heterozygous splice site mutation/ missense mutation in the other.

Little is known about the function of FBX07, but it is clear that these mutations in this gene lead to a pre-synaptic dopaminergic deficit confirmed by DaTscan imaging. Once the molecular mechanisms that lead to neurodegeneration due to mutations in this gene are known, there may be potential implications (in terms of pathways of neurodegeneration) for more common forms of parkinsonism. – Tom Foltynie

Di Fonzo et al.

FBX07 mutations cause autosomal recessive, early-onset parkinsonian-pyramidal syndrome. *NEUROLOGY* 2009;72;240-5.

Pigment & PD – it's in the genes

There have been documented associations between melanoma and PD for many years without clear insights into the mechanisms that may underlie the association. Weak evidence that the use of L-dopa increased melanoma risk nevertheless led to the drug being "contra-indicated" in some countries among PD patients with melanoma. Patterns of pigmentation related to and including a variant in the melanocortin 1 receptor (MC1R) gene have been associated with an increased risk for both melanoma and PD.

This paper uses two of the largest prospective cohort studies in the world (the Nurses Health study and the Health Professionals Study), to examine the risk of PD among individuals with and without a family history of melanoma in a first degree relative. Over 14-20 years of prospective follow up, 616 incident cases of PD were identified. Using Cox proportional hazards models to allow for person-time of follow up, a family history of melanoma in a first-degree relative was shown to be associated with a higher risk of PD (relative risk 1.85), after adjusting for known PD risks such as smoking and caffeine intake. The association is specific to a family history of melanoma in contrast to other forms of cancer. The risk of PD associated with family history of melanoma is slightly diminished after adjustment for hair colour suggesting that genetic factors influencing pigment may well be responsible for this observed association rather than being due to shared environmental factors.

These findings support the notion that melanoma and Parkinson disease (PD) share common genetic components, and further undermine any link between L-dopa use and melanoma risk. The genetic determinants of melanoma (such as MC1R and cyclin dependent kinases) should be explored as susceptibility candidate genes for PD. – Tom Foltynie

Gao et al.

Family history of melanoma and Parkinson disease risk. *NEUROLOGY* 2009;73;1286-91.

See also page 4, Family history of Melanoma increases PD risk, by Michelle Hu

So, who cares about pesticides?

Non-genetic risk factors for PD have been difficult to find and confirm. Factors that add to the degree of oxidative stress of vulnerable neurons remain the most plausible candidates. For many years, there has been concern regarding pesticide use and the development of PD. Pesticides are particularly strong suspects in view of the close relationship between the neurotoxin MPP+ (used to create animal models of Parkinsonism, and a rare cause of parkinsonism in humans) and the herbicide "paraquat". This study by Elbaz et al. adds further evidence to this concern using detailed exposure data regarding pesticide use among 247 agricultural workers with PD and 557 control individuals affiliated with the same agricultural insurance agency (Mutualite Sociale Agricole). The authors use very thorough and sophisticated methods to calculate pesticide exposure for all participants. An occupational history, details of work with pesticides used for crops/ animals, frequency, duration and spraying methods were all documented and multiple categories of cumulative lifetime pesticide exposure calculated. Appropriate analyses ultimately revealed a strongly positive association between PD and professional pesticide use in France, in particular the use of organochlorine insecticides (OR 2.4), such as lindane and DDT. (The organochlorines have been shown by other authors to lead to dopaminergic neurotoxicity in the laboratory, inducing mitochondrial dysfunction and protein aggregation). The association was stronger in men with older onset PD, than in those with younger onset PD, and showed a convincing dose-effect relation in the older onset group. Presumably individuals with younger onset PD have a greater genetic predisposition to PD irrespective of specific environmental exposures. While this work is highly relevant to individuals who are involved in professional use of pesticides, the importance of lower levels of pesticide exposure in e.g. during domestic gardening remains to be definitively proven.

– Tom Foltynie

Elbaz et al.
Professional Exposure to Pesticides and Parkinson Disease.
ANN NEUROL 2009;66:494-504.

Anaemia-the final straw?

At the 2009 Movement Disorders Society meeting in Paris, Paul Bolam described his work detailing the vast numbers of synapses (170 000 to 400 000) that each dopaminergic neuron must maintain. This compares to ~2000 synapses for a typical pallidal neuron. The selective vulnerability of dopaminergic neurons in PD may relate to the metabolic demand placed on the cell body by this degree of complexity. Any factor that places an additional metabolic burden on neurons may therefore be a risk for neurodegeneration.

In this paper, the medical records-linkage system of the Rochester Epidemiology Project was used to assess the frequency of anaemia predating diagnosis of PD among cases compared to controls. Anaemia has been previously associated with increased risk for both Alzheimer's disease and Restless Legs syndrome. Using 196 cases, anaemia was found to be a risk factor for the development of PD (OR 2.0). The association remained significant after adjustment for cigarette smoking, and exposure to pesticides, and was not significantly different between men and women. The authors propose several theoretical mechanisms to explain this association including bone marrow involvement being an early systemic symptom of PD, iron deficiency having a direct negative effect on dopaminergic neurons, or unknown confounding factors leading to both anaemia and PD. The explanation could be even more simple- i.e. chronic mild cerebral hypoxia may accelerate neurodegeneration of vulnerable neurons i.e. complex dopaminergic ones.

– Tom Foltynie

Savica et al.
Anemia or low hemoglobin levels preceding Parkinson disease: A case-control study.
NEUROLOGY 2009;73:1381-7.

The PD Biomarker DTI 3T (..Ghia, turbo injection)

The finding of effective treatments for PD is hindered by inadequate biomarkers of disease (particularly early disease) during life. Advances in neuro-imaging may ultimately solve this problem. Diffusion tensor imaging (DTI) measures the directional diffusivity of water molecules and has been

extensively used to identify white matter tracts in the brain. In animal models of PD, DTI measurement of directions of water molecule diffusion (fractional anisotropy) has been shown to correlate with the degree of neuronal loss in the substantia nigra (SN). Previous attempts to use this technology in patients with PD with 1.5 Tesla scanners showed group level differences but had insufficient sensitivity and specificity to distinguish each and every individual with PD. In this study, a high-resolution DTI protocol at 3Tesla was used to study specific segments of the substantia nigra (SN) in 14 early stage, untreated PD patients and 14 age- and gender matched controls. Fractional anisotropy (FA) was reduced in the SN of subjects with PD compared with controls (p=0.001) with a sensitivity and specificity of 100% for distinguishing patients with PD from healthy subjects. Most impressively, this technique seems able to identify individuals even with early PD, which may represent an advantage over current PET or SPECT imaging and data from earlier studies hint that this technique may also be a way of distinguishing PD patients from individuals with Multiple systems atrophy or Progressive Supranuclear palsy. This technique therefore adds to our armamentarium of biomarkers of SN degeneration, and longitudinal evaluations will no doubt follow.

– Tom Foltynie

Vaillancourt et al.
High-resolution diffusion tensor imaging in the substantia nigra of de novo Parkinson's disease.
NEUROLOGY 2009;72:1378-84.

Are my mitochondria working, Dr?

There is growing evidence that mitochondrial dysfunction may play a critical role in PD pathogenesis. This is based upon descriptions of patients with autosomal recessive juvenile parkinsonism carrying mutations in the mitochondrial protein kinase - PINK1 or the mitochondrial matrix localising gene DJ-1, as well as the identification that parkin plays a critical role in mitochondrial function in *Drosophila* and mouse parkin models. Being able to detect mitochondrial dysfunction in vivo would be a very useful strategy in screening individuals for risk of PD, to study the effect of disease modifying agents at the earliest possible stage. Magnetic resonance spectroscopy at 1.5T has been used previously to study metabolic processes in

PD, but in this study by Hattingen et al, imaging at 3T together with comprehensive evaluation of both high energy and low energy phosphates has revealed more useful results than previous investigations. The substantia nigra and striatal region was imaged in 16 early and 13 advanced patients with Parkinson's disease and compared to 19 age-matched controls at 3T. In the putamen and midbrain of both Parkinson's disease groups, there was a bilateral reduction of ATP and phosphocreatine, while low-energy metabolites such as ADP and inorganic phosphate were within normal ranges. Even among patients with unilateral symptoms, a bilateral reduction in high energy phosphates could be detected suggesting mitochondrial dysfunction is occurring early before widespread dopaminergic cell death. These results provide further evidence that mitochondrial dysfunction is a consistent phenomenon in sporadic Parkinson's disease and not just autosomal recessive juvenile parkinsonism, which occurs early in the course of the disease. – Tom Foltynie

Hattingen et al. Phosphorus and proton magnetic resonance spectroscopy demonstrates mitochondrial dysfunction in early and advanced Parkinson's disease. *BRAIN* 2009;132;3285–97.

Gene therapy - safety, efficacy & the learning curve

There are 4 major gene therapy programmes being evaluated as treatments for PD. Neurturin, an analogue of GDNF showed disappointing results in a double blind 12 month evaluation in view of improvements that occurred in both treated and sham-operated patients groups. Further evaluations of dual striatal and nigral administration with prolonged follow up are planned. ProSavin gene therapy involves combination of 3 genes all involved in dopamine biosynthesis, (tyrosine hydroxylase, aromatic acid decarboxylase (AADC) and GTP cyclohydrolase) inserted into a single vector –and preliminary results showed reduction in off medication motor disability scores in 6 patients receiving open label treatment. An extension study including patients blinded to active or sham treatment is awaited. The administration of gene therapy encoding the GAD enzyme in an attempt to reduce the excitatory activity of the subthalamic nucleus has also shown promising initial results.

The administration of gene therapy encoding the GAD enzyme in an attempt to reduce the excitatory activity of the subthalamic nucleus has also shown promising initial results

This paper reports the preliminary results of the 4th major gene therapy programme that administered bilateral intraputamenal infusion of the single AADC vector to patients with moderately advanced PD. The enzyme AADC catalyses the conversion of L-dopa to dopamine. In these initial results of low-dose and high-dose cohorts (5 patients in each) using standardised clinical rating scales at baseline and 6 months, the total UPDRS and motor UPDRS scores improved in both cohorts and motor diaries showed increased on-time without dyskinesia and reduced off-time. However there were 1 symptomatic and 2 asymptomatic intracranial hemorrhages following the operative procedures. This level of adverse effect will cast a shadow over gene therapy programmes and surgical techniques must improve to make this potentially exciting and valuable technology, acceptable. – Tom Foltynie

Christine et al. Safety and tolerability of putamenal AADC gene therapy for Parkinson disease. *NEUROLOGY* 2009;73;1662-9.

Zebrafish, models and mitochondria

Using rodents or non-human primates to model PD, is a lengthy, and expensive task and raises recurrent ethical issues. Successful treatments in animal models do not necessarily translate to effective treatments in PD patients. Improved models of PD are thus required and these models need ideally to be cheap, quick to reproduce and of minimal ethical concern. Zebrafish are vertebrates (in contrast to *Drosophila* and *C. elegans*), can reproduce quickly, can be genetically modified and are transparent. In the current study, the authors have developed a further "parkin" zebrafish model to add to the previous alpha-synuclein, DJ-1 and PINK1 zebrafish models.

The authors identified a zebrafish orthologue of the human parkin gene and used morpholino antisense oligonucleotides to determine the effect of transient parkin deficiency in zebrafish embryos. The zebrafish gene that was knocked down in this study was presumed to be the equivalent of human parkin based on similar amino acid sequences particularly in the functional domains. Parkin knockdown resulted in a 45% reduction in mitochondrial Complex I activity and a 20% reduction in dopaminergic neurons without impairment of overall brain development, but without any change in swimming behaviour. This model is disadvantaged by causing only a transient loss of "parkin" function, and perhaps a stable loss of parkin model would be associated with even greater dopaminergic loss and behavioural change.

Impaired mitochondrial function is an important mechanism leading to neuronal cell loss in both genetically determined forms of early onset Parkinson's Disease and late onset sporadic Parkinson's disease. This zebrafish model may perhaps therefore have relevance for patients with late onset PD as well as the less common parkin patients. What distinguishes this paper however, is the observation that these parkin deficient zebrafish show electron dense abnormalities on electron microscopy in T-tubules known to play a role in fast depolarisation and rich in L-type Ca²⁺ channels. There is growing interest in the role of these Ca²⁺ channels in neuronal cell death in PD, therefore this zebrafish model may lead to breakthroughs in our understanding of mitochondrial function, Ca²⁺ channels function and PD pathophysiology. – Tom Foltynie

Flinn et al. Complex I deficiency and dopaminergic neuronal cell loss in parkin-deficient zebrafish (*Danio rerio*). *Brain* 2009;132;1613–23.

The Glucocerebrosidase gene and Lewy body pathology

Mutations within the glucocerebrosidase (GBA) gene were originally discovered to be associated with Gaucher disease in Ashkenazi Jewish patients over a decade ago. Subsequent studies looking at the association of GBA with other Lewy pathologies, such as Parkinson Disease (PD), identified only a small proportion of patients with GBA mutations. These studies were not in large populations, and only looked for certain GBA mutations. This year several papers have enhanced our understanding in this area. Two papers published in the same edition of Archives of Neurology reported a much higher degree of association between GBA polymorphisms and Lewy-related pathology (LRP). Mitsui and colleagues sequenced the GBA allele in over 500 Japanese PD patients, and over 500 controls. They identified over 27 GBA variants, 11 of which were associated with PD. The total prevalence of GBA mutations was 9.4% (50 patients), with the most common allele (R120W) present in 2.8% (15) PD patients, and none of the controls. The previously identified L44P GBA allele was identified in 14 PD patients and 2 controls.

The paper by Clarke et al looked at the association of GBA variants in pathologically confirmed DLB with and without AD, by sequencing the gene rather than looking for certain pre-determined alleles. They identified a higher association between GBA and cortical LRP than brainstem LRP; but they also had fewer PD cases. This study was unique in using so many pathologically confirmed cases of LRP.

Given the high degree of association between GBA and PD identified by these papers, and the fact GBA codes for a lysosomal storage pathway, this novel association may open the door for alternative therapeutic approaches to PD.

– Nin Bajaj/Tim Soane

Clark LN, Katsaklis LA, Wolf Gilbert R, Dorado B, Ross BM, Kisselev S, Verbitsky M, Mejia-Santana H, Cote LJ, Andrews H, Vonsattel JP, Fahn S, Mayeux R, Honig LS & Marder K. Association of glucocerebrosidase mutations with dementia with lewy bodies. *Arch Neurol*, 2009;66:578-83.

Mitsui J, Mizuta I, Toyoda A, Ashida R, Takahashi Y, Goto J, Fukuda Y, Date H, Iwata A, Yamamoto M, Hattori N, Murata M, Toda T, Tsuji S. Mutations for Gaucher disease confer high susceptibility to Parkinson disease. *ARCH NEUROL*, 2009;66:571-6. See also page 10, Time to invest in GBA, by Tom Foltynle

Over diagnosis of Parkinson's disease may account for SWEDDs

The literature on the diagnosis of Parkinson's disease (PD) reveals a wide range of accuracy, with positive-predictive values ranging from 53% in a community setting to over 98% in a specialist movement disorder clinic. The identification that between 4 and 15% of clinically diagnosed cases of PD entered into clinical trials (REAL-PET, CALM-PD and ELLDOPA) had no FP-CIT SPECT corroboration (these patients were designated SWEDDs, or scans without evidence of dopaminergic deficit) raised the question of whether the imaging was not sensitive enough or whether PD was overdiagnosed. A large multicentre prospective longitudinal study carried out by Marshall and colleagues sought to identify the accuracy of FP-CIT SPECT to identify PD at baseline when compared to a clinical diagnosis made three years later. The study focused on patients where clinical diagnostic uncertainty existed, and imaged them at baseline, 18 months and 36 months. These results of the molecular imaging studies were compared to a clinical diagnosis made by two established specialists blinded to the SPECT findings. This study is the largest study of its kind following through a cohort of SWEDDs. It shows that for the majority of patients, a normal baseline scan remained normal over subsequent scans, in keeping with smaller studies previously (Marek et al., 2005). The proportion of SWEDDs in this study (35% at baseline) was predictably higher than the REAL-PET, CALM-PD and ELLDOPA trials due to the intentional inclusion of difficult diagnostic patients. Comparing the gold standard diagnosis at 36-months to the baseline diagnosis showed that PD was initially incorrectly diagnosed in 53.6% of non-PD patients. These results shed light on the nature of SWEDD patients, providing further evidence that they are likely to represent misdiagnoses.

– Nin Bajaj/Tim Soane

Marshall VL, Reininger CB, Marquardt M, Patterson J, Hadley DM, Oertel WH, Benamer HT, Kemp P, Burn D, Tolosa E, Kulisevsky J, Cunha L, Costa D, Boonij J, Tatsch K, Chaudhuri KR, Ulm G, Pogarell O, Hoffken H, Gerstner A & Grosset DG. Parkinson's disease is overdiagnosed clinically at baseline in diagnostically uncertain cases: a 3-year European multicenter study with repeat [123I]FP-CIT SPECT. *MOV DISORD*, 2009;24:500-8.

Olfaction and SWEDDs

The nature of patients with a clinical phenotype resembling Parkinson's disease (PD) but with normal molecular imaging scans (designated SWEDDs: scans without evidence of dopaminergic deficit) have been the subject of serious debate over the past half-decade. Silveira-Moriyama and colleagues investigated the sense of smell in 21 SWEDD patients, and compared their UPSIT (University of Pennsylvania Smell Test) score with 26 essential tremor (ET) patients, 16 dystonic patients, 191 PD patients and 136 controls. The authors proposed that if SWEDD patients represented something other than PD, their olfaction would be normal. The results indicated that SWEDD patients UPSIT scores were comparable to all the non-PD control groups, which were statistically better than the PD patients.

One interesting aspect of this paper is that an UPSIT suggestive of a low probability of PD was still found in 15% of PD patients and in 23% of SWEDD patients. The literature on UPSIT in ET has also been mixed with recent reports suggesting an UPSIT score with mild abnormality but not normal, again continuing the debate on the nature of "benign tremor" disorders. – Nin Bajaj/Tim Soane

Silveira-Moriyama L, Schwingenschuh P, O'donnell A, Schneider SA, Mir P, Carrillo F, Terranova C, Petrie A, Grosset DG, Quinn NP, Bhatia KP, & Lees AJ. Olfaction in patients with suspected parkinsonism and scans without evidence of dopaminergic deficit (SWEDDs). *J NEUROL NEUROSURG PSYCHIATRY*, 2009;80:744-8.

What is the incidence of Parkinson's disease in Essential tremor?

The research carried out in this paper addresses the often-questioned association between essential tremor (ET) and Parkinson's disease (PD) by investigating the incidence of PD in a cohort of ET patients and a control population. Over 3500 participants, 207 with ET, were followed for a median of 3.3 years. The incidence of PD within this time frame was 0.7% in the control population, and 3.0% in the ET population, whilst the incidence of parkinsonism was 1.8% and 5.8% respectively. The rate of drug induced parkinsonism was over 4-fold higher in the ET populations, whilst all other forms of parkinsonism (such

as vascular parkinsonism) was similar between the populations.

The authors discuss the potential overlap in pathology between PD and ET as a potential causative link, indicating that around 25% of ET patients have Lewy body pathology restricted to the locus coeruleus, which they believe may extend into the substantia nigra in cases of PD associated with ET. There is resistance to this theory, with others proposing the underlying pathology of ET to be potentially reversible neurogenic oscillation. Furthermore, the authors defend the lack of functional imaging in the ET patients to verify that they were not cases of tremor dominant PD all along! – Nin Bajaj/Tim Soane

Benito-Leon J, Louis ED, & Bermejo-Pareja F. (2009) Risk of incident Parkinson's disease and parkinsonism in essential tremor: a population based study. J NEUROL NEUROSURG PSYCHIATRY, 2009;80:423-5.

Subthalamotomy in Parkinson's disease

Alvarez and colleagues followed patients who received thermocoagulative subthalamotomy for Parkinson's disease over 36 months. 86 patients received a unilateral lesion to treat their most disabled side, of which only 25 were available for follow up by three years. Their symptoms before and during follow up were quantified using Unified Parkinson's disease rating scores (UPDRS) in off and on states, their L-Dopa dosing requirements were monitored, and side effects were noted. These authors and others have previously followed up subthalamotomy patients for shorter durations, noting contralateral symptomatic improvement. This was a follow up study, effectively using the non-lesioned side as a control, and the physicians' carrying out the clinical ratings were not blinded to the nature of the surgery. The authors here confirm that clinical benefit of subthalamotomy is still present at three years, whilst axial and ipsilateral features continue to deteriorate. Nonetheless, daily requirements for L-Dopa were significantly reduced. One of the most important findings reported is the very large proportion of patients (>50%) with surgery induced dyskinesias, with eight patients requiring pallidotomy to control symptoms. This is despite excluding patients with severe

The authors conclude that subthalamotomy remains an experimental procedure, but that even taking into account the high proportion of side-effects it may be of use in some situations

dyskinesias from taking part.

The authors conclude that subthalamotomy remains an experimental procedure, but that even taking into account the high proportion of side-effects it may be of use in some situations. Where patients have marked unilateral symptoms not well controlled by pharmacology, and where deep brain stimulation (DBS) may not be viable, for instance due to the cost, previous failure, or personality difficulties, then subthalamotomy may be a viable alternative. If there are any predisposing factors relating to surgery induced dyskinesias which can be identified, then this surgery may have wider application. Until then, DBS is likely to remain the surgical alternative of choice in Parkinson's disease. – Nin Bajaj/Tim Soane

Alvarez L, Macias R, Pavon N, Lopez G, Rodriguez-Oroz MC, Rodriguez R, Alvarez M, Pedrosa I, Teijeiro J, Fernandez R, Casabona E, Salazar S, Maragoto C, Carballo M, Garcia I, Guridi J, Juncos JL, Delong MR & Obeso JA. Therapeutic efficacy of unilateral subthalamotomy in Parkinson's disease: results in 89 patients followed for up to 36 months. J NEUROL NEUROSURG PSYCHIATRY, 2009;80:979-85.

Can autonomic failure usefully help distinguish Parkinson's disease from multiple system atrophy?

For many of us it can be difficult to distinguish MSA from PD with autonomic impairment especially in the early stages of these disorders. Generally the faster progression in MSA gives the game away but perhaps only after gloomy predictions on prognosis have been made.

A longitudinal cohort study was carried out by Lipp and colleagues on 52 patients with Gilman probable MSA and 29 PD patients who underwent extensive autonomic

testing to try and identify differences between PD with autonomic failure patients and MSA patients. The study confirms that whilst orthostatic hypotension is present in nearly all MSA patients, it is also present in 41% of PD patients at baseline testing. The authors tested autonomic function using a variety of tests that they propose are common to many test-centres. They show that there is more widespread anhidrosis in MSA than PD. The authors also show that COMPASS score (composite autonomic symptom scale, which gives an indication of autonomic symptoms and approximate severity) progresses must faster in MSA than PD (almost 3-fold faster over 12 months).

The study is interesting because it addresses an area of potential misdiagnosis, and whilst it looks to autonomic testing to discriminate these conditions it makes little mention of imaging discriminating tests such as MRI which can show putaminal pathology in MSA type P and cerebellar pathology (including the hot cross bun sign) in MSA type C. A potential limitation is that these are clinical MSA cases for the most part, with only five subsequently pathologically confirmed. – Nin Bajaj/Tim Soane

Lipp A, Sandroni P, Ahlskog JE, Fealey RD, Kimpinski K, Iodice V, Gehrking TL, Weigand SD, Sletten DM, Gehrking JA, Nickander KK, Singer W, Maraganore DM, Gilman S, Wenning GK, Shults CW & Low PA. (2009) Prospective differentiation of multiple system atrophy from Parkinson disease, with and without autonomic failure. ARCH NEUROL, 2009;66:742-50.

Parkinson's disease and race

Studies on ethnicity and disease are important. PD is not a disease found only in white patients and yet most drug trials in PD are conducted in majority white populations. The subsequent drugs when marketed are done so world-wide with the implicit

assumption that drug response amongst different ethnic groups will be broadly similar. Recent genetic studies have however, shown, inter alia, that genetic heterogeneity in apparent sporadic PD can differ markedly between ethnic groups (see LRRK2 story amongst Ashkenazi and Berber Arab populations). How different drugs will interact on differing baseline genetic backgrounds in the different ethnic groups is a greatly under-researched area. Furthermore, whatever the biological differences between PD in different ethnic groups, there are undoubtedly important social, financial and psychological reasons that contribute to health inequality amongst different societal groups.

Dahodwala and colleagues carried out a cohort study in Pennsylvania to identify incidence of PD diagnosis relating to race/ethnicity. Previous studies have suggested a lower prevalence of PD in African-Americans than in the white population, whilst the only two previous incidence studies are contradictory. The data for this study was abstracted from Medicaid adjudicated claims over a four-year period. The researchers identified that African-Americans were diagnosed at half the rate of the white population with age, sex, location of care and reason for Medicaid eligibility all controlled for. Whilst this study is on a limited subgroup of the population who were relatively young, poor and disabled, the results mirror the only other incidence study amongst adults with the same insurance access. The study had limited ability to determine the effect of geography upon PD incidence, only looking at degree of urbanisation. Using this method they found no link between geography and incidence, which could potentially have explained the differing racial incidences.

The study is still not able to give an indication on whether variance in incidence relates to a biological difference, although this is felt to be less likely on the basis of other US based studies on PD prevalence in Afro-Americans. Many other causes of the observed racial disparities are considered by the authors including patient, physician, and system level factors. Patient-level factors might include education, culture, aging beliefs, trust, and stigma. Provider-level factors such as clinician biases, stereotyping and medical uncertainty might also play a role in racial disparities. Healthcare system factors include financing, accessibility, fragmentation

of health coverage and legal policy are also discussed. Finally the authors discuss how different clinical phenotypes in different race/ethnicities may prevent the appropriate diagnosis as diagnostic criteria are largely based on white patients.

– Nin Bajaj/Tim Soane

Dahodwala N, Siderowf A, Xie M, Noll E, Stern M & Mandell DS. (2009) Racial differences in the diagnosis of Parkinson's disease. *MOV DISORD*, 2009;24:1200-5.

Thinking and walking with Parkinson's disease

This interesting study examined the effect of "dual-tasking" upon gait in patients with Parkinson's disease, that is, the effect of simultaneously performing a higher-level cognitive task whilst walking. Plotnik and colleagues studied the bilateral coordination of gait quantitatively using a phase coordination index (PCI), which compares the phase between the left and the right side, with 180 being the 'normal', and greater deviation from this indicating poorer coordination. The time spent on each lower-limb was measured using pressure sensors placed in the shoes of the participants. The patients taking part were studied during their "ON" phase of their medication, were not prone to freezing, and were not demented.

The researchers found that performing serial 7 subtractions whilst walking caused the Parkinson's patients' gait to become more poorly coordinated, whilst not affecting the control subjects. The speed of gait was reduced in both Parkinson's disease patients and control patients. Whether gait analysis using PCI, a relatively new technique, corresponds to clinical freezing or falling remains to be seen.

Whilst the mechanism behind this phenomenon is outside the scope of this study, the authors discuss the possibility that the frontal lobe, involved in the control of gait coordination and the attention required to perform a higher cognitive task, may only have limited resources. These limited resources could stem from the fact that the areas of the frontal cortex involved in these activities both have connections from the basal ganglia. – Nin Bajaj/Tim Soane

Plotnik M, Giladi N & Hausdorff JM. (2009) Bilateral coordination of gait and Parkinson's disease: the effects of dual tasking. *J NEUROL NEUROSURG PSYCHIATRY*, 2009;80:347-50.

Brain derived neurotrophin factor polymorphisms and L-dopa induced dyskinesia

L-dopa induced dyskinesias (LID) such as chorea, athetosis and dystonia are a serious problem for Parkinson's disease (PD) patients, affecting up to half of patients taking L-dopa for 5 years. The threat of this can cause some patients to hold off receiving L-dopa for as long as possible. A number of patient risk factors associated with earlier LID onset have been identified, including younger age, later stage disease, higher L-dopa dosing and genetic factors including D2 receptor polymorphisms, and now brain derived neurotrophin factor (BDNF) polymorphisms. Foltynie and colleagues have shown that the BDNF Val66Met polymorphism is associated with a dose dependent increased risk for earlier onset LID. The protein produced by this minor allele (G196A) is secreted from neurons in response to depolarisation at a slower rate than that coded for by the more common allele. BDNF is thought to be an activity dependent neuromodulator.

Foltynie et al genotyped 315 patients meeting the UK Parkinson's Disease Society Brain Bank criteria and free of LID on the first assessment. Patients were subsequently rated for LID, UPDRS and other cognitive assessments at follow up of 1 to 2 years. The patients baseline equivalent L-dopa dosing was taken into account for the analysis. The frequency of the Met/Val genotype was 36% (112/315) and Met/Met was 4% (13/315). This study revealed a hazard ratio of developing LID of 2.21 per Met allele.

The main interest of this finding lies predominantly within the realm of the basic rather than applied sciences, since this knowledge as it stands is unlikely to affect clinical practice, although it may provide a novel pharmaceutical target in the form of BDNF agonists to increase the effective LID free L-dopa treatment window.

– Nin Bajaj/Tim Soane

Foltynie T, Cheeran B, Williams-Gray CH, Edwards MJ, Schneider SA., Weinberger D, Rothwell JC, Barker RA & Bhatia KP. (2009) BDNF val66met influences time to onset of levodopa induced dyskinesia in Parkinson's disease. *J NEUROL NEUROSURG PSYCHIATRY*, 2009;80:141-4.

Therapeutic Trials in Parkinson's Disease in 2009

By Huw R Morris

The year 2009 has seen a continued focus on potential disease modifying therapy in PD and further work on therapies for cognitive impairment in PD. The quest for disease modifying therapy, which slows or arrests the progression of Parkinson's disease (PD), remains the primary aim of a substantial part of pre-clinical and clinical research. The identification of symptomatic benefit related to selegiline in the DATATOP study, confounding an apparent disease modifying drug effect in the 1990s has highlighted the difficulties in using clinical measures in PD to identify a disease modifying effect (Stocchi, and Olanow, 2003). Often, these studies hinge on the clinical and treatment characteristics of patients in the first few years of their disease. In September 2009 the National Institutes of Health Exploratory Trials in Parkinson Disease (NET-PD) investigators published an analysis of factors determining the need for drug treatment in early PD. This followed on from two "futility" studies of creatine, minocycline, co-enzyme Q10 and GPI-1485 which used the time from baseline assessment to the initiation of symptomatic therapy as a marker for a potential disease slowing drug effect (Parashos et al., 2009). As expected, baseline motor impairment (measured by the UPDRS part III) and disability (measured by the UPDRS part II) were independently associated with an increased likelihood of needing to start symptomatic therapy within the trial period. Surprisingly, higher educational level was also independently associated with an increased need for therapy suggesting that patient-doctor interaction and expectation, over and above motor impairment, influences therapeutic decision making. This highlights the need to

look for an equivalent educational level in trials that include a therapeutic decision as an endpoint. The highest profile disease modifying therapy trial in 2009 was the ADAGIO (Attenuation of Disease Progression with Azilect Given Once-daily) study reporting a randomising trial of the monoamine oxidase type B inhibitor rasagiline in September 2009 (Olanow et al., 2009). The pitfalls of previous studies of disease modifying therapy in PD were avoided, with the use of a delayed start design. One thousand one hundred and seventy six patients were randomised to receive rasagiline 1 or 2mg or placebo for 36 weeks followed by add-in rasagiline in the placebo/delayed start group. The confounding effects of symptomatic treatment on the measurement of disease progression were avoided by equivalent treatment regimes in the early and delayed start groups at the study end. Despite appropriate baseline matching following randomisation, and similar drop out rates in each study group there was a difference in the outcomes for the rasagiline 1 mg and 2 mg groups. The 1 mg Rasagiline early start group showed a significant attenuation in disease progression as measured by decline in the UPDRS Motor Subscale (2.82 ± 0.53 points in the early-start group vs. 4.52 ± 0.56 points in the delayed-start group) whereas the 2 mg Rasagiline early start group did not (3.47 ± 0.50 points in the early-start group and 3.11 ± 0.50 points in the delayed-start group). The reasons for these differences are unexplained and lead to some uncertainty over a possible disease modifying role of rasagiline in PD.

Cognitive impairment is a major L-DOPA unresponsive feature of Parkinson's disease.

Two small studies were reported with memantine, an NMDA-receptor antagonist, in a total of 97 patients with Parkinson's disease dementia and Lewy body dementia reporting that it is well tolerated and presenting preliminary evidence of a beneficial effect (Aarsland et al., 2009; Leroi et al., 2009). Further large scale randomised controlled trials will establish whether memantine is a helpful therapeutic agent in dementia with Lewy body pathology, and a further trial including 199 patients has been completed and the results are awaited (Emre, 2009).

The evidence supporting the choice of initial therapy in Parkinson's disease remains uncertain with strengths and weaknesses of all the commonly used therapies. A major criticism of some therapeutic studies in PD has been the relatively short follow up and the difficulty in distinguishing between the relative importance of previous and current treatments in patient groups. During 2009 the CALM-PD investigators (Comparison of the Agonist Pramipexole With Levodopa on Motor Complications of Parkinson's Disease (CALM-PD)) reported extended open label follow up of patients initially randomised to either pramipexole or L-DOPA (Parkinson Study Group CALM Cohort Investigators, 2009). Six years after randomisation both groups had a similar overall quality of life score, with a persistent benefit in the initial pramipexole group in reduced motor complications (wearing off, on-off fluctuations and dyskinesias) and a persistent benefit in the L-DOPA groups in reduced somnolence. In the earlier trial reports as anticipated there was a large difference in L-DOPA dosage in the initial pramipexole group as compared to the initial L-DOPA group (average L-DOPA daily dose

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264 vs. 509 mg) whereas in the naturalistic follow up study the L-DOPA dosages were much more similar in both groups (average ordinary release L-DOPA daily dose 407 vs. 394 mg). Although the numbers of patients in the follow-up studies are now relatively small the maintenance in differences in rates

of dyskinesias suggest that dopamine agonists such as pramipexole have a persistent effect on motor complications despite an equivalent current L-DOPA regime. However, the authors point out that disabling dyskinesias were uncommon and conclude that "Over the long-term, there is no strong

evidence favoring either of these initial treatment (pramipexole or L-DOPA) strategies over the other." Further information on the relative benefits of alternative initial therapy in PD are likely to become available over the next 18 months in the anticipated results of the large PD MED study.

Science in Parkinson's Disease

By Roger Barker

Trying to decide what is really new in terms of scientific breakthroughs is hard to discern in the short term, as often what seem like very exciting new insights dissipate with time as there is a failure to replicate what was originally reported. Nevertheless this is the job I have given myself, so here are what I think are the two most exciting new scientific findings in PD this year (excluding the work on the Genome Wide Association Studies (GWAS) that John Hardy has written about in this supplement).

iPS cells:

The discovery a few years ago that one could take an adult somatic cell and redirect it to a pluripotent stem cell in mice was greeted with great excitement, as well as a degree of scepticism. However, it soon became apparent that the technique was a robust one and that it could be used with other mammalian cells, including humans. Over the last couple of years since this was achieved, the original technique has been refined such that safer agents can be used which has obvious implications if these techniques are ever to be used to make cells for transplantation in patients¹. Indeed the ability to do this, relies on making such induced pluripotent cells (iPS cells) into dopaminergic neurons, which has been achieved in the murine system², although not with human iPS cells as of yet. However human iPS cells have been used to study neurological disease, although to date this has been in non-PD conditions such as forms of motor neuron disease and inherited neuropathies^{3,5}. Thus we now have a method for making cells from patients that can be used to study disease and/or effect repair which avoids the practical and ethical issues of ES cells. The question is will the promise that these offer really turn into new insights and therapeutic breakthroughs?

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The prion hypothesis of PD:

Truly new theories on the pathogenesis of PD are rare, but the description last year of Lewy body pathology in the young dopaminergic neurons in fetal grafts in patients with PD^{a,b}, opened up a new line of thinking that the disorder may be a prion like disorder the disease spreading through the pathological transfer of alpha synuclein from cell to cell, as is seen in disorders such as CJD with prion protein^{c,d}. Over the last year evidence in support of such a spread of proteins associated with a number of chronic neurodegenerative disorders of the CNS, has emerged including tau^{e,f} and more recently

alpha synuclein^g. In this latter paper it was shown that alpha-synuclein could spread from one cell to another (including) neurons in vitro, and that a similar phenomena could also be seen in the CNS in grafted cells. In other words, cells transplanted into the adult brain could acquire the alpha-synuclein that was expressed in the transgenic host but not in the grafted cells. If true, then our understanding of how PD comes about will need to be radically rethought, as will our approach to disease modifying therapies and that includes any iPS transplants!!

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Identification of risk factors for Parkinson's disease through whole genome analysis

By John Hardy

The last decade has been remarkable for the understanding of the aetiology of Parkinson's disease. Until 1996, almost universally, Parkinson's disease was regarded as a non-genetic disorder and grant applications to look for genetic factors went unfunded because, whenever the disease was seen to be familial, it was interpreted as a shared environment. Now, through the analysis of kindreds with disease we know of at least 7 genes for mendelian forms of the disease. These are SNCA and LRRK2 which are autosomal dominant and PKRN, PINK1, DJ1, ATP13A2 and PLA2G6 which are recessive (see OMIM #168600, and ref 1). Whether mutations in these 7 genes all cause the same pathogenic syndrome is open to debate²; however, it is clear that they all give rise to clinical parkinsonism. Mutations in PKRN and PINK1 are together responsible for a large proportion of early onset cases and mutations in LRRK2 are, in some populations responsible for a high proportion (up to 25%) of typical disease late onset².

However, in addition to these Mendelian diseases, there has also been enormous progress in understanding the "sporadic" forms of the disease. This has come from two contrasting directions: the discovery of heterozygous loss of function mutations in glucocerebrosidase (GBA) as a risk locus for Parkinson's disease through acute clinical observation and the discovery of SNCA and MAPT (and other) loci as risk loci through the application of new genetic technologies in genome wide association studies.

Glucocerebrosidase mutations as a PD risk locus

Homozygous loss of function mutations cause Gaucher's disease: a (usually paediatric) lysosomal storage disease³. Some cases of Gaucher's disease develop Lewy bodies⁴, but more surprisingly, Lwin and colleagues⁵ noted that the relatives of Gaucher's patients often had Parkinson's disease, and when this was observed, the relative always was heterozygous for a loss of function GBA mutation⁵. This surprising observation was extended to the analysis of Parkinson's disease in the general population (e.g.⁶), including pathologically proven

disease⁷. It is now clear that these loss of function mutations increase ones risk of getting Parkinson's disease by about 5 fold⁸. This is really a surprising finding and, in some populations, especially the Ashkenazim, about 40% of Parkinson patients have a GBA mutation. Since the function of the GBA is known (it hydrolyses glucocerebroside to ceramide and glucose), this should be an enormously helpful clue as to the more general aetiology and pathogenesis of the disorder.

Whole genome associations

Whole genome associations rely on the observation that, within a certain population, genetic variability at one point predicts ("tags"), with reasonable accuracy, the other genetic variability within ~20kb⁹. This means that variability across the whole genome can be captured by genotyping these tagging single nucleotide polymorphisms (tagging SNPs). In practice, this means that genetic variability across the genome can be systematically tested for association with disease by genotyping about 500,000 tagging SNPs in large numbers of cases and controls. The larger the series of cases and controls, the smaller the effect that can be detected.

Several whole genome associations have now been reported for Parkinson's disease¹⁰⁻¹⁴. In these investigations, a consistent finding has been that genetic variability at the SNCA locus contributes to disease risk: this had previously been reported on a candidate gene analysis¹⁵. In Caucasian samples, but not Asian samples¹³ the MAPT locus also showed association: again, this had been suggested before from a candidate gene analysis¹⁶ though in this case the mechanisms of the association is more mysterious since there is typically no tau pathology in idiopathic Parkinson's disease. However, we know that the association with the MAPT locus is, in part, driven by genetic variability in tau expression with high expressors being at greater risk of disease¹².

Although both loci that have been proved to be associated with Parkinson's disease were known before the era of genome wide studies and have odds ratios of ~1.3, it is clear that, as the number of samples analysed is

increased, that other and novel loci will be discovered. The largest study reported to date included about 2000 Parkinson's disease samples and was powered to find loci with odds ratios of >1.3. In analysis now are studies with ~6000 Parkinson's disease samples and it is clear, in unpublished data, that other loci will be found.

The aims of genetic analysis

Our analysis of Parkinson's disease has two aims: the first is to understand completely our risk of getting the disorder, and the second is to understand the pathogenesis. We are some way off both goals, but the genetic findings made so far, explain in the order of 25%, our risk for disease. Significantly contributing to this rough estimate are LRRK2 mutations (perhaps 2% of UK samples), GBA mutations (perhaps 5% of samples), PKRN mutations (about 40% of young onset disease, and therefore about 2% of disease in total), genetic variability at the SNCA locus and genetic variability at the MAPT locus (perhaps about 8% each). In terms of understanding the pathogenesis of disease: we believe that there should be a very limited number of pathways to disease: one or two, and that all the genes we discover should map onto those pathways. While this is our belief, and despite the clues afforded by the identification of GBA in particular, we have not yet identified these key pathways. This is like a jigsaw, and perhaps the pathways will become clearer when we have identified more pieces.

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Non-motor Symptoms

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Non-motor Symptoms and Parkinson's Disease

By Vinod Metta, Alexandra Rizos, K Ray Chaudhuri.

In Parkinson's disease (PD), non-motor symptoms (NMS) occur in up to 90% of patients across all stages and include a range of symptoms from neuropsychiatric and autonomic disorders to sleep disturbance and sensory symptoms.^{1,3} NMS correlate strongly with advancing disease, but some such as REM behaviour disorder (RBD) and olfactory deficit precede the onset of motor symptoms by a number of years.⁴ There is a body of data suggesting that NMS has a key negative impact on quality of life (QoL) although recent studies also suggest that NMS often remain undiagnosed and therefore, untreated.⁵

PD affects about 1-2% of the population over 65 years and up to 3-5% of people 85 years and older.¹ NMS include a range of symptoms (Table 1) of which some precede the onset of motor symptoms by up to 10 years or more.² NMS create a significant burden for people with PD and caregivers and studies suggest that NMS is a greater determinant of quality of life than motor features.⁴ In recent years, NMS questionnaires and NMS scales have been validated specifically for use in PD.^{2,6} A recent international survey showed that up to 62% of NMS in PD might remain undeclared to health care professionals because patients are either embarrassed or unaware that the symptoms are linked to PD.

ASPECTS OF NMS RELATED TO PD (Table 1): A. NEUROPSYCHIATRY

Depression and Anxiety: Episodes of major depression may precede motor symptoms and in community-based samples of patients with PD, depression is reported to occur in approximately 30-40%. Studies suggest that depression is likely to be the most significant predictor of QoL in patients with PD,^{7,8} although the role and contribution of anxiety disorders is unclear – despite being present in up to 55.8% of patients.² Future studies will address the specific impact of depression on QoL in comparison to other key NMS such as sleep disorders, pain, sexual health and autonomic disorders using validated non motor tools for PD. Other symptoms such as apathy are important and are listed in Table 1.

Psychotic Symptoms/Hallucinations

25% of treated PD patients may suffer from psychosis which ranges from visual hallucinations to more sinister symptoms such as delusions, paranoid ideation and delirium.

Psychotic symptoms are associated with high NMS co-morbidities, and pose a significant risk factor for nursing home placement and higher mortality.⁹ Psychotic symptoms such as visual hallucinations are closely linked to dopaminergic treatment but also severe depressive symptoms and cognitive impairment. Auditory hallucinations are rare but can occur. Other potential risk factors for the development of psychotic symptoms include dementia, increased age, disease duration, disease severity, depression and sleep disorders.¹⁰

Cognitive impairment

Cognitive dysfunction such as mild cognitive impairment (MCI) may affect 24% of patients with newly diagnosed PD¹¹ while dementia may occur in up to 80% of PD patients with advanced disease. In PD, the correlation between cognitive impairment and QoL is controversial and the relative impact is thought to be less than other NMS. However, dementia poses a major societal burden and is a source of major caregiver stress.

Dopamine Dysregulation Syndrome (DDS) and Impulse Control Disorders (ICD):

DDS and ICD have been linked to addictive and reward seeking behaviour (listed in Table 1) related to abnormal limbic system response to dopaminergic therapy, particularly dopamine agonists.² Compulsive gambling is the most topical while DDS may be related to levodopa abuse and addiction. Close monitoring and counselling are important to prevent damaging social and personal impacts of these conditions.

B. SLEEP DISORDERS

Sleep disorders are a frequent NMS, present in up to 90% of people with PD,^{2,12} and usually start early in the disease course. Pre-motor sleep disorders include most notably RBD, while insomnia and excessive daytime sleepiness (EDS) may also occur in the pre-motor stage. Sleep disorders are related to neurodegenerative sleep architecture defects causing sleep wake cycle disorders, impaired sleep due to nocturnal motor problems, restless legs syndrome (RLS), sleep disordered breathing and EDS. Although it is intuitive that sleep disorders would have a negative impact on patient QoL, this has not yet been adequately measured in PD.

Non-motor Symptoms

REM sleep behaviour disorder

RBD may occur in about a third of patients and may precede development of cardinal motor features.¹³ A 50% chance of developing PD at 10 years is suggested. The problem is not benign as self-injury and injury to the partner can occur during attacks.

Excessive daytime somnolence (EDS)

EDS affects 15-50% of people with PD and may also be a preclinical marker of the disease.^{2,3} Neuronal degeneration of the suprachiasmatic nucleus and degeneration of the lateral hypothalamic "hypocretin" containing neurons may be implicated. Hypocretin is a key awake promoting peptide and abnormalities of it have been found in several neurological conditions, most notably narcolepsy.

Restless Legs Syndrome and Periodic Limb Movements (PLM)

The frequency of RLS in PD is not well established; study estimates range from 8% to 20%, but some authors have found no difference in prevalence between PD patients and controls. PLM is common in PD and sensitive to dopaminergic therapy.^{2,3}

Insomnia

The prevalence of insomnia in PD varies from 18% to 88% depending on definition used and population assessed. Many factors associated with PD may contribute to insomnia, including: dopamine deficiency related alteration of sleep architecture, effect of anti-parkinsonian medication, nighttime motor disability and motor fluctuation, autonomic impairment and pain. Insomnia and depressive symptoms have been found to be most strongly predictive of impaired overall QoL. Many other sleep problems occur in PD and include the under-recognised sleep disordered breathing as well as non REM parasomnias.

C. FATIGUE

Fatigue appears to be the single most important reason cited by Americans for obtaining disability insurance payments for their PD. Prevalence in PD may be as high as 81% as reported in the PRIAMO study.¹⁴ Although often reported to be associated with depression, there is evidence that fatigue is a prominent feature of PD independent of depressive symptoms.

The disability due to fatigue is significant and over half of patients with PD list fatigue as one of their three most disabling symptoms. Central fatigue exists, as well as peripheral fatigue; central fatigue may be driven by a limbic dopaminergic deficit.

D. SENSORY SYMPTOMS

Sensory symptoms such as pain, hyposmia and visual dysfunction are prevalent in patients with PD and have a negative impact on QoL. Pain is particularly relevant and exists in various forms in PD.

Pain

Pain affects up to 74% of PD patients² and can be secondary to PD (dystonic pain or akathitic discomfort), due to comorbid conditions (RLS), due to PD (central pain) or result from PD symptoms aggravating underlying non-PD pain (abnormal gait worsening osteoarthritic hip pain). Pain negatively impacts QoL in patients with PD and appears to be significantly influenced by depression and motor symptoms. Patients with PD have less frequent analgesic consumption than non-PD patients, which may reflect under-reporting or under-treatment.

Olfactory disturbance

Olfactory dysfunction may affect up to 90% of PD patients and it has been shown to be a preclinical marker for the disease.^{2,3} The clinical impact of olfactory dysfunction is unclear, but this symptom may play an important part in the clinical diagnosis of parkinsonian syndrome.

Visual disturbance

These are relatively under-researched and may be related to fluctuations. Diplopia may occur as well as blurred vision and impaired contrast sensitivity.

E. AUTONOMIC DYSFUNCTION

Autonomic dysfunction is an important non-motor feature of PD and includes a range of problems such as urinary, cardiovascular, sexual and gastrointestinal symptoms. These problems can occur early or late in the disease course and are not necessarily related to disease duration or severity.^{2,14} Autonomic symptoms have a major impact on the daily life of those with PD.

Bladder dysfunction

Bladder dysfunction, includes urgency, nocturia, frequency and incontinence and these can cause urogenital infections which are a frequent cause of death in parkinsonism. Studies show that patients with PD had a significantly higher rate of urinary urgency, daytime and nighttime frequency, incontinence, hesitancy, poor stream and straining than a control group.

Sexual dysfunction

Sexual dysfunction is common in PD and decreases in libido, sexual intercourse and

orgasm and problems with erection and ejaculation occur significantly more frequently in patients with PD than in controls.

Sweating abnormalities:

Abnormalities of sweating (usually excessive sweating or hyperhidrosis) can affect 50% of PD patients, however, there is little information on the impact of this troublesome symptom on QoL. Hyperhidrosis can occur as part of non motor fluctuations or dyskinesias.²

Orthostatic hypotension

Orthostatic hypotension is the most frequent cardiovascular symptom and usually occurs late in PD and can be experienced by 50% of hospital in-patients with PD.¹⁴ Blood pressure not only drops significantly upon rising, but also fails to normalise again over many minutes. Patients may complain of nonspecific symptoms such as giddiness, transitory defective vision, nausea, and lightheadedness. Loss of consciousness is rare but can lead to serious injury.

F. GASTROINTESTINAL SYMPTOMS

Dribbling of saliva

Dribbling of saliva is a frequent complaint in patients with PD, ranging from 30% to 74% of patients, and results not only from excess production of saliva but also from infrequent or impaired swallowing. It appears that drooling and or dribbling of saliva can also predate the diagnosis of PD and is often undertreated.

Dysphagia

Although dysphagia could be considered a motor symptom, the origin is autonomic and as such an aspect of NMS of PD. Nine out of ten patients with PD develop dysphagia during the course of their disease.² The consequences are severe as aspiration pneumonia is the leading cause of death in this group. There are few studies investigating the impact of dysphagia on QoL in patients with PD. Studies also suggest that dysphagia is an important issue throughout all stages of disease, not only in advanced disease. Dysphagia leads to difficulty chewing and swallowing in addition to activities surrounding mealtimes such as shopping, preparation and socialisation.

Constipation

Constipation is a common non-motor feature of PD and may precede development of motor symptoms.¹⁴ Constipation is likely to be a predictor of QoL and studies suggest that PD patients have a significantly higher frequency of constipation and difficulty in expulsion and had more dissatisfaction with bowel function than a control group.

Non-motor Symptoms

G. NON MOTOR FLUCTUATIONS:

Non motor fluctuations may co-exist with motor fluctuations and have been classified into three subtypes, dysautonomic, cognitive/psychiatric and sensory/pain. The cause appears to be secondary to pulsatile dopaminergic therapy similar to the pathogenesis of motor fluctuations.²

TREATMENT:

Non-motor symptoms are common in patients with PD although these remain under-reported and they are often overlooked. NMS result in significant burden for people with PD and negatively impact on quality of life. A range of NMS of PD appear to have a dopaminergic contribution and as such it is possible that some of these symptoms may respond to targeted dopaminergic therapy.¹⁵ Evidence for this strategy is emerging based on recent studies of dopamine agonists such as rotigotine patch, ropinirole slow release, apomorphine infusion and intra-jejunal levodopa infusion. However, some NMS may actually be precipitated by dopaminergic drugs (Table 1). Non dopaminergic drugs are also being explored for use in key NMS such as EDS, RBD, constipation and pain.

CONCLUSION

NMS result in a significant burden for people with PD and negatively impact on quality of life. Future treatment of PD will incorporate holistic assessments of NMS of PD using validated tools such as the NMSQuest.

ACKNOWLEDGEMENTS:

All founding members of EUROPAR (Pablo Martinez-Martin, Angelo Antonini, Per Odin and Cristian Falup-Pecurariu).

Table 1: Spectrum of non-motor symptoms in PD.

Symptoms in italics indicate poorly understood or lesser known symptoms. MCI = mild cognitive impairment

Neuropsychiatric symptoms

Depression – anxiety – apathy – hallucinations, delusions, illusions – delirium (may be drug-induced) – cognitive impairment (dementia, MCI) – dopamine dysregulation syndrome (drug induced) – impulse control disorders (drug induced) – panic attacks

Sleep disorders and symptoms

REM sleep behaviour disorder (possible pre-motor)
Excessive daytime somnolence, narcolepsy type "sleep attack"
Restless legs syndrome, periodic leg movements
Insomnia
Sleep disordered breathing
Non REM parasomnias

Fatigue

Central fatigue – peripheral fatigue

Sensory symptoms

Pain – olfactory disturbance *visual disturbance (blurred vision, diplopia), impaired contrast-sensitivity*

Autonomic dysfunction

Bladder urgency, frequency, nocturia – sexual dysfunction (may be drug-induced) – sweating abnormalities (hyperhidrosis) – orthostatic hypotension

Gastrointestinal symptoms

Dribbling of saliva – dysphagia – constipation – *nausea, vomiting, reflux, fecal incontinence*

Drug-induced NMS

Hallucinations, delusions – dopamine dysregulation syndrome – impulse control disorders (*e.g. compulsive gambling, hypersexuality, binge eating*)

Non-motor fluctuations

Dysautonomic – cognitive/psychiatric – sensory/pain

Other symptoms

Weight loss – weight gain (*may be drug-related*)

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The Parkinson's Disease Society

2009 was a fantastic year for research at the Parkinson's Disease Society, and a fitting celebration of our 40th Anniversary and four decades of discovery. The charity invested more than £4million in 24 cutting edge research projects, exploring everything from what causes Parkinson's, to better treatments and a cure.

Since 1969 the Parkinson's Disease Society has invested over £45million in groundbreaking research. Our research programme has helped to transform the treatment and care provided for people living with Parkinson's all over the world.

Donating your brain to the Parkinson's Brain Bank

The Parkinson's Disease Society funds a Brain Bank at Imperial College, London. Research using tissue from the Parkinson's Brain Bank has contributed to crucial research breakthroughs, revealing vital clues to why nerve cells die in the brains of people with Parkinson's and identifying potential ways in which this may be slowed down, halted or even reversed. There has been a desperate shortage of donated brain tissue, and during Parkinson's Awareness Week in April 2009 we launched our Brain Donor Appeal.

The Appeal was hugely successful, resulting in over 2,300 people joining the Brain Donor register, including pledges from celebrities including Jane Asher and Jeremy Paxman. New donors pledging to donate their brains to the Parkinson's Brain Bank will ensure researchers all over the world have access to the essential tissue they need as we work towards a cure for Parkinson's.

Major new lead for Parkinson's treatment

In August, researchers funded by the Parkinson's Disease Society at the University of Sheffield uncovered a major lead for potential new treatments for Parkinson's. Using both fruit

fly models of Parkinson's and skin cells from people with the condition, the researchers identified a pathway inside nerve cells that could be stimulated to protect the dying cells affected by Parkinson's.

The drug rapamycin was shown to protect cells against the damaging effects of two mutant genes, known to cause inherited forms of Parkinson's. Although this drug is unlikely to be used to treat Parkinson's directly, clues from this research will help scientists develop effective new treatments.

The importance of exercise

In September, a two-day conference took place in London to explore the potential benefits of exercise for people with Parkinson's. The conference, hosted by the charity's Special Parkinson's Research Interest Group (SPRING), attracted international researchers from neuroscience, sports medicine and physiotherapy, and led to the development of new ideas that may form the basis for international collaborative research projects.

The Monument Discovery Award

One of our key achievements in 2009 was the announcement in October of the research group who were awarded The Monument Discovery Award – our largest ever research grant worth £5million over 5 years.

A team of world-class researchers at the University of Oxford, led by Dr Richard Wade-Martins, will focus upon three central themes of research to accelerate our progress towards a cure for Parkinson's. The themes are what happens inside the nerve cells that causes them to die in Parkinson's; developing better animal models that truly reflect Parkinson's; and diagnosing the condition earlier and more accurately before the symptoms develop.

Diagnosing Parkinson's before the earliest

movement symptoms appear, combined with more effective treatments that tackle the root causes of nerve cell death, will be crucial steps towards developing an effective cure.

Other highlights of 2009

During 2009 twenty five new Parkinson's nurse posts were created across the country to provide much needed support for people with Parkinson's and their families. Our new national network of Information and Support Workers helped 11,000 people living with Parkinson's and accessed over £6.8million in unclaimed benefits. In addition, our local educational staff trained 10,000 professionals in hospitals and care homes on how to recognise the symptoms and care for people with Parkinson's.

Campaigning for change

Our Fair Care for Parkinson's campaign got important messages about inequalities of care and support across to decision makers in all four UK countries, and we have a review of neurology services on the agenda for England in 2010.

Looking ahead

Everything the Parkinson's Disease Society does is about putting people with Parkinson's and their families first. We need to raise more than £110million over the next five years to be able to find a cure and improve life for everyone affected by Parkinson's and we are totally dependent on public donations.

To find out more about the work of the Parkinson's Disease Society or to make a donation visit www.parkinsons.org.uk

*Claire Bale,
Research Communications Officer
Jill Davis, Media and Communications Officer
Parkinson's Disease Society.*

The European Parkinson's Disease Association

The social and economic burden of Parkinson's disease is significant and increasing; however, there is substantially less cost to society when Parkinson's is treated early and properly. The European Parkinson's Disease Association (EPDA) has been trying to reinforce this important message for many years, but regrettably any change in attitude and actions are still very slow. We still see throughout Europe, inflexible pricing and reimbursement schemes, doctor appointment time limitations and concerns over the availability and access to medication.

2009 represented 12 years since the EPDA launched its Charter for people with Parkinson's, supported by the World Health Organisation, as well as other notable individuals, including the late Pope John Paul and Muhammed Ali. One of our main focuses

in 2009 was to take stock and to look at the changes that have taken place in Parkinson's management in Europe in the years since the launch of the Charter.

Worryingly, the EPDA has received reports from a number of countries indicating that many people with Parkinson's are still waiting a long time to see a Parkinson's specialist, have access only to limited support services and do not have a Parkinson's disease Nurse Specialist (PDNS) service. Furthermore, many of the therapy services – such as speech and language, physiotherapy and occupational – are very limited or non-existent.

All these reports provided the drive for our Move for Change (<http://www.epda.eu.com/projects/moveForChange/2009>) initiative launched in 2009. Running alongside our evolving awareness campaign, Life with

Parkinson's (www.parkinsons-awareness.eu.com), we see these two initiatives as a powerful combination that will effect change. They are tools that will raise awareness, enable lobbying from a European – as well as a national – level and reinforce the message to governments and healthcare professionals that action is urgently needed if the economic and social burden of Parkinson's is to be reduced.

In 2010 and beyond, the EPDA is confident that by working in partnership with our 43 European member organisations, change can be effected for the betterment of people with Parkinson's, their families and friends throughout Europe.

*Lizzie Graham Secretary General,
European Parkinson's Disease Association.*

Healthy Alliance

Healthy Alliance is a unique collaboration between GlaxoSmithKline (GSK) and the Parkinson's Disease Society (PDS), to provide a dedicated package of support and training for HealthCare Professionals (HCPs) with an interest in Parkinson's covering the UK. The funding for Healthy Alliance is provided by GlaxoSmithKline.

There are a range of resources and information to help those with an interest in Parkinson's to develop or improve local services. These include developing core services, Professional development, Educational Development and Patient support.

Personal Health Records

Healthy Alliance is working with consultant neurologist Dr Alec Ming to empower patients with Parkinson's and improve management of their condition. Dr Ming, who is based at Hull Royal Infirmary, approached Healthy Alliance in 2009 seeking support to develop his idea for Personal Health Records. These will provide patients with a portable record of their treatment history which could be used by all healthcare professionals with whom they come into contact. Juliet Ashton of Healthy Alliance says, "The great thing about Personal Health Records as they are being proposed, is that they support both Personal Care Planning and Information Prescriptions, two of the hottest topics on our agenda at the moment. Lesley Carter, Head of Influence and Service Development at the PDS has gained agreement from the East of England Strategic Health Authority to incorporate their 'Health Plan' into the records."

Dr Ming's aim is for patients to have better information about their treatment and for all healthcare professionals involved in their care to see what their colleagues are doing. Having all the information in one place will assist treatment and empower patients to have more control and understanding of their condition. Patients would be given a pack by their consultant or Parkinson's Disease Nurse Specialist (PDNS). The pack will comprise a folder for the patient containing sections for all aspects of treatment, including titration sheets and care plans. The folder would also be used by others involved in providing care, such as physiotherapists. An accompanying CD-ROM would be used by the healthcare professional.

The draft folder is first being piloted at Dr Ming's PD centre in Hull.

Eighth Healthy Alliance Annual Conference

Information and inspiration were the two key take home messages from the annual conference held in July 2009. The agenda covered a wide range of topics aimed at increasing understanding of Parkinson's, improving services to patients – and supporting professional development.

A new tool that makes it easy to capture patient information proved a big hit at conference. The Parkinson's Information Tool has been developed by Healthy Alliance to make it easy for PDNSs to capture key data about their current patient population. Managers are increasingly asking for evidence of activity outcomes and meeting targets

and the new tool allows relevant information about patients and their management to be captured and used in a variety of ways. Juliet Ashton of Healthy Alliance explained, "The tool is an evolution of the Parkinson's Audit Support Service and it allows you to consolidate all patient data into one place, providing a snapshot of your current patient population, as well as individual patients. "This makes it easy to review current caseload and keep track of different aspects of the service, such as patients who are due for a follow-up. And the great thing is that it also creates graphs, making it easy too present information to others such as consultants or managers."

Parkinson's Disease Nurses Association

2009 saw the launch and completion of the All Party Parliamentary Inquiry into Parkinson's Disease. Richard Glasspool provided written and verbal evidence in his role as Chair of the PDNSA. This inquiry identified inequalities in services for PwP and their carers, which PDNSs can use to support their existing and developing services.

2009 also saw the 20 year anniversary of the PDNS role and this was the focus of the annual PDNSA conference in October. Audrey Stainton gave an overview of the past 20 years in PD nursing. Other topics included a look into the ABPI regulations, psychogenic movement disorders and several interactive workshops.

*Juliet Ashton,
Healthy Alliance.*

The Cure Parkinson's Trust

It was a strange quirk of fortune that brought four people with Parkinson's together. Sir Richard Nichols and Air Vice Marshal Dicken were City of London dignitaries, Sir David Jones, a retail giant and business legend, and Tom Isaacs whose walk of 4,500 miles around the coastline of Britain was the cement out of which the four bonded and became a new constructive force.

The Cure Parkinson's Trust was launched in 2005 with the simple aim to find a cure for Parkinson's. This will not be achieved by a single scientific event, but through a process: we have to delay it, reverse it, prevent it and then we have to obliterate it once and for all. The key to achieving this process is through innovation and through responding to the real-life needs of people with Parkinson's. Once novel treatments have been identified, it is critical that they are nurtured through the development process and delivered quickly, but safely, into the clinic.

The Cure Parkinson's Trust believes that the science is out there which can dramatically improve the lives of people living with Parkinson's. It feels that a sense of urgency can be instilled into the Parkinson's community and make a tangible difference to the speed of the development of new therapies.

The Trust has directed more than £2 million into projects globally. In 2009 The Trust approved

funding for Dr David Dexter to investigate the role of voltage-gated calcium channels in neuronal susceptibility in Parkinson's. This 18-month study will provide an insight into calcium's effect in Parkinsonian cells, and follows on from CPT's Scientific meeting on the role of calcium in Parkinson's. The world class speakers presented on the role of Vitamin D and usage of treatments for hypertension. Our head of research Dr Richard Wyse asked the question whether there is a role for Calcium Channel Blockers in screening people for Parkinson's prior to the manifestation of any physical symptoms?

The Trust has also used innovative methods to bring investment into the Parkinson's arena by generating credibility for exciting prospective therapies which might well have been left on the shelf without its involvement.

Cogane moved into patient trials in 2009. The compound has shown excellent results in pre-clinical studies, showing the potential to reverse neural damage to the brain caused by Parkinson's. There is every reason to expect similar results in the Phase 2b study which will start in 2010. In May 2009 we funded a Key Opinion Leaders meeting to ensure this trial will be supported by the best possible protocol.

Also in 2009 The Trust approved funding for a pilot study of 20 patients into using Exendin which

could be a revolutionary new treatment for Parkinson's. It also has the potential to fast-track through the regulatory system as it is already in use as a licensed therapy for Type 2 Diabetes. Exendin has shown the capacity not only to fully protect against the onset of Parkinson's in pre-clinical models but it has also been shown to have a neurogenic effect. In other words, it is possible that when administered to people with Parkinson's, their condition could be reversed and functionality restored.

The aim of The Cure Parkinson's Trust is to put people with Parkinson's back in control of their lives. In 2009 it coordinated conferences concentrating on patient priorities, and scientific communication and collaboration, most notably the Genetics conference in December 2009.

Perhaps above all else The Cure Parkinson's Trust has brought about a change in momentum. It has captured the mood of a more optimistic and determined group of people from across the Parkinson's community, including researchers and patients, who see the importance of and are willing to work together as a team to wage war on Parkinson's.

*Helen Matthews
Coordinator,
The Cure Parkinson's Trust.*

Contributors



Roger Barker is co-editor of ACNR, and is Honorary Consultant in Neurology at The Cambridge Centre for Brain Repair. His main area of research is into neurodegenerative and movement disorders, in particular Parkinson's and Huntington's disease. He is also the university lecturer in Neurology at Cambridge where he continues to develop his clinical research into these diseases along with his basic research into brain repair using neural transplants.



Nin Bajaj graduated in medicine from Oxford University after pre-clinical training at Cambridge. He was a Wellcome clinical training fellow in Molecular Neuroscience at The Institute of Psychiatry, London, and his subsequent neurology training was undertaken at the National Hospital for Neurology and King's Hospital, London. He was appointed Consultant Neurologist at Nottingham University Hospitals in 2002, specialising in movement disorder. He was the Lead Clinician for the Hospital Doctor Parkinson's Disease team of the year in 2007. Dr Bajaj is currently Clinical Director of the National Parkinson Foundation Centre of Excellence in PD between Derby Hospitals NHS Foundation trust and the University of Nottingham.



K Ray Chaudhuri is Consultant Neurologist and Professor in Neurology/Movement Disorders at Kings College Hospital NHS Foundation Trust, University Hospital Lewisham. He is one of the medical directors of the National Parkinson Foundation International Centre of Excellence at Kings College, London. He also serves as chairman of the RLS:UK and International PD non motor group and EUROPAR and serves on the committee of the Movement Disorders Society and the World Federation of Neurology.



Tom Foltynie trained at Cambridge and Queen Square and now is a senior lecturer and Movement disorders consultant at the National Hospital for Neurology & Neurosurgery in Queen Square. He is involved in the Deep Brain Stimulation service and is carrying out research into both DBS and new treatments for Parkinson's disease.



John Hardy is a geneticist and molecular biologist whose research interests focus on neurological disease. In 2007 he took up the Chair of Molecular Biology of Neurological Disease at the UCL Institute of Neurology. With over 23,000 citations, Prof Hardy is the most cited Alzheimer's disease researcher in the UK (5th internationally). In recognition of his exceptional contributions to science, he was elected a Fellow of the Royal Society in 2009.



Michele Hu is a Consultant Neurologist at the Milton Keynes and the John Radcliffe Oxford Hospitals, and Honorary Senior Clinical Lecturer in Neurology at the University of Oxford. She is a member of the Parkinson's Disease Clinical Study Group of the National Dementias and Neurodegenerative Disorders Network (DeNDroN) and is clinical lead for Parkinson's disease in the Thames Valley DeNDroN research network. She is a member of the Oxford Parkinson's Disease Centre which was recently awarded the Monument Discovery Award funded by the Parkinson's Disease Society to understand the early pathological pathways in PD.



Vinod Metta is Research and Clinical Registrar for Neurology and Movement Disorders at Kings College Hospital NHS Foundation Trust and University Hospital Lewisham. His research interests include fatigue and functional imaging in PD.



Huw Morris is a senior lecturer and consultant neurologist at Cardiff University, the Royal Gwent Hospital and Cardiff and Vale Trust. His clinical and research training took place at the National Hospital, Queen Square, the Mayo Clinic and the Western Pacific island of Guam. His main interests are Neurogenetics, Movement Disorders and Dementia.



Alexandra Rizos has a Masters in human biology and is interested in pharmacotherapy of PD. She is the honorary international co-ordinator for EUROPAR, an academic group promoting non motor research across Europe.



Tim Soane is a medical student in his final year on the University of Nottingham's Graduate Entry Medicine programme. He previously completed a PhD investigating the role of the 26S proteasome in neurodegeneration at the University of Nottingham, sponsored by the Alzheimer's Research Trust. He will undertake his foundation training in Edinburgh, on the Academic Foundation Programme. He hopes to train in neurology.



George Tofaris is an Academic Clinical Lecturer in Neurology at the University of Oxford. His research interests are in movement disorders and, in particular, the molecular neuropathology of Parkinson's disease.