

European Neurological Society Meeting

7-11 June, 2008; Nice, France.

European
Neurological Society



This year the scientific programme of the European Neurological Society meeting, which was held in Nice (France) on June 7-11, included six symposia devoted to important topics. The Presidential symposium covered disorders of consciousness, with talks by prominent researchers, including Gustave Moonen (Liege, Be) on differentiation of vegetative state from minimally conscious state and the classical locked in syndrome in which pain and emotional perceptions are preserved. In this symposium, Brain-computer interfaces in the locked-in syndrome, Doctor A Kubler, exposed the remarkable work on voluntary regulation of neuro-electrical activity or brain activity as a response to sensory stimulation which is used to control cursor movements or switches on a computer. Such technology is aimed at restoring communication in the locked-in syndrome. The second symposium focused on Behavioural disorders and dementia, which represent an increasing health problem worldwide. Dr Cappa reported on behavioural changes in synucleinopathies. Such manifestations include executive dysfunction, which reflect the pathological involvement of fronto-subcortical mechanisms rather than the specific mechanism of disease. Depression or agitation may be due to environmental interactions, or represent side effects of symptomatic pharmacological treatments. Some features of cognitive and behavioural dysfunction may be relatively specific for the synucleinopathies. In the case of Parkinson's disease (PD), depression is an important clinical issue, which may be more frequent in this disorder than in other neurodegenerative disorders, reflecting the complex combination of neurotransmitter abnormalities, involving dopamine, serotonin and norepinephrine. Another clinically important aspect in the management of PD is impulse control disorders, such as pathological gambling and hypersexuality, and which appear to be related to dopaminergic medication. It has been proposed that a form of parasomnia (REM sleep behaviour disorder) may be a relatively specific behavioural marker of the synucleinopathies.

E Scarpini and D Galimberti reported on mutations in the progranulin gene associated with highly variable clinical phenotypes, including progressive supranuclear palsy and corticobasal degeneration syndrome. They suggested that unidentified environmental and genetic factors produce considerable phenotypic variability in patients carrying the same mutations.

In the symposium on autoimmune disorders



Building in Nice

of the nervous system, Professor Angela Vincent discussed myasthenia gravis (MG), in which thymoma occurs in up to 10% of patients, mostly presenting between the ages of 30 and 60 years. Ocular MG occurs in about 20% of patients, and only 50% of these have acetylcholine receptor (AChR) antibodies. About 10% to 15% of all patients with MG and generalised symptoms do not have anti-AChR antibodies detectable by radioimmunoprecipitation test. A proportion of patients without AChR antibodies have antibodies to MuSK which is a receptor tyrosine kinase restricted to the neuromuscular junction in mature muscle. Interestingly, the prevalence of MuSK antibodies among patients without AChR antibodies is highly variable

between different centres around the world, suggesting a possible environmental interaction. MuSK antibodies are mainly IgG4 class, and are almost never found in patients with AChR antibodies or with thymoma. The distinctive features of MuSK-MG comprise marked ocular, bulbar, neck or respiratory symptoms and, in contrast to AChR-MG, the patients may have normal electrophysiology in limb muscles with evidence of neuromuscular defects in facial muscles. They respond to immunosuppression with prednisolone and azathioprine but alternative immunosuppressive treatments are often required. Two other autoimmune diseases of the neuromuscular junction, the Lambert Eaton myasthenic syndrome (LEMS) and acquired neuromyotonia, are associated with antibodies to voltage-gated calcium and potassium channels, respectively. In LEMS the antibodies are found equally in cases with or without small cell lung cancer (or rarely other tumours) but those with cancer may also develop cerebellar ataxia. The peripheral symptoms tend to improve with treatment whereas the central symptoms rarely show a good response. About 20% of cases of acquired neuromyotonia are associated with thymoma and/or myasthenia. Most patients may be managed with anti-epileptic drugs and do not need immunosuppression.

Another symposium focused on the much debated treatment of multiple sclerosis, especially when to start disease-modifying treatment and which treatment. The issues of early treatment of MS patients were summarised by Professor Compston (Cambridge, UK). The results of clinical trials support the hypothesis that inflammation is necessary for new lesion formation and leads to axon degeneration. The implication is that immunological therapies will best prevent sustained accumulation of disability and disease progression if given early in the course and before the cascade of events leading to axon degeneration is irretrievably established. This may explain the present limitations of immunotherapy in patients with secondary progressive multiple sclerosis. But it raises the dilemma of exposing individuals who may never develop disability from multiple sclerosis to the unpredictable hazards of prolonged immunosuppression.

Besides these symposia, 887 free papers were presented. The courses were enthusiastically followed by an ever-growing number of neurologists in training.

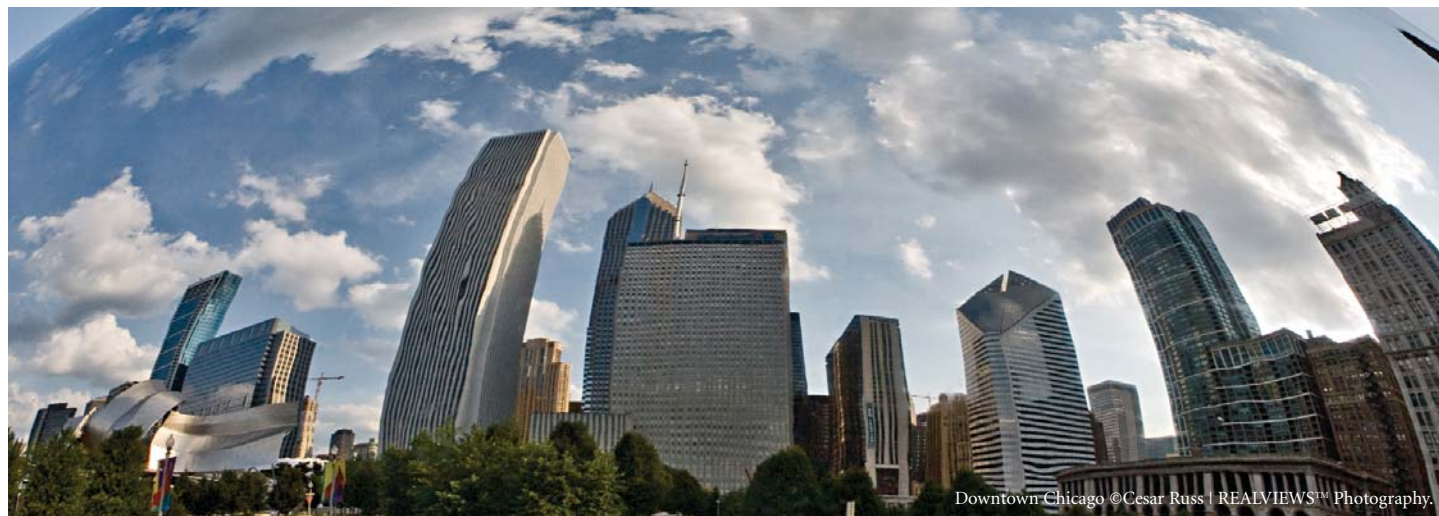
*Professor Gérard Said, FRCP,
Secretary General of the ENS.*

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12th International Congress of Parkinson's Disease and Movement Disorders

22-26 June, 2008; Chicago, IL USA.



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The 12th MDS conference was the largest so far, with over 3500 delegates attending the Chicago Hilton. The conference remains accessible to non-movement disorder specialists, with well chosen speakers, background reviews and teaching sessions while presenting the most up to date, sometimes unpublished, findings in Parkinson's disease and other movement disorders for the specialist. The following account encompasses those aspects of the five day conference that I found the most interesting but are naturally biased by my own interests.

Parkinson's disease Pathophysiology

More and more people seem to be knowingly saying 'calcium channels' in reference to the pathophysiology of PD. More specifically there appears to be growing interest in the calcium dependent pacemaker activity of substantia nigra pars compacta (SNc) neurons and the relevance of this activity to the vulnerability of these neurons to premature death in PD. James Surmeier spoke about SNc neurons in the mouse as pacemakers, the function of which depends on a specific calcium channel – the Cav1.3 pore. In contrast other DA neurons e.g. in the nearby ventral tegmentum, do not have this pacemaker activity. Recording from dendrites of SNc neurons show regular oscillations of the membrane potential with simultaneous fluctuations in dendritic Ca^{2+} levels. It is proposed that the dependence on calcium influx creates an ATP demand requiring oxidative phosphorylation, and thus particular vulnerability to mitochondrial stresses. This was demonstrated by showing films of the oscillatory mitochondrial fluorescence that occurs specifically in these SNc neurons. Blocking Ca^{2+} input through the Cav1.3 pore with dihydropyridine calcium antagonists leads to cells reverting to non-calcium dependant mechanisms, reduces signs of abnormal mitochondrial oscillations and reduces rotenone, 6-

OH-DA, and MPTP-toxicity in animal models. In a single epidemiological study, Ca^{2+} antagonist treatment for hypertension has also been associated with lower PD risk. The hypothesis is that SNc neurons are simply vulnerable to cell loss with age and this may be accelerated by any genes and environmental factors influencing mitochondrial function and may be protected by calcium antagonists which may restore healthy pacemaker activity of these neurons. While very interesting, a great deal more evidence is required to substantiate this theory.

Of course as expected, there is also much continued interest in pharmacological methods of reducing alpha synuclein levels and interfering with its tendency to form protofibrils/oligomers; the amelioration of LRRK-2 associated toxicity through inhibitors of GTP binding and kinase activity; the susceptibility to oxidative stress of DJ-1 knockout animal models; and the accumulation of the dopaminergic toxins AIMP2 and FBP1 through loss of parkin E3 ligase activity in patients with parkin mutations and perhaps also sporadic PD.

In her tribute lecture to David Marsden, Ann Graybiel reviewed what we know about basal ganglia function, including new findings regarding the CalDAG-GEF1 gene which is required for long term potentiation (LTP) induction in the striatum. Knockout mice for this gene do not exhibit features of plasticity, (seen through absence of drug induced movements) and a manuscript by Crittenden et al regarding this is in preparation. It seems that changes in CalDAG-GEF1 plasticity through this mechanism may influence the development of L-dopa induced dyskinesias (LID) in PD and this is substantiated by experiments looking at mRNA expression in the 6-OH DA mouse model.

Diagnosis and preclinical period

If patients at high risk of developing the motor features of PD can be identified, based on hav-

ing a family member affected with PD, olfactory dysfunction, abnormal cardiac MIBG scintigraphy or REM sleep behaviour disorder (RBD), then earlier diagnosis, understanding of pathophysiological mechanisms and trials of potential neuroprotective treatments might all be facilitated. A longitudinal cohort of such people is being recruited in multiple centres in the USA led by Dr Matthew Stern, with a view to performing clinical trials of potentially neuroprotective agents. In line with this it seems that at least two thirds of patients with RBD will develop parkinsonism if followed up long enough, which is in keeping with the Braak stages of PD onset starting in the medulla. An inconsistency is that if patients with HY stage 1 PD are investigated RBD is rare but at stage 2, RBD is common. In a discussion regarding this presumed preclinical period, Anthony Schapira suggested that during this time, there is most likely a period of cerebral compensation through brain plasticity, perhaps by down-regulation of DA transporters, upregulation of D2 receptors, and the effects of trophic factors like GDNF and BDNF.

The utility of functional and structural imaging in multiple aspects of PD assessment was reviewed by David Brooks. Both PET and SPECT can be used to correct mistaken diagnoses of PD and allow the discrimination of drug induced parkinsonism from drug 'unmasked' PD, while glucose metabolism scans and the more widely available diffusion weighted-MRI imaging can discriminate PD from patients with established MSA, PSP or CBD. Patients with these atypical parkinsonisms all have reduced glucose metabolism in basal ganglia regions, although it is not yet confirmed whether these scans can be useful in the early phase of these diseases when it is clinically most difficult to diagnose them. Imaging has also shown that the presence of depression in PD is related to noradrenergic neuronal loss rather than serotonergic, and this has implica-

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Treatment with domperidone (typical dosage 20mg three times a day) before and during apomorphine HCl therapy is essential. The optimal dosage of apomorphine HCl has to be determined on an individual patient bases; individual bolus injections should not exceed 10mg and the total daily dose should not exceed 100mg. **Contraindications:** Children and adolescents (up to 18 years of age). Known sensitivity to apomorphine or any other ingredients of the product. Respiratory depression, dementia, psychotic disease or hepatic insufficiency. Intermittent apomorphine HCl treatment is not suitable for patients who have an "on" response to levodopa which is marred by severe dyskinesia or dystonia. **Pregnancy and lactation:** Caution should be exercised if prescribing apomorphine to pregnant women and women of childbearing age. Breast-feeding should be avoided during apomorphine HCl therapy. **Interactions:** Patients should be monitored for potential interactions during initial stages of apomorphine therapy. Particular caution should be given when apomorphine is used with other medications that have a narrow therapeutic window. It should be noted that there is potential for interaction with neuroleptic and antihypertensive agents. **Precautions:** Use with caution in patients with renal, pulmonary or cardiovascular disease, or who are prone to nausea or vomiting. Extra caution is recommended during initiation of therapy in elderly and/or debilitated patients. Since apomorphine may produce hypotension, care should be exercised in patients with cardiac disease or who are taking vasoactive drugs, particularly when pre-existing postural hypotension is present. Neuropsychiatric disturbances are common in Parkinsonian patients. APO-go should be used with special caution in these patients. Apomorphine has been associated with somnolence and other dopamine agonists can be associated with sudden sleep onset episodes, particularly in patients with Parkinson's disease. Patients must be informed of this and advised to exercise caution whilst driving or operating machines during treatment with apomorphine. Haematology tests should be undertaken at regular intervals as with levodopa with given concomitantly with apomorphine. Pathological gambling, increased libido and hypersexuality have been reported in patients treated with dopamine agonists, including apomorphine. **Side Effects:** Local induration and nodules (usually asymptomatic) often develop at subcutaneous site of injection leading to areas of erythema, tenderness, induration and (rarely) ulceration. Pruritus may occur at the site of injection. Drug-induced dyskinesias during "on" periods can be severe, and in a few patients may result in cessation of therapy. Postural hypotension is seen infrequently and is usually intransient. Transient sedation following each dose of apomorphine may occur at the start of therapy, but this usually resolves after a few weeks of treatment. Nausea and vomiting may occur, particularly when APO-go treatment is initiated, usually as a result of the omission of domperidone. Neuropsychiatric disturbances (including transient mild confusion and visual hallucinations) have occurred during apomorphine therapy and neuropsychiatric disturbances may be exacerbated by apomorphine. Positive Coombs' tests and haemolytic anaemia have been reported in patients receiving apomorphine and levodopa. Local and generalised rashes have been reported. Eosinophilia has occurred in only a few patients during treatment with apomorphine HCl. Patients treated with dopamine agonists, including apomorphine, have been reported as exhibiting signs of pathological gambling, increased libido and hypersexuality (especially at high doses). Apomorphine is associated with somnolence. Breathing difficulties have been reported. *Prescribers should consult the Summary of Product Characteristics in relation to other side effects.* **Presentation and Basic NHS Cost:** Apo-go ampoules contain apomorphine hydrochloride 10mg/ml, as follows: 20mg in 2ml – basic NHS cost £37.96 per carton of 5 ampoules. 50mg in 5ml – basic NHS cost £73.11 per carton of 5 ampoules. APO-go opens (disposable multiple dosage injector system) contain apomorphine hydrochloride 10mg/ml, as follows: 30mg in 3ml – basic NHS cost £123.91 per carton of 5 pens. APO-go Pre-filled syringes contain apomorphine hydrochloride 5mg/ml, as follows: 50mg in 10ml – basic NHS cost £73.11 per carton of 5 syringes.

References: 1. Pietz K, Hagell P, Odin P, 1998. Subcutaneous apomorphine in late stage Parkinson's disease: a long term follow up. *J Neurol Neurosurg Psychiatry*. 65:709–716. 2. Lees A, Turner K, 2002. Apomorphine for Parkinson's Disease. *Practical Neurology*, 2:280-287. 3. Deleu D, Hanssens Y, Northway M G, 2004. Subcutaneous Apomorphine: An Evidence-Based Review of its Use in Parkinson's Disease. *Drugs Aging*, 21(11), 687-709. 4. Ellis C, Lemmens Get al 1997. Use of Apomorphine in Parkinsonian Patients with Neuropsychiatric Complications to Oral Treatment. *Parkinsonism & Related Disorders*, 3 (2), 103-107.

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tions for choice of anti-depressant medication type. Perhaps most interestingly, it seems that 11C-PIB PET imaging can detect differences in amyloid deposition between patients with PD +Dementia (PDD) and Dementia with Lewy Bodies (DLB) and this too may eventually have implications for treatment with e.g. γ -secretase blockers. In line with this, Glenda Halliday showed that in her post mortem series, amyloid plaques occur in both AD and DLB but not in PDD until much later.

Therapy

A press release one week prior to the conference regarding the positive results of the ADAGIO delayed start trial of Rasagiline as a possible neuroprotective treatment in early PD raised expectations of a major announcement. The drug is already licensed as symptomatic monotherapy or add on therapy at several stages of PD. However even in the pharmaceutical sponsored sessions, all discussion focussed on critique of the different types of design and analysis of trials of neuroprotective therapies. The main criticisms of the delayed start approach include the effects of differential dropout due to symptomatic effects and the differential effects that may occur depending on the absolute UPDRS scores at baseline, i.e. an interaction between symptomatic effect and severity. The message seems to be that neuroprotection is a difficult claim to prove, but despite this there is growing evidence that earlier treatment of PD may benefit patients regardless of the underlying mechanism.

Matthew Stern suggested that patients ought to be on multiple treatments even in the early stages of PD based on a recent publication suggesting a lower risk of LID among patients on L-dopa who were supplemented with slow release Ropinirole rather than having increasing doses of L-dopa. Anthony Schapira suggested that early treatment of patients with PD allows favourable plastic changes to take place and this may be the mechanism underlying the 'neuroprotective' effects seen in delayed start trials such as TEMPO and ADAGIO. To support the possible relevance of plasticity to PD, he showed experiments of an animal model of PD that used immobilisation of normal limbs to force the animals to use their parkinsonian limbs, leading to restoration of normality and upregulated VMAT2 binding on neuroimaging. In contrast, immobilisation of their affected limbs led to worse outcomes for the animals. With relevance to the subject of inter-individual variation in disease progression, the under-explored role of pharmacogenetics was discussed by Olivier Rascol in a talk on tailoring therapy to individual patients. Of proven relevance is the DRD2 polymorphism on dyskinesia risk, with other candidates including the other dopamine receptor polymorphisms DRD1-5, DAT, COMT, MAO-B, CCK, hypocretin, and APOE. However, in all likelihood multiple genes will be relevant, and he suggested that, in the future, whole genome screening of genes that influence response to treatment should be considered.

The non-motor aspects of PD were also discussed including suggestive but not unequivocal data of benefit from modafinil in management of excessive daytime sleepiness in PD, and a study in press of a 6 point improvement in Epworth scores from the use of sodium oxybate which currently is a licensed therapy for narcolepsy. While rivastigmine is licensed for the treatment of the dementia associated with PD, the maximum benefit seems to occur among patients with hallucinations, since this group appears to decline particularly quickly without treatment. Although there is an ongoing study of the use of memantine in PDD and DLB, there is insufficient evidence currently to recommend its use. (Editor's note: A small double-blind trial of memantine in PDD from the UK, presented as a poster, failed to show significant benefits, although this could simply reflect a type II error.)

Robert Gross reviewed the beneficial effects and limitations of deep brain stimulation (DBS) of the subthalamic nucleus (STN-DBS) for PD and the need to search for new targets to help the axial and dopa unresponsive symptoms. There are ongoing trials to compare further DBS of the STN and the globus pallidus pars interna (GPI) to help explore the benefits and risks of medication reduction afforded by STN DBS and the safety with respect to cognitive or behavioural side effects with GPI DBS. There are mixed expectations from the use of pedunculopontine nucleus (PPN) stimulation, which has been shown to benefit L-dopa unresponsive symptoms such as postural instability and gait freezing in centres in Bristol, Toronto and Rome. Bilateral stimulation

is probably more useful than unilateral but there is possibly a wearing off effect, and in reality there are many questions remaining that require double blind trials to answer. As with STN-DBS the benefits seem to relate to removal of pathological oscillatory activity. Stimulation of the CM/Pf nucleus of the thalamus (which has a pathway back to the striatum) can also lead to inhibition of GPi and thus increased basal ganglia output, and there is animal work and early human studies suggesting that the addition of CM/Pf stimulation to GPi stimulation improves both freezing and involuntary movements. There appears to be an intra-target difference in the mechanisms through which DBS exerts its effects, whether inhibitory, excitatory and whether axons are 'en passant' adjacent to the electrode contacts. Expansion into these new targets will likely characterise the next decade of functional neurosurgery for PD.

Cell-based and gene therapies were reviewed by Warren Olanow. He highlighted again the subgroup analysis of PD patients with UPDRS scores less than 49 at baseline who had received foetal transplants some years ago and did show significant improvements, as did the younger subgroup of patients seen in the Curt Freed trial, and he commented that future trials of transplantation are being considered for these subgroups. The off-medication dyskinesias occurring in 50% of transplanted patients which affected lower extremities and coincided with the presence of parkinsonism in other body regions, were presumably due to hot spots within the transplanted graft or perhaps were akin to biphasic dyskinesia due to suboptimal DA replacement or non-physiological replacement of dopamine. In a single patient it appears that alpha synuclein and thioflavin-staining Lewy bodies and neurites are seen within the grafted cells (which themselves are chronologically only 13 years of age) i.e. implanted cells seem to also be affected by the PD process. This observation is potentially hugely instructive in the mechanisms underlying Lewy body formation and PD pathogenesis.

Gene therapy techniques rely on appropriate choice of the therapeutic gene to be expressed, the target within the brain and the viral vector, but have been shown to have persistence of expression, safety and efficacy based on early clinical trial data. Both the AAV2 virus and one of the lentiviruses are being used, as there is good data to suggest they are not pathogenic in humans but can infect the target neurons. They are not thought to induce an inflammatory response in humans. These viruses are being used in open label trials to deliver neurturin - an analogue of GDNF into the striatum, or the GAD enzyme into the STN, or a combination of three dopamine related genes in the ProSavin trial. Initial safety studies have shown few or no adverse effects, and improvements in UPDRS off medication scores. Delivery of neurturin currently requires 4 needle tracks into the striatum and therefore will be associated with potential surgical problems. Inevitably there will be some time before theoretical concerns regarding the unregulated growth of virus, immune reactions, fears of unanticipated side effects are allayed together with uncertainty

regarding how gene therapy will benefit the non-motor features of PD. In the future the 'gene de jour' (Dr J Kordower) may be DJ1, parkin or PINK1 as they all appear to be neuro-protective when over-expressed.

Restless legs syndrome

There have been genetic discoveries in restless legs syndrome (RLS) and periodic limb movements in sleep with association of several genetic SNPs in the BTBD9 gene (associated with lower iron stores) with populations with both RLS and PLMS in a dose dependent manner i.e. the more kicks per hour the stronger the association. Estimates suggest that this gene is responsible for ~50 % of cases of RLS. While this seems to be important in Europeans, with ~50% of affected individuals being homozygous for the at risk polymorphism, the finding of RLS in African populations should prompt a search for another (more likely metabolic) cause for their symptoms.

An analysis of the evidence underpinning the treatment of RLS by Claudia Trenkwalder is about to be published in *Movement Disorders*. Levodopa can be helpful for the first few hours of sleep but kick counts in the latter parts of the night become identical to placebo. Doses of 2mg Ropinirole, 0.75mg Pramipexole or 2mg Rotigotine are efficacious for a more prolonged period, however it seems that there is an optimal level of dopaminergic stimulation and too high a dose in some patients can exacerbate symptoms. There are no trials to support the use of benzodiazepines, and oral iron supplements are only of use in patients who are substantially iron deficient, whereas low grade opioids, gabapentin, some of the other anti-convulsants and clonidine have evidence to support their efficacy and are useful second line agents but may be limited by side effects.

Dystonia

The DYT-1 gene, which encodes the torsin A protein, is autosomal dominant but has a penetrance of only ~30%. Alberto Albanese reviewed studies of individuals positive for the DYT-1 gene but not manifesting dystonia, who nevertheless show subtle physical abnormalities and abnormal motor plasticity when tested in the laboratory with transcranial magnetic stimulation. Paolo Calabresi discussed the recent functional imaging evidence showing excessive activity in globus pallidus and putamen in dystonia, and microstructural changes revealed by DTI imaging. He presented the evidence from both animal models and human subjects also, showing that dystonia seems to be associated with abnormally long term potentiation/ plasticity.

Susan Bressman reviewed the range of phenotypes and endophenotypes (patients with subclinical disease features) associated with DYT1 dystonia. Although these patients usually present in the first few decades as a generalised dystonia, they can rarely present late and remain focal, particularly among Ashkenazi Jews. She also presented comparisons of non-manifesting gene carriers to healthy controls finding abnormalities on FDG PET scans, D2 receptor binding, abnormal DTI, abnormal

motor sequence learning (absence of cerebellar activation and decreased prefrontal activation) and differences in neurophysiological measures of cortical inhibition. Depression can occur early and also seems to be part of the endophenotype. She presented evidence of an interaction between the DYT1 GAG deletion and another genetic polymorphism which appears to reduce torsin A expression. Seemingly, manifestation of dystonia in DYT1 carriers is only 3% in carriers of one allele compared to 35% with the other.

Aside from those few patients with Wilson's disease and dopa responsive dystonia in whom medical therapies are very beneficial, the only class A evidence of efficacy of oral treatments for dystonia is of a moderate benefit from anticholinergics. Impact of treatments on dystonia need to be measured against the impact on QOL, and the most significant improvement in QOL is from treatment with Botox for cervical dystonia in the long term. We heard that in addition to the effect of Botox on ACh release from motor synapses, among patients with focal dystonia or post stroke, injection of Botox can reduce feedback from intrafusal fibres which in turn may reduce the sensory drive to the dystonia. Benefits for cervical dystonia from the use of Botox persists for more than 10 years in 60% of patients.

A task force has been set up to review the literature and publish guidelines regarding the use of DBS for dystonia similar to the previous special issue focussing on DBS for PD – the main questions are how to optimally programme the implantable pulse generator (IPG), how to alter medication, including Botox, post operatively, how commonly are adverse effects occurring, what happens to non-dystonic extremities and when to change the IPG battery. There are published results in more than 250 patients with GPi DBS for primary generalised dystonia with improvements in motor scores between 40-91% and accompanying improvements in QOL that persist long term. Positive results have also been seen in focal, segmental, tardive and some secondary dystonias.

Ataxia

Thomas Klockgether described how histone deacetylase (HDAC) inhibitors can reduce Frataxin mRNA expression and are now being tried in phase 1 clinical trials in the treatment of Friedreich's ataxia. Other investigators have shown that mutated frataxin reduces iron-sulphur clusters which in turn decreases the activity of complexes 1-3 of the mitochondrial respiratory chain. Idabenone has a dose dependent effect on ataxia through its effects on this pathway. Treatment of the spinocerebellar ataxias is at a less advanced stage but it seems that polyglutamine repeats common to many of the SCAs lead to both a gain of a toxic protein complex and loss of a protective protein complex, and potential treatment avenues are being discovered. There may be a therapeutic benefit from either Rapamycin or perhaps even Lithium, based on animal models of SCA (Editor's note: the scientific rationale for the use of lithium in this context is not entirely clear).

Chorea

Phenocopies of Huntington's Disease are characterised by a combination of chorea, dystonia, parkinsonism, cognitive disturbance and psychiatric disturbance. Sarah Tabrizi presented cases of her favourite HD phenocopies. HDL-2 should be considered early in black South Africans with chorea, which is caused by mutated junctophilin-3 function, a calcium channel sensor and associated with ubiquitin positive inclusions at post mortem. HDL-4 due to SCA17 has similar motor impersistence of tongue protrusion and eye movements, poor saccadic initiation but more ataxia than usually seen in HD. Neuroferritinopathy has chorea at onset in 50% but normal eye movements, and cognitive dysfunction only in the late phases, in contrast to HD, serum ferritin levels are low, there is iron deposition in the basal ganglia and occasionally the eye of the tiger sign can be seen on MRI. Varying mutations in the prion protein can also cause chorea seen in vCJD and associated with psychi-

atric symptoms, ataxia, and myoclonus at presentation. From her series of HD phenocopies, and somewhat despairingly, it seems that if HD gene tests are negative, then 97% of patients will never receive a genetic diagnosis, and of the remaining 3%, SCA17 is the most common positive finding.

Myoclonus

The contribution of Queen Square and particularly David Marsden to our understanding of myoclonus and its origins were discussed by Jose Obeso, followed by recommendations for treatment with various anti-convulsant medications and often the need for polypharmacy. Myoclonus dystonia with epsilon sarcoglycan mutations is one of the few causes of myoclonus of subcortical origin and should be considered if neurophysiology suggests that a myoclonic disorder has a basal ganglia origin.

A highlight of the conference was the video Olympics that was hugely entertaining as the 'expert' panel were invited to comment on excel-

lent cases of movement disorders that included – cerebrotendinous xanthomatosis, secondary hyperekplexia and cardiac pacemaker-driven abdominal myoclonus. There was a sense of pleasure in watching the panel publically struggle with these esoteric phenomena. There were over 1200 posters presented during the week in ample space at the venue, and there were the usual controversies and 'how to do it' workshops. Lifelong honorary membership to the society was awarded to Mahlon Delong and Alim Benabid for their contributions to the understanding and treatment of Movement Disorders. As the size of the MDS meeting continues to grow, the society is clearly flourishing and hopefully is on the brink of several important breakthroughs in the treatment of common movement disorders – Let's see what is announced next summer in Paris....

Tom Foltynie, Senior Lecturer & Honorary Consultant Neurologist, National Hospital for Neurology & Neurosurgery, London, UK.

Federation of the European Neurosciences Societies Forum

12-16 July, 2008; Geneva, Switzerland.

The Swiss Society for Neuroscience was honored and privileged to host the sixth Forum of the Federation of the European Neurosciences Societies (FENS) from July 12th to 16th, 2008 at the Palexpo Congress Center in Geneva. This biennial congress is the largest European event in the field of Neurosciences and attracted 5300 scientists, clinicians, and decision makers, mainly from Europe, but also from North America, Japan, and Australia. Previous FENS meetings have been held in Berlin, Brighton, Paris and Lisbon and have had a strong resonance in the respective countries. The purpose of the FENS Forum is to foster research and education in neuroscience by strengthening the links between the 33 national and supranational societies that make up the federation. At this meeting, more than 400 travel stipends were offered by FENS, IBRO, SfN and member societies.

The format of the meeting consisted of nine plenary lectures given by the world's outstanding neuroscientists, 56 symposia highlighting recent progress in all areas of neuroscience, and 3700 poster presentations, giving senior and young

scientists the opportunity to present and discuss their work with their peers. In addition, ten satellite meetings took place shortly before the main congress. The FENS Forum has also become the opportunity for presenting prestigious Awards funded by private Foundations and commercial companies. These awards bring outstanding contributions of young scientists to the attention of the public and serve to promote their future career in research. Finally, a rich social program fostering interactions between participants, sponsors and officers of the FENS societies took place. One of the outstanding social events was organised by the students of the Lemanic doctoral school; they provided three evenings of entertainment for young scientists at the Lakeside of Geneva, a beautiful site that is ideally equipped for social gatherings during the summertime. For more information on these events, please visit our website (<http://fens2008.neurosciences.asso.fr>).

The city of Geneva has a long tradition in holding summits of prime political, economic and scientific importance and was an ideal location for a successful FENS Forum. The city

offered everything needed to accommodate and entertain the 5300 participants and accompanying persons. Geneva is very attractive for its rich history, vibrant cultural scene, and prime quality of life. An additional major asset of Geneva is its central location, easy to reach from anywhere in Europe.

An international program committee, chaired by Eckart Gundelfinger, University of Magdeburg, was nominated by the FENS council to ensure a balanced representation of major research areas in basic and clinical Neuroscience, thereby maximising the impact of the Forum. The local organising committee was chaired by Ann Kato, University of Geneva, and was formed by officers of the Swiss Society for Neuroscience and pre-eminent researchers from all major Swiss universities. Everyone who participated esteemed that the Congress was a huge success. Please note in your diaries that the next FENS Forum will be held in Amsterdam from July 3rd to 7th, 2010.

Professor Ann Kato, Chairman of the Local Organising Committee (Swiss Neuroscience Society).

INVITATION TO A MEETING

9th Annual UK Movement Disorders Meeting

**Friday 10th and Saturday 11th October 2008
Near Chester, UK**

Chaired by **Professor Anthony Schapira**

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The Clock over the Eastgate entrance to the city of Chester

International Conference on Alzheimer's Disease (ICAD)

26th-31st July 2008; Chicago, USA.

Since its inception 20 years ago, when 300 delegates attended a meeting in Las Vegas, the International Conference on Alzheimer's Disease has grown dramatically, reflecting the increasing interest in this field. Over 5000 delegates attended this 11th congress, at the Lakeside Center in Chicago, adjacent to the shores of Lake Michigan, and such is demand and progress that the congress will henceforth be an annual, rather than biennial, event.

With over 2000 abstracts, clearly no summary report can do more than scratch the surface, and for this reason this article will focus exclusively on therapeutic issues. This is not to belittle in any way the developments in neuroimaging, biochemistry and genetics which featured significantly during the congress, but the ultimate aim of all these might fairly be said to be the successful treatment of AD, which still seems elusive (e.g. *Los Angeles Times*, 28/07/08: F1, F4).

The prize for the most headlines garnered in press and TV must go to the report on the use of a new drug, methylthioninium chloride (MTC), trade name Rember, presented by Claude Wischik (Aberdeen). This drug dissolves tau paired helical filaments (PHF) and prevents aggregation of tau molecules in animal models, and hence is the first specific tau aggregation inhibitor to reach clinical trials, a personal triumph for Wischik, who first characterised tau as the principal component of PHF some 20 years ago.¹ In a trial conducted in the UK and Singapore, oral MTC improved outcome (ADAS-Cog) relative to placebo over 24 weeks and stabilised disease progression over 50 weeks, suggesting a disease-modifying, rather than simply a symptomatic, effect. These promising data mandate further trials, the outcomes of which will be awaited with great anticipation by clinicians, their patients and carers.

The fact that the burden of tau pathology correlates better with clinical markers of dementia than amyloid pathology has always been a thorn in the side of the dominant, but not exclusive, hypothesis of AD aetiology, namely the amyloid hypothesis, wherein amyloid is understood to mean peptides in their soluble ($A\beta$) or oligomeric forms, rather than the amyloid aggregates visible as plaques in brain tissue. Experimental therapies targeting amyloid have been with us for some time, most notably the $A\beta$ vaccine. Follow-up of a phase 1 study of the Elan AN1792 vaccine (not the ill-fated 201

study which was halted because some patients developed meningoencephalitis) found neuropathological evidence for amyloid clearance in patients coming to post-mortem, but no overall improvement in survival or time to severe dementia (Nicoll, Southampton).²

A problem with this active immunisation/vaccine approach is that it may take up to 6 months to develop anti-amyloid antibodies, a problem which may be circumvented by passive immunisation. Bapineuzumab, Elan-Wyeth's humanised monoclonal antibody raised against the N-terminus of $A\beta$, was reported to be safe in a phase 2 study. Although not powered for efficacy, the data suggested clinically favourable results in ApoE4 negative patients. A phase III trial is getting underway.

Despite the recent setbacks with other possible anti-amyloid treatments, such as tarenfluril /Flurizan³ and alzemed / tramiprosate,⁴ there may be other candidates to examine. Antihypertensive medications may have effects on $A\beta$, for example carvedilol apparently prevents oligomerisation, and valsartan lowers brain $A\beta$ activity (Pasinetti, New York), interesting findings in view of the fact that vascular factors are risk factors for the development of AD, and treatment of these factors has been reported in some studies to prevent the development of disease. Certain NSAIDs have long been known to alter $A\beta$ metabolism (Weggen, Dusseldorf), and even the proton pump inhibitors may reduce $A\beta$ production (Takeda, Osaka). Development of any of these drugs as AD therapies might be quicker than is the case with novel drugs since their side effect profiles, pharmacodynamics and drug interactions are already well understood. Statins, which may affect $A\beta$ through interactions with cholesterol, have also been examined: a placebo-controlled trial of simvastatin in AD patients (Sano, New York) proved robustly negative on all outcome parameters.

Thiazolidinediones (TZDs), PPAR-gamma agonists, may improve brain insulin sensitivity in AD (Craft, Seattle), and trials have suggested some benefit with rosiglitazone in ApoE4 negative patients.⁵ Thiadiazolidinediones (TDZDs) are inhibitors of glycogen synthase kinase-3 (GSK-3), an enzyme thought to be important in tau phosphorylation and the initiation of tau pathology. TDZDs have been proposed as small molecules which might target tau, $A\beta$, and neurodegeneration simultaneously (Martinez,

Madrid).

Dimebon has emerged as the surprise package in AD therapy in recent months: a non-selective antihistamine used in Russia for many years, a trial has now reported efficacy in the treatment of AD.⁶ Evidence was presented at ICAD that dimebon does not act as a cholinesterase inhibitor (ChEI), nor is its activity likely to be mediated by NMDA receptors, but it enhances mitochondrial function in the context of cellular stress, as well as being a low potency 5HT₆ receptor antagonist. Hence this drug may not be selective simply for AD, but might find a role in Parkinson's disease and disorders characterised by mitochondrial dysfunction.

Despite these many new therapeutic possibilities, the current neurotransmitter-based therapies (ChEI, memantine) are far from obsolete (Frolich, Mannheim): their modest but consistent effects may be required in established disease, including severe disease, although it is now clear from recent trials that both rivastigmine⁷ and galantamine,⁸ like donepezil, do not slow progression from MCI to AD.

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Chicago skyline courtesy of Tom Foltynic.

