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Professor Nils Erik Gilhus, Norway: Professor of Neurology at the University of Bergen and Haukeland University Hospital.

E-MAG Active – Limbless Association award

Otto Bock Healthcare has received an award for 'Prosthetic or Orthotic Product Innovation' from The Limbless Association for E-MAG Active, a newly launched electronically controlled knee-joint system.

E-MAG Active enables patients with partial or complete paralysis as a result of stroke to achieve a natural, smoother gait pattern when walking. Users are therefore able to maximise mobility and benefit from improved quality of life.

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Gaynor Norris, Marketing Manager at Otto Bock Healthcare, receiving the 2009 Limbless Association award for 'Prosthetic or Orthotic Product Innovation' for E-MAG Active.

New ways to produce dopamine cells for studying Parkinson's

Prof Matthew Wood at the University of Oxford has been awarded a 12 month innovation grant of £35,000 from Parkinson's UK, to develop a ready supply of the dopamine nerve cells needed for research into a cure. Producing nerve cells from stem cells is complex and the current success rate is low. However, molecules called microRNAs can direct the way cells develop and one known as miR-124a specifically helps dopamine cells. People with Parkinson's typically have less miR-124a than others do. The team will investigate whether miR-124a will improve results. They'll also search for other microRNAs that might push stem cells in the right direction.
For more information see www.parkinsons.org.uk

Prof John Duncan appointed as NIHR Senior Investigator

Professor John Duncan (Institute of Neurology, London) has been appointed as a National Institute for Health Research (NIHR) Senior Investigator. Senior Investigators are NIHR's most pre-eminent researchers and include some of the nation's most outstanding leaders of patient and people based health and social care research.

Prof Chris Frith awarded 2009 Fyssen International Prize

Professor Malcolm Grant, President and Provost of UCL said, " This is a truly exceptional achievement. Fyssen is a French Foundation that promotes scientific inquiry into the cognitive mechanisms, including thought and reasoning, which underlie animal and human behaviour; their biological and cultural bases, and phylogenetic and ontogenetic development. Its prize is awarded annually to a scientist who has conducted distinguished research in the areas supported by the Foundation such as ethology, paleontology, archaeology, anthropology, psychology, epistemology, logic and the neurosciences. The Foundation offers a range of research grants and post-doc study grants, but only one prize."

Prof Andrew Lees awarded the First Lord Brain Memorial Lecture

'Brainwashed by the Black Stuff'' will be delivered at the Royal London Hospital on June 24th at 5pm. Professor Lees is an alumnus of the Royal London and the lecture will be introduced by Professor John Hardy.

Inauguration of Prof Gérard Said as President of the ENS

Professor Gérard Said of Paris, France, President-elect of the ENS, will assume office in a ceremony on Monday, 21 June 2010, during the 20th Meeting of the ENS. The inauguration as President will take place at the International Congress Center of Berlin prior to the start of the Presidential Symposium of this Meeting. Professor Said succeeds Professor José Ferro of Lisbon, Portugal, as President of the Society, and will occupy the office of President until the next Meeting of the European Neurological Society convenes in Lisbon, Portugal, on 28-31 May 2011.

CONTENTS

MAY/JUNE 2010

Cover Photograph: Francis Lees, and Nathan Doidge (seated) –
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The younger generation have provided the review articles for this issue of ACNR – Adam Cassidy from Newcastle writes about focal dystonia and Mike Zandi on the neuropsychiatry of SLE.

In the first of the review articles, Mike Zandi explores the neuropsychiatric features of lupus and highlights the difficulty in knowing what this means in terms of clinical features and the problems this creates for diagnosis and treatment. For anyone who has seen such patients this dilemma is a real one, and Mike offers helpful advice on how to approach this issue.

Adam Cassidy discusses the pathophysiology of idiopathic focal dystonia and explores the basis of the sensorimotor cortical reorganisation of body parts that seems to lie at the heart of this condition. This discussion also draws in the basal ganglia which feed out into these cortical regions, and by so doing contribute to the development of this movement disorder. This article is a very interesting and stimulating account of idiopathic focal dystonia, as it attempts to knit the different strands of evidence into a unifying pathophysiological model for this condition.

In the Rehabilitation article, Fitness to Fly by Michael Bagshaw takes us through the physics of flight in terms of partial pressures of oxygen, before going on to discuss relevant issues relating to pilots, cabin crew and passengers. This clearly written account is very helpful, not just in better understanding what happens when one flies oneself, but also helps in advising others, including patients with neurological problems.

Andrew Larner introduces us to Trevor, a right hand with a functional movement disorder. In this short article, Andrew describes the personification of neurologically affected limbs which has its origins in the writings of Macdonald Critchley.

How do you investigate a child with developmental delay or an adult with a neurological problem in which this was a feature of their history? Angharad V Walters tells us how to approach this problem and the likely causes in the next article in the series on Paediatric Neurology edited by Anna Maw.

One of the most successful recent series in ACNR has been the one edited by Boyd Ghosh on academic neurology and how one can engage with it at all levels of medical training. This series sadly comes to a conclusion in this issue, but ends in style with a feast of very helpful articles by a range of authors including an overview of academic neurology past, present and future by the current ABN President, Alastair Compston.

Continuing in this theme, one of the most outstanding clinical scientists in Neurology of the late 20th century was the late David Marsden – a man who published a paper on average every 12 days of his professional life! For those of us who were fortunate enough to know him and be taught by him, he was inspirational and encyclopaedic in his knowledge, but to me his greatest attribute was his ability to listen and learn from others regardless of "rank", always striving to know and understand more about how the brain works in health and disease. We are therefore very fortunate to have a personal account on David Marsden written by someone who spent many years working (and drinking) with him – Niall Quinn – and which is a real testament to an extraordinary man.

Not that many may know of the Dancing eyes syndrome, but this rare condition can strike early in life sometimes in the context of neuroblastomas. This devastating condition causes opsoclonus and myoclonus and results in significant disability including ataxia, behavioural and cognitive deficits. Mandy Caunter, in our Personal Perspectives section, describes the journey she has made with her daughter Ellie Marie who was to develop this condition in 2000 just after she was one-year-old. This is a moving account of the struggles of diagnosis and the long term consequences that such disorders cause within the developing CNS.

Finally, as the general election comes closer, Heather Angus-Leppan calls us to be more active and get involved with the ABN so that we can all play our part and influence what No10 does about neurology and our health service post May 6th.

Finally, we have our usual reviews, as well as a Supplement for the forthcoming ENS meeting in Berlin in June. We hope you enjoy this new issue of the journal. ◆
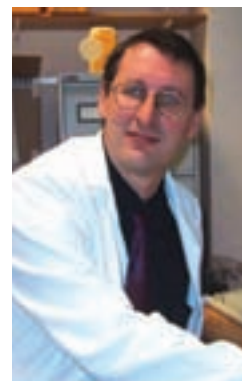
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Advances and Challenges in Neuropsychiatric Systemic Lupus Erythematosus

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Systemic lupus erythematosus is a common autoimmune disease (4.71 per 100,000 age-standardised incidence in the UK in the 1990s),[1,2] and many lupus patients have heterogeneous neurological and psychiatric symptoms (collectively termed neuropsychiatric or NP 'events'; see table) at some point in their lives. But is this neuropsychiatric lupus (NPSLE), and is NPSLE one, two or many diseases? Research criteria and attempts at classification of NPSLE have been overly inclusive, which has set back the field.[3] For example, in these criteria, headache is generally attributed to lupus and is the most common manifestation, but careful analysis of published data shows no association between headache and lupus.[4] Underpinning the clinical hetereogeneity is pathological heterogeneity. I shall argue that it is useful to split the pathology into two groups. First, symptoms and signs due to antibody-mediated and inflammatory pathology, and second, collectively, the rest: cerebrovascular disease, low mood, anxiety, migraine, or functional symptoms (of course, this second group has a natural divide between vascular disease and the others). The latter collective group is far more prevalent, and the distinction between groups important because of treatment implications. Cerebrovascular disease is arguably the most important manifestation of NPSLE, but requires conventional preventative therapy, and is not likely to respond to immunotherapy. In contrast, antibodies or inflammation may cause some forms of myelopathy, psychosis, seizures and epilepsy, and thus immunosuppression may work (although with which drug is as yet unclear). Thus, we need markers to distinguish between these two groups, as such an aetiological classification is likely to prove more useful in diagnosis and therapy than a neuroanatomical one.

Recent modifications to the 1999 American College of Rheumatology criteria for NPSLE have moved the criteria forward in this regard (summarised in the table). In these modifications, laid out by the Systemic Lupus International Collaborating Clinics (SLICC) group, neurological symptoms and signs are attributed to or not to lupus on the basis of severity, exclusion of mimics and temporal relation to lupus diagnosis (without acknowledgment of aetiology).[5,8] This already cuts a 40% prevalence of NPSLE to 13% using the most stringent criteria in the largest prospective study, but more needs to be done.[8] In this brief review I shall summarise the current understanding of the pathogenesis of NPSLE, progress in the search for markers of immunotherapy-responsive forms, and the evidence base for therapy. The figure below gives a timeline of selected clinical and immunological advances.

Pathogenesis

Let us consider lupus generally and then NPSLE. Lupus, like multiple sclerosis, is a complex genetic trait. Genome wide association studies have started to add risk loci to multiple regions within HLA, complement components and other genes already known to confer risk.[9] A current model is of multiple paths to lupus, with a general 'compromise' of innate and adaptive immunity.[10] A critical number of 'hits' may be required before disease develops. There are defects in clearance of apoptotic cellular debris; activation of innate mechanisms which sense DNA and other nuclear material; and B and T cell over-activity.[10] For CNS disease, rare monogenic forms of lupus with striking CNS associations may provide clues. Inherited complement component C1q deficiency is rare but associated with a severe CNS vasculitis, the mechanism of which is uncertain.[11] There are many reports of antibodies in lupus sera binding to neurons *in vitro*.[12] The rare childhood encephalopathy Aicardi-Goutières Syndrome is due to mutations in the gene for DNA three prime repair exonuclease 1, *TREX1*, and is associated with high CSF levels of interferon-alpha (IFNα) and serological markers typical of lupus.[13] This, together with the type 1 IFN peripheral blood signature seen in active lupus,[14] and a lupus-like cognitive syndrome seen in patients with Hepatitis C or melanoma treated with IFNα,[15] provides sufficient support for a study of the role of IFNα in CNS lupus. Antibodies and cytokines may therefore have a role in the pathogenesis of some forms of NPSLE. See the figure for a summary of animal models which support this.

Pathological and serological studies show that ischaemia is the main pathology, but less common antibody mediated mutations also exist. The neuropathological studies from the 1970s and 1980s paint a picture of vasculopathy, infection, and infarction - with vasculitis a rarity.[16,21] Other studies, limited generally by the choice of control group, suggest that subcortical, white matter lesions (see later) are linked to the cognitive deficits of lupus, and associated with sustained

Figure: Timeline of selected clinical (top) and immunological (bottom) developments.
Abbreviations. ACR, American College of Rheumatology. BAFF, B cell activating factor. BLISS-52 and -76, A Study of Belimumab in Subjects With Systemic Lupus Erythematosus (52 and 76 week studies). BLK, B lymphoid tyrosine kinase gene. CNS, central nervous system. EXPLORER, A Study to Evaluate the Efficacy and Safety of Rituximab in Patients With Severe Systemic Lupus Erythematosus. ITGAM, integrin alpha M. lpr, lymphoproliferation gene. LUNAR, A Study to Evaluate the Efficacy and Safety of Rituximab in Subjects With ISN/RPS Class III or IV Lupus Nephritis. MRL, murine lupus. NPSLE, neuropsychiatric lupus. NZB/NZW, New Zealand Black/New Zealand White. NZM88, New Zealand mixed strain 88. RCT, randomised controlled trial. STAT4, signal transducer and activator of transcription 4 gene. TNFAIP3, tumor necrosis factor alpha-induced protein 3 gene. TREX1, three prime repair exonuclease 1 gene. References are not given due to space limitiations.

and high titre cardiolipin antibodies (which are not specific to CNS disease).[22,23] Atherosclerosis is accelerated in lupus.[24] Vascular damage may well account for many neurological symptoms, especially in long-standing disease. But this is not the whole story. It is now well-accepted that myasthenia gravis,[25] and some forms of longitudinally extensive transverse myelitis (LETM) and recurrent optic neuropathy (aquaporin-4 antibody associated)[26] are associated with lupus. For the latter, aquaporin-4 immunity may explain some cases of myelopathy in lupus and Sjögren's. In a recent series, all six lupus patients with LETM and both of the two with recurrent optic neuritis possessed aquaporin-4 antibodies.[26] For common manifestations such as seizures (42% of 41 patients in a recent retrospective series from southwestern England and south Wales, in which visual failure and movement disorders were also prominent[27]), the pathology therefore may be ischaemic damage in the majority, but in some the same phenotype may be due to pathogenic antibody (see below).

Finding a marker of immunotherapy-responsive NPSLE

Antibodies hold the most promise as markers of forms of NPSLE, as SLE is characterised by their abundance. The discovery of aquaporin-4 immunity in lupus and Sjögren's disease has shed light on the nature of myelopathy in these conditions, which has yet to happen for other forms of NPSLE because no antibody has been found. Meanwhile, the evidence that antibodies to native forms of neuronal channels can cause various forms of encephalitis has been reproduced by several groups (See Vincent update, ACNR 10.1).[28] Studies of neu-

Table. Evolving research classifications of neuropsychiatric lupus (NPSLE)	
1. American College of Rheumatology (ACR) 1999 case definitions of neuropsychiatric lupus: the 'NP events'.[3] **Central nervous system** Aseptic meningitis Cerebrovascular disease Demyelinating syndrome Headache (including migraine and benign intracranial hypertension) Movement disorder (chorea) Myelopathy Seizure disorders Acute confusional state Anxiety disorder Cognitive dysfunction Mood disorder Psychosis **Peripheral nervous system** Acute inflammatory demyelinating polyradiculoneuropathy (Guillain-Barré syndrome) Autonomic disorder Mononeuropathy, single/multiplex Myasthenia gravis Neuropathy, cranial Plexopathy Polyneuropathy 'exclusions' and 'associations' for the above found here: http://www.rheumatology.org/publications/ar/1999/aprilappendix.asp (accessed 30 Mar 2010)	**2. Systemic Lupus International Collaborating Clinics (SLICC) attribution models, 2007.**[6] **strict model 'A'** 1. use ACR 'exclusions' and 'associations' 2. exclude cases which fall out of an enrollment window up to six months prior to diagnosis of SLE and up to 15 months after diagnosis 3. exclude "minor" neuropsychiatric events (Ainiala[5]): all headache, anxiety, 'mild' cognitive dysfunction (<3 domains), polyneuropathy unconfirmed by nerve conduction studies and electromyography. **modified model 'B'** As above, but a 10-year window prior to diagnosis of SLE is allowed, and use of ACR 'exclusions' but not 'associations'. **3. Published SLICC results so far:** **2008, antibody associations.** For 214 events in 133 of 412 patients (32.3%) (model A: 32/214, model B: 77/214), there was no strong association between NP events, however attributed, and anti-ribosomal P, DWEYS-NR2(see text), lupus anticoagulant(LAC), cardiolipin, and 2-glycoprotein I antibodies measured at variable times after the NP event. However, a suggestive signal exists for ribosomal P and psychosis, and LAC and cerebrovascular disease.[7] **2010, outcome.** For 843 events in 486 of 1206 (40%) patients (model A: 149/843, model B: 258/843), attributable events occur early and have a favourable outcome compared to non-attributable events. A therapeutic window?[8]

ropil encephalitis and variants have shown that cell surface antigens are the only ones likely to be clinically meaningful,[28] but in lupus the literature is full of intracellular targets with soft associations. A couple of candidates have come close. Antibodies to ribosomal protein subunits have been variably reported in lupus psychosis, and one group

has reported a novel neuronal surface antigen to which some of these antibodies cross-react, though this study has not been replicated.[29] Some lupus ds-DNA antibodies have been reported to cross react with a short peptide sequence, DWEYS, on the NR2a and NR2b subunits of the NMDA receptor (long before recognition of NMDAR encephalitis[30]), but rou-

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tine serological testing has not proved to be useful, due to lack of specificity.[7,31] Conversely, only one patient in the published data so far from patients with neuropil encephalitis, with AMPAR antibodies, has had lupus serology, namely dsDNA antibodies. But, this patient was not given a diagnosis of lupus and also had a thymic carcinoma, which was the probable driver of AMPAR antibody.[32] It is probably the strategies used by groups working on neuropil encephalitis, including proteomic approaches, that will discover cell surface antigens in lupus.[33]

What is the role of brain imaging? In a diagnostic work-up, brain imaging (and CSF examination) is done first to exclude other pathology, principally vascular or infection, including progressive multifocal leucoencephalopathy (PML) which was on the scene long before the biological therapeutics era.[34,35] Small white matter lesions in lupus are common, non-specific and may reflect ischaemic damage. One small study by Appenzeller in a Brazilian population revealed some correlation of such lesions (present in roughly half of the patients studied) in time with steroid dosage, cardiolipin antibodies, or previous neurological symptoms.[23] A few studies have revealed white matter atrophy and altered neurometabolic profiles on spectroscopy in patients with lupus, correlating with cognitive dysfunction.[36] So although imaging seems unlikely to offer a diagnostic test for immunotherapy responsive NPSLE, it has use in longitudinal follow up of vascular disease and in the detection of PML.

SLE as a differential diagnosis in neurology

SLE features among many lists of differential diagnoses in neurology, and the serological tests now available can be misleading. Antinuclear antibody (ANA) and double stranded DNA (dsDNA) antibody tests are both problematic. ANA is over-sensitive and positivity is common in the general population, in particular with increasing age. dsDNA antibody is much more specific for lupus but less sensitive, and absolute levels are not useful in monitoring response to therapy.[37] A good rule of thumb when faced with a discordant ANA result in a neurology clinic, without clinical features of systemic lupus, is to ignore it at first. Antiphospholipid syndrome (either primary or secondary to lupus) is an important diagnosis that can mimic multiple sclerosis, and the presence of sustained high titre phospholipid antibodies are useful in diagnosis.

Treatment

There is no clear evidence base for the treatment of NPSLE. However, to put this in context, neither is there a standard of care in lupus nephritis, which is more common and better studied. Achieving sustained remission with minimal steroid usage is the ultimate goal. There remains just one published randomised controlled study in NPSLE – a small study in which 18 of 19 patients treated with intravenous schedules of cyclophosphamide responded compared to 6 of 13 in the methylprednisolone group.[38] But, the case mix of NPSLE manifestations (mainly seizures, transverse myelitis and peripheral neuropathy) and the differences between the groups make firm conclusions from this study difficult to make. Well designed retrospective studies exist, and show that intensive immunotherapy is probably a good thing. The University College London group have reported 10 of 11 cases of lupus psychosis from a 485 patient cohort, in whom a variety of treatments including steroids, plasmapheresis, cyclophosphamide and azathioprine were used. Most of the patients had a good long term outcome with no recurrence, particularly if treated aggressively.[39] The best controlled studies of immunosuppression in lupus have been in nephritis, and support the use of low-dose-cyclophosphamide, azathioprine, and mycophenolate mofetil (MMF). Ten-year follow up data from the Euro-lupus nephritis trial reveals that low dose cyclophosphamide followed by azathioprine is effective at inducing and maintaining sustained remission.[40] MMF is probably as effective as cyclophosphamide in inducing remission in nephritis, but safer.[41]

B cell depletion therapy, with the monoclonal chimeric anti-CD20 antibody, rituximab, has had the most promising open label data in the last few years, for refractory lupus in particular. The drug appears effective in open studies of refractory severe NPSLE[42,43], but there have been no randomised controlled trials. Two phase III trials in which severe NPSLE was an exlusion criterion (EXPLORER,[44] all lupus; and LUNAR,

nephritis) have shown no increased efficacy of rituximab over conventional treatment. This could be due to inclusion of mild disease, fixed 'damage', and concomitant immunosuppression usage.[45] One should be alert to the risk of PML after rituximab, but this seems small.[35] Another B cell centred agent, belimumab, a monoclonal antibody which inhibits B-cell activating factor (BAFF), suffered similar negative results at phase II, but after rigorous trial re-design has recently had success (in all lupus, but again with CNS lupus excluded) in phase III studies, BLISS-52 and BLISS-76.[46] The consensus among rheumatologists who have led these studies is that trial design may have let rituximab down. But even the very basics of trial design in NPSLE have not yet been achieved.

So, having excluded infection and vascular pathologies, a pragmatic treatment approach is to use steroids, followed by plasmapheresis or intravenous immunoglobulin if the disease manifestation seems antibody-mediated (e.g. LETM, and possibly psychosis), for induction of remission,

and then azathioprine or MMF for maintenance therapy. Cyclophosphamide or rituximab are reserved for severe refractory disease. Warfarin is used for thrombotic events associated with the antiphospholipid syndrome, but the intensity and duration of therapy remains unclear.[47]

Conclusion

NPSLE is heterogeneous, and current classification criteria are misleading. We need a marker that distinguishes immunotherapy-responsive disease from ischaemic, infectious or other aetiologies. One marker exists for LETM and optic neuritis in lupus: aquaporin-4 antibodies. There is a small evidence base for therapy of NPSLE, which suggest, for carefully selected cases, initial treatment with steroids followed by MMF or azathioprine. Cyclophosphamide and rituximab are reserved therapies for severe refractory disease. ◆

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Pathophysiology of Idiopathic Focal Dystonia

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The term dystonia refers to a group of conditions in which sustained muscular contractions lead to abnormal posturing and repetitive movements.[1] The primary or idiopathic dystonias are non-degenerative conditions where dystonia (with the possible exception of a co-existent tremor) is the only clinical abnormality. Within this group are the focal dystonias in which dystonic movements of the eyelids (blepharospasm), neck (cervical dystonia), mouth and jaw (oro-mandibular dystonia), vocal cords (laryngeal dystonia) or hand (focal hand dystonia) develop in adulthood. Focal hand dystonia is often task specific, affecting fine, repetitive hand movements. The commonest forms are writer's cramp and musician's dystonia. This article will give a brief overview of the aetiology of idiopathic focal dystonia, concentrating on insights gained from neurophysiological abnormalities detected in patient studies.

Genetics

To date, no causative genetic mutations have been identified in late onset idiopathic focal dystonia. In those patients with a positive family history, inheritance is mostly complex and non-mendelian, although a small number of families with autosomal dominant inheritance have been reported. DYT4 has been described in a single family, with the majority of affected members presenting with laryngeal dystonia, which eventually becomes generalised.[2] No chromosomal locus has been identified. DYT7 was identified in a family with affected members displaying either cervical or focal hand dystonia.[3] Linkage analysis has mapped this condition to chromosome 18. The same locus has been implicated in a separate family with three brothers affected by writer's cramp.[4] DYT13 has been reported in a family with dystonia presenting in the head and neck or in the arms[5] and has been mapped to chromosome 22.[6]

A mutation within the DYT1 gene (torsin A) is the commonest identifiable cause of primary generalised dystonia. It most commonly presents in childhood with focal lower limb dystonia followed by generalisation, with a tendency to spare the head and neck.[7] However, there is a degree of phenotypic variability and mutations have been identified in patients with multifocal or segmental dystonia presenting as writer's cramp in both childhood and adulthood.[8] DYT6 is a more recently recognised form of generalised dystonia caused by mutations in the THAP1 gene on chromosome 8.[9] It typically presents in childhood or adolescence with focal onset dystonia of the head, neck or limbs and there is often generalisation. Frequent involvement of the cervical, laryngeal and cranial muscles differentiates this condition from DYT1. Again, there is wide phenotypic variability and it can present with late onset focal or segmental dystonia.[10]

The above points clearly demonstrate that a particular gene can be associated with a variety of forms of dystonia. This suggests that different forms of late onset focal dystonia share a common genetic background, and that the expression of a particular dystonic phenotype rests on the interplay between other genetic and environmental factors.[11]

Cortical reorganisation

Monkeys trained to carry out repetitive hand movements over many months can develop abnormal posturing reminiscent of focal hand dystonia.[12] Subsequent recordings from individual neurones in sensory cortex of these monkeys revealed enlarged receptive fields and overlapping representations of individual digits. This change in cortical representation is presumed to be because the maintenance of precise somatotopy depends upon the temporal and spatial separation of afferent inputs, which breaks down during unnaturally repetitive fine motor tasks.[13] Such movements are comparable with those required for hand writing or playing a musical instrument and similar abnormalities of cortical reorganisation have been demonstrated in patients with musician's dystonia.[14] It has been hypothesised that these enlarged receptive fields map inappropriately onto networks of neurones in the motor system and in doing so produce dystonic movements.[13]

Sensory overload from repetitive hand movements may well contribute to the development of focal hand dystonia. Given that painful stimuli[15] and peripheral nerve injury[16] are also known to produce abnormal cortical reorganisation, such forms of sensory overload could contribute to other types of focal dystonia. In keeping with this idea, case control studies have revealed an association between blepharospasm and ocular disease,[17] cervical dystonia and blunt neck trauma[18] and laryngeal dystonia and sore throat.[19] There are also a number of reported cases of oro-mandibular dystonia occurring shortly after facial injury or surgery.[20]

Similar abnormalities of cortical organisation have been found in the motor system. A study using transcranial magnetic stimulation (TMS) has demonstrated displacement of upper limb
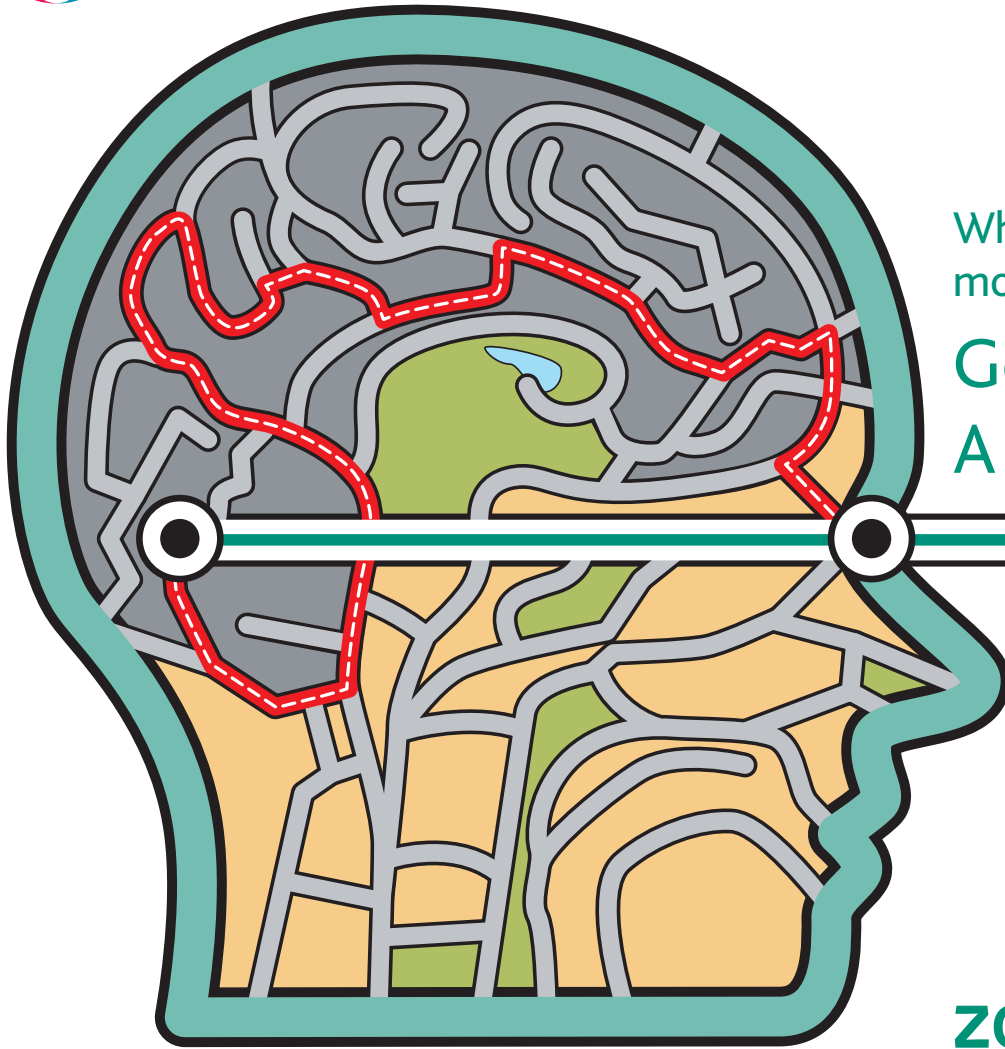
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prior stone formation, a family history of nephrolithiasis and hypercalcuria. Evaluate and monitor serum bicarbonate levels in patients who have: underlying conditions which might increase the risk of metabolic acidosis; increased risk of adverse consequences of metabolic acidosis; symptoms suggestive of metabolic acidosis. If metabolic acidosis develops and persists, consider reducing the dose, discontinuing or alkali treatment. Use with caution in patients treated with carbonic anhydrase inhibitors, e.g. topiramate. Decreased sweating, elevated body temperature and heat stroke have been reported. Patients should maintain hydration and avoid excessive temperatures. Monitor pancreatic lipase and amylase levels in patients taking Zonegran who develop clinical signs and symptoms of pancreatitis, consider discontinuation. In cases of severe muscle pain/weakness with or without fever, assess markers of muscle damage and consider discontinuation. Zonegran 100 mg capsules contain E110. Caution in patients less than 40 kg. In patients with weight loss consider dietary supplement, increased food intake or discontinuation. *Drug Interactions:* No clinically relevant pharmacokinetic effects on carbamazepine, lamotrigine, phenytoin, sodium valproate, oral contraceptives (ethinylestradiol or norethisterone). Insufficient data with carbonic anhydrase inhibitors, e.g.topiramate. Zonegran was not affected by lamotrigine or CYP3A4 inhibitors. Caution with drugs which are P-gp substrates. Avoid concomitant administration with drugs causing urolithiasis. Zonisamide is metabolised partly by CYP3A4, N-acetyl-transferases and conjugation with glucuronic acid; therefore caution with substances that can induce or inhibit these enzymes. *Side effects:* The most common adverse reactions in controlled adjunctive-therapy studies were somnolence, dizziness and anorexia. Adverse reactions associated with Zonegran in clinical studies and post-marketing surveillance: Very common effects (≥1/10): anorexia, agitation, irritability, confusional state, depression, ataxia, dizziness, memory impairment, somnolence,

diplopia, decreased bicarbonate. Common effects (≥1/100, <1/10): ecchymosis, hypersensitivity, affect lability, anxiety, insomnia, psychotic disorder, bradyphrenia, disturbance in attention, nystagmus, paraesthesia, speech disorder, tremor, abdominal pain, constipation, diarrhoea, dyspepsia, nausea, rash, nephrolithiasis, fatigue, influenza-like illness, pyrexia, weight decreased. Uncommon (≥1/1000, <1/100): pneumonia, urinary tract infection, hypokalemia, anger, aggression, suicidal ideation, suicidal attempt, convulsion, vomiting, cholecystitis, cholelithiasis, calculus urinary. For very rare side effects see SmPC. Isolated cases of Sudden Unexplained Death in Epilepsy Patients (SUDEP). Post-marketing data suggests patients aged ≥65 years report a higher frequency of Stevens-Johnson syndrome and Drug Induced Hypersensitivity syndrome. *Legal Category:* POM. *Basic UK NHS cost:* Zonegran 25 mg: packs of 14 £8.82, Zonegran 50 mg: packs of 56 £47.04, Zonegran 100 mg: packs of 56 £62.72. *Irish price to wholesaler:* Zonegran 25 mg: packs of 14 €10.95, Zonegran 50 mg: packs of 56 €58.07, Zonegran 100 mg: packs of 56 €77.59. *Marketing authorisation numbers:* Zonegran 25 mg 14 capsules: EU/1/04/307/001, Zonegran 50 mg 56 capsules: EU/1/04/307/003, Zonegran 100 mg 56 capsules: EU/1/04/307/004. *Marketing authorisation holder:* Eisai Ltd. *Further Information from/Marketed by:* Eisai Ltd, European Knowledge Centre, Mosquito Way, Hatfield, Hertfordshire, AL10 9SN. *Date of preparation:* July 2009.

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corticomotor maps in patients with writer's cramp,[21] a finding that was later extended to patients with cervical dystonia.[22] These abnormalities were temporarily reversed following the injection of botulinum toxin into the affected muscles, leading the authors to speculate that the observed change in cortical topography was caused by altered afferent feedback from the dystonic muscles. At the same time, the presence of neurophysiological abnormalities in clinically unaffected body parts suggests that this may occur against a background of a more generalised disturbance of sensorimotor control.

Sensory abnormalities

While dystonic patients do not have clinically apparent sensory loss they are impaired in measures of both temporal and spatial tactile discrimination.[23] These impairments are not just limited to body parts affected by dystonia; they have been found bilaterally in the hands of patients with unilateral focal hand dystonia,[24] cervical dystonia and blepharospasm.[25] They have also been found in unaffected relatives of patients with dystonia, suggesting that they may be carrying a genetic risk factor for the future development of the condition.[26] In addition to these behavioural findings, a study using magnetoencephalography in patients with unilateral focal hand dystonia showed abnormalities in the somatotopic organisation of the sensory cortex.[27] Similar to the results detailed above, these abnormalities were bilateral in patients with unilateral symptoms.

These findings may result from a failure to adequately focus sensory afferent inputs. When somatosensory evoked potentials (SEPs) are produced simultaneously from both the ulnar and median nerves, the combined SEP is smaller than the sum of the individual SEPs. Similarly, when two SEPs are evoked in quick succession from the same site, the first SEP inhibits various components of the second. These inhibitory interactions are either impaired or absent in patients with focal hand dystonia and it has been suggested that this may be secondary to a generalised defect in lateral inhibition.[28]

Impaired motor inhibition

Abnormalities in motor inhibitory circuits are seen at all levels of the central nervous system in patients with dystonia. For example, patients with writer's cramp have reduced levels of reciprocal inhibition in forearm muscles[29] and TMS protocols have revealed underactivity of cortical inhibitory circuits.[30] These changes are not, however, sufficient to generate dystonic movements as they can be seen bilaterally in patients with unilateral symptoms.

There is evidence to suggest that the output of the motor system is controlled by a process of surround inhibition.[31] It has been shown that at the onset of a voluntary contraction of a hand muscle, both neighbouring and contralateral hand muscles are less readily stimulated with TMS. In this way the motor system can focus muscle activity and facilitate precise, individuated movements. In patients with focal hand dystonia this mechanism is impaired[32] and this could help to explain the co-contraction and overflow of muscle activity that typifies this condition.

Excessive neuroplasticity

Neuroplasticity refers to the ability of neuronal circuits to undergo structural and functional changes in connectivity and underlies the process of learning and memory. Paired associative stimulation (PAS) is a paradigm used to measure plasticity in the human brain.[33] Repeated afferent impulses generated by electrical stimulation of the median nerve are timed to reach the cerebral cortex just before the delivery of a TMS pulse sufficient to activate muscles of the thumb supplied by the same nerve. Depending on the exact interstimulus interval used, subsequent TMS pulses can lead to either enhanced or depressed motor evoked potentials, and this change is restricted to those muscles supplied by the median nerve. These alterations outlast the conditioning protocol by around thirty minutes and are thought to represent long-term potentiation and long-term depression. When applied to patients with writer's cramp this facilitation is exaggerated and the spatial specificity is lost.[34] Such changes are unlikely to be secondary to dystonic movements as they are also present in the asymptomatic hands of patients with blepharospasm and cervical dystonia.[35] Excessive neuroplasticity could drive the maladaptive reorganisation of cortical sensorimotor maps thought to underlie the generation of dystonic movements.

Basal ganglia involvement

Secondary dystonia is the term used to describe dystonia that is the result of an identifiable metabolic insult or structural lesion. The majority of such lesions are found to affect the basal ganglia, thalamus or their connections[36] and it is likely that abnormal activity in basal ganglia–thalamo–cortical loops plays a large part in the aetiology of all forms of dystonia. Indeed, neurophysiological studies on patients undergoing deep brain stimulation (DBS) for generalised dystonia have found patterns of neuronal activity in the globus pallidus internus (GPi) and motor thalamus that correlate with dystonic EMG activity.[37] Imaging studies in dystonia have yielded many conflicting results, likely due to variation in methodology and patient selection, but a relatively consistent finding is the presence of both increased functional activity and increased grey matter volume in the basal ganglia.[38] Perhaps the strongest evidence for the role of abnormal basal ganglia output in the pathogenesis of dystonia is the simple fact that modulation of the GPi and motor thalamus with DBS is an effective treatment for both generalised[39] and focal dystonias.[40]

Cerebellar involvement

While the basal ganglia undoubtedly play a key role in the genesis of dystonic movements there is mounting evidence to suggest that the cerebellum may also be involved.[41] Recent work looking at eye blink classical conditioning, a process that is dependent on cerebellar function,[42] has been particularly informative. Within this experimental paradigm an auditory tone is played immediately prior to the delivery of an electrical stimulus to the supraorbital nerve. After repeated stimulus pairings normal subjects produce conditioned responses consisting of eye blinks that begin after the onset of the tone but prior to the onset of the electrical stimulus. Data from stroke patients have localised this process to the territory of the superior cerebellar artery.[43] This area includes lobules V and VI of the cerebellar cortex, which have been shown to be structurally abnormal in patients with focal hand[44] and cervical dystonia.[45] The finding that patients with focal dystonia have impaired eye blink conditioning provides physiological evidence for cerebellar dysfunction in this group of conditions.[46]

Putting it all together

Research into focal dystonia has revealed abnormalities in basal ganglia function, cerebellar function, sensory processing, motor

> *...the emerging model is that genetically mediated abnormalities of basal ganglia function, sensorimotor inhibition and neuroplasticity culminate in a brain state that, when exposed to particular patterns of sensory stimulation, facilitates a process of maladaptive cortical reorganisation that ultimately leads to dystonic movements.*

inhibition, neuroplasticity and somatotopic cortical organisation. How these separate strands interact to explain the development of dystonia is uncertain and a perennial difficulty is establishing which elements are causative and which are simply epiphenomena. Despite this, some necessarily speculative suggestions can be made.

The diffuse abnormalities of sensory processing and motor inhibition may be secondary to a fundamental problem with lateral inhibition, which could in turn reflect a general functional disturbance of cortical GABAergic interneurones.[28] Such a mechanism could account for reorganisation of the sensory and motor cortices, as pharmacological blockade of cortical inhibitory neurones with the GABA antagonist bicuculline has been shown to expand cortical representations in rat brain,[47] presumably by unmasking preexisting lateral excitatory connections. A generalised reduction in inhibitory activity could also fail to adequately gate synaptic inputs and so lead to circuits that more readily undergo long-term potentiation and depression. In this way enhanced neuroplasticity could be a direct consequence of impaired inhibition.[28] However, in patients with psychogenic "fixed" dystonia, cortical inhibition is reduced[48] while measures of neuroplasticity remain normal.[49] Similarly, measures of cortical inhibition have been found to be abnormal in both manifesting and non-manifesting carriers of the DYT1[50] mutation while levels of neuroplasticity were found to be enhanced only in manifesting carriers.[51] Furthermore, non-manifesting carriers were found to have reduced levels of plasticity when compared to normal subjects, suggesting that underactivity of this mechanism confers protection to individuals who are otherwise at risk of becoming symptomatic. These findings would place abnormalities in the control of neuroplasticity as a primary force behind the development of dystonic symptoms, with impaired surround inhibition resulting from an increased tendency of the brain to form new excitatory connections.

The basal ganglia are generally accepted to be involved in both the activation of appropriate motor programmes and the concurrent inhibition of competing patterns of motor activity[52] and so are well placed to control surround inhibition in the sensory and motor cortices. On this basis it has been proposed that abnormal basal ganglia activity could drive the aforementioned impairment of inhibitory interneurone function.[28] In dystonic patients the basal ganglia generate abnormal patterns of oscillatory activity and neuronal synchrony. Given that neuronal oscillations have been shown to enhance cortical plasticity,[53] it has also been suggested that abnormal basal ganglia oscillations could directly underlie the aberrant levels of plasticity seen in dystonia.[54]

The relevance of abnormal cerebellar function in the aetiology of dystonia remains
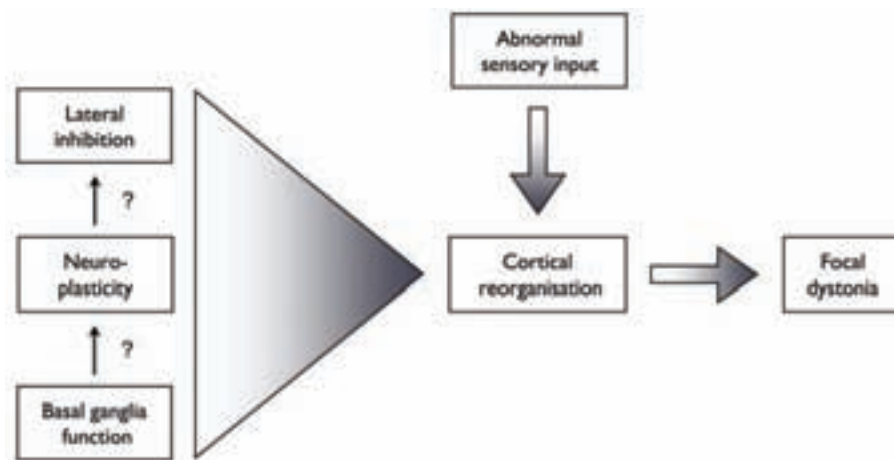
Figure 1: A possible model for the development of focal dystonias
Abnormalities of neuronal inhibition, neuroplasticity and basal ganglia function appear to promote a state of cortical reorganisation. The relative importance of each factor and the interactions between them remain unclear, but a number of findings point to enhanced neuroplasticity as having a central role (see main text). In combination with particular patterns of sensory input, further focal cortical reorganisation presumably occurs, with dystonic movements appearing when this reaches a threshold.

unclear. One possibility is that the cerebellum represents simply one node within a complex motor network that also includes the dopaminergic system, the basal ganglia and cerebral cortex.[55] Dysfunctional activity at any of these sites could disrupt the activity of the network as a whole and contribute to the neurophysiological abnormalities detailed in this review.

Abnormalities of sensory processing, somatotopic organisation, motor inhibition and neuroplasticity have been found repeatedly in areas not displaying dystonic movements. These changes may represent genetically mediated risk factors for the future development of focal dystonias and are often referred to as endophenotypic traits.[27] Against this background of generalised disturbed sensorimotor function and enhanced neuroplasticity, an external drive to further plastic change (repetitive hand movements, excessive blinking, peripheral injury etc) could then lead to further, localised somatotopic reorganisation. Once this reaches a level where the sensorimotor feedback loop is sufficiently compromised, motor control is disturbed and dystonic movements ensue.[56]

Evidence to support this general schema comes from studies that demonstrate a normalisation of various neurophysiological parameters in response to treatment. Sensorimotor retuning is one of a number of rehabilitative strategies found to be partially effective in the treatment of musician's dystonia. This strategy involves splinting the unaffected digits and exposing individual affected digits to systematic training with the relevant musical instrument. It has been shown that clinical improvement is associated with a normalisation of somatotopic organisation as assessed by magnetoencephalography.[57] In

general, such rehabilitative approaches produce only temporary clinical improvements,[58] a finding that is to be expected if there is an underlying defect in sensorimotor processing and plasticity that is continually driving further aberrant cortical reorganisation.

DBS of the GPi is an effective treatment for generalised dystonia, although its precise mechanism of action is unknown. In contrast to the immediate response of parkinsonian symptoms to DBS in patients with Parkinson's disease, the clinical response in patients with dystonia is progressive, taking place over a number of months. Serial measures of brainstem[59] and spinal cord[60] inhibition taken pre-operatively and over a period of six months post-operatively have been shown to normalise in line with this clinical improvement. Furthermore, measures of PAS in patients treated with DBS for six months show levels of neuroplasticity comparable to those seen in normal controls.[61] These findings suggest that modulating the oscillatory output of the basal ganglia may normalise levels of inhibition and neuroplasticity, allowing for the gradual replacement of aberrant sensorimotor networks with more physiological patterns of activity.[54]

Conclusion

A number of consistent physiological abnormalities have been identified in various forms of idiopathic dystonia. How these elements interact to produce dystonia remains uncertain but the emerging model is that genetically mediated abnormalities of basal ganglia function, sensorimotor inhibition and neuroplasticity culminate in a brain state that, when exposed to particular patterns of sensory stimulation, facilitates a process of maladaptive cortical reorganisation that ultimately leads to dystonic movements (Figure 1). ◆

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XEOMIN® Abbreviated Prescribing Information.
Please refer to Summary of Product Characteristics (SmPC) before prescribing. **Presentation:** 100 LD50 units of Clostridium Botulinum neurotoxin type A (150 kD), free from complexing proteins, as a powder for solution for injection. **Indications:** Symptomatic management of blepharospasm and cervical dystonia of a predominantly rotational form (spasmodic torticollis) and of post-stroke spasticity of the upper limb presenting with flexed wrist and clenched fist in adults. **Dosage and Administration:** Please refer to SmPC for full information. Reconstitute with sterile unpreserved normal saline (0.9% sodium chloride for injection). *Blepharospasm:* The initial recommended dose is 1.25-2.5 U injected into the medial and lateral orbicularis oculi of the upper lid and the lateral orbicularis oculi of the lower lid. The initial dose should not exceed 25 U per eye but this can be subsequently increased. The total dose should not exceed 100 U every 12 weeks. *Spasmodic torticollis:* Xeomin® is usually injected into the sternocleidomastoid, levator scapulae, scalenus, splenius capitis and / or the trapezius muscle(s). However the dosing should be tailored to the individual patient. The maximum total dose is usually not more than 200 U but doses up to 300 U may be given. No more than 50 U should be given at any one injection site. *Post-stroke spasticity of the upper limb:* The exact dosage and number of injection sites should be tailored to the individual patient based on the size, number and location of muscles involved, the severity of spasticity, and the presence of local muscle weakness. The maximum total recommended dose is up to 400 units per treatment session. **Contra-indications:** Known hypersensitivity to Botulinum

neurotoxin type A or to any of the excipients, generalised disorders of muscle activity (e.g. myasthenia gravis, Lambert-Eaton syndrome) and presence of infection at the proposed injection site. Dysphagia has also been reported following injection to sites other than the cervical musculature. **Warnings and Precautions:** Adrenaline and other medical aids for treating anaphylaxis should be available. Xeomin® contains albumin a derivative of human blood. Prior to administration the physician must make himself familiar with the patients anatomy and any changes due to surgical procedures. Side effects related to spread of botulinum toxin have resulted in death which in some cases was associated with dysphagia, pneumonia and /or significant debility. Patients with a history of dysphagia and aspiration should be treated with extreme caution. Patients or caregivers should be advised to seek immediate medical care if swallowing, speech or respiratory disorders arise. Xeomin® should be used with caution if bleeding disorders occur, in patients receiving anticoagulant therapy, patients suffering from amyotropic lateral sclerosis or other diseases which result in peripheral neuromuscular dysfunction and in targeted muscles which display pronounced weakness or atrophy. Reduced blinking following injection of the orbicularis muscle can lead to corneal exposure, persistent epithelial defects and corneal ulceration. Careful testing of corneal sensation should be performed in patients with previous eye operations. Xeomin® as a treatment for focal spasticity has been studied in association with usual standard care regimens, and is not intended as a replacement for these treatment modalities. Xeomin® is not likely to be effective in improving range of motion at a joint

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David Marsden 1938-1998

Prof Niall Quinn
is Emeritus Professor of Neurology at the UCL Institute of Neurology and Honorary Consultant Neurologist at the National Hospital for Neurology and Neurosurgery, Queen Square. He worked with David Marsden first as SHO in 1976, and later continuously for 18 years from 1980 to 1998, and has been secretary of MDS and Chair of MDS-ES.

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The portrait of David Marsden is by David Graham and was commissioned by the Movement Disorder Society and hangs in the Gilliatt Lecture theatre in the Institute of Neurology, Queen Square. It is reproduced with the permission of the President of the Movement Disorder Society, Philip Thompson.
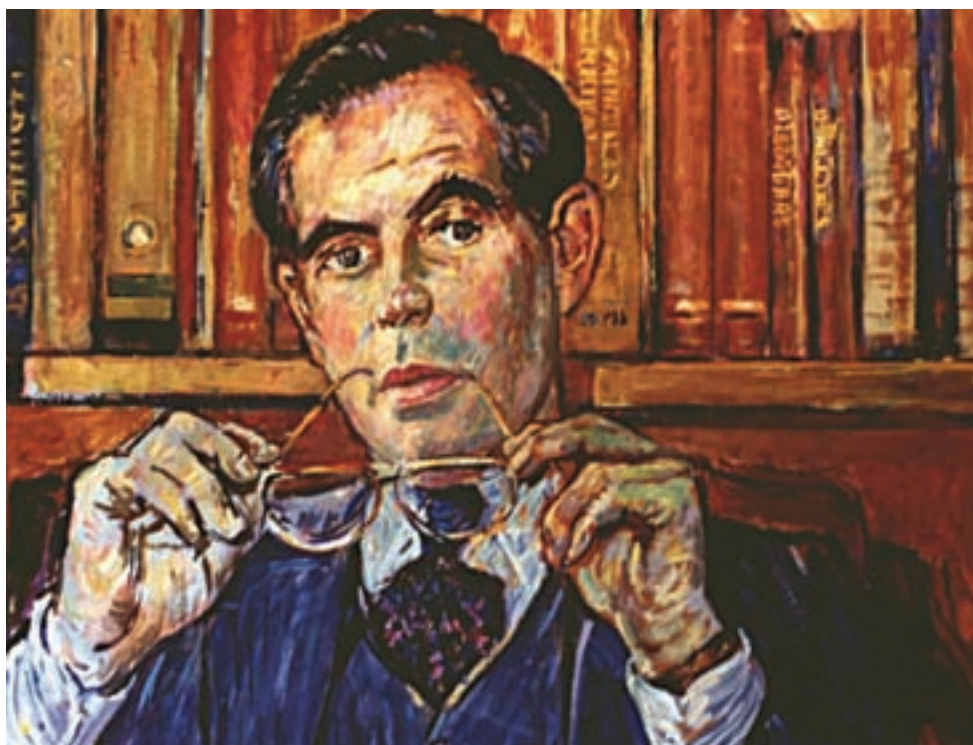
(Charles) David Marsden ("CDM") died in Baltimore, USA, in September 1998 at the age of 60, just three weeks into his first ever sabbatical, at NIH. He was arguably the leading academic neurologist and neuroscientist of his generation in the UK and was responsible, together with Stanley Fahn in New York, for putting movement disorders firmly on the map as a distinct and leading subspeciality.

Born in Croydon, he was educated at Cheltenham College (from which he was suspended for smoking, but allowed to sit his A levels). He then went to St Thomas' Hospital in 1956 to read medicine. There, in addition to winning three scholarships, an exhibition, five prizes, and two medals, he also represented the hospital at cricket and rugby (he had earlier captained England Schoolboys as scrum half), and was clearly going places.

After preclinical training he got a first in his intercalated BSc in 1959, and went on to obtain an MSc in 1960 with a thesis on pigmentation in the substantia nigra that established his abiding interest in diseases of the basal ganglia. He qualified in 1963. By 1965, when he became MRCP, he had seven papers to his name, including two in the *Journal of Anatomy*, two in *Nature*, and two on parkinsonian tremor in the *Lancet* with Dr (now Lord) David Owen. He was then lecturer in medicine at St Thomas' for two years, and following this spent two years as senior resident house physician at The National Hospital, Queen Square, where he co-authored papers on spinal muscular atrophy and painful legs and moving toes, and continued to develop his work on human neurophysiology, first with John Meadows, and later as part of the "3M's"

(Marsden, Merton and Morton).

In 1970, only seven years after qualifying, he was appointed Senior Lecturer in Neurology at the Institute of Psychiatry and Honorary Consultant Neurologist to the Maudsley and Bethlem Royal Hospitals and to King's College Hospital. Two years later, aged thirty-four, he was the first appointee to the newly established joint chair of neurology at the Institute of Psychiatry and King's College Hospital Medical School. There he founded and directed the Medical Research Council Human Movement and Balance Unit (HMBU). This was the vehicle for several strands of research – first experimental neuropharmacology, together with Peter Jenner, then human neurophysiology, with John Rothwell and Brian Day, and then the neuropsychology of movement disorders with Richard Brown and later Marjan Jahanshahi. He also co-founded, with Andrew Lees, the UK's first PD Brain Bank.

Marsden's time at Denmark Hill really constituted his golden years of productivity and camaraderie with a host of Fellows and visiting researchers drawn by his growing reputation. The first was Roger Duvoisin (USA), followed by many others including Paul Bedard (Canada), Mark Hallett and Dan Tarsy (USA), Eldad Melamed (Israel), Wolfgang Oertel and Reiner Benecke (Germany), Alfredo Berardelli, Alberto Albanese, Giovanni Abbruzzese and Fabrizio Stocchi (Italy), Tony Lang (Canada), Jose Obeso (Spain) and Philip Thompson (Australia), all since professors and international leaders in the field of movement disorders. He established the UK's first specialist PD clinic with David Parkes, and with David Chadwick

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Please refer to the SmPC before prescribing. **Presentation:** Tablets containing 800 mg eslicarbazepine acetate. **Indication:** Adjunctive therapy in adults with partial-onset seizures with or without secondary generalisation. **Dose and administration:** May be taken with or without food. Starting dose is 400 mg once daily which should be increased to 800 mg once daily after one or two weeks. The dose may be increased to 1200 mg once daily. Withdraw gradually to minimise the potential of increased seizure frequency. **Elderly patients:** Caution (See SmPC). **Children and adolescents <18 years of age:** Not recommended. **Patients with renal impairment:** The dose should be adjusted according to creatinine clearance (CL_{CR}) (see SmPC). Not recommended in severe impairment. **Patients with hepatic impairment:** No dose adjustment in mild to moderate impairment. Not recommended in severe impairment. **Contra-Indications:** Hypersensitivity to the active substance, other carboxamide derivatives (e.g. carbamazepine, oxcarbazepine) or any excipients. Known second or third degree AV block. **Pregnancy:** No data on the use of Zebinix in pregnant women. If women receiving Zebinix become pregnant or plan to become pregnant, the use of Zebinix should be carefully re-evaluated. Minimum effective doses should be given. Zebinix interacts with oral contraceptives. An alternative, effective and safe method of contraception should be used during treatment and up to the end of the current menstrual cycle after treatment has been stopped. **Lactation:** Excretion in human breast milk is unknown. Breastfeeding should be discontinued during treatment. **Warnings and precautions:** Zebinix has been associated with some CNS reactions such as dizziness and somnolence. Concomitant use with oxcarbazepine is not recommended. Rash has been reported. If signs or symptoms of hypersensitivity develop, Zebinix must be discontinued. Presence of HLA-B*1502 allele in individuals of Han Chinese and Thai origin has been shown to be strongly associated with the risk of developing Stevens-Johnson syndrome (SJS) when treated with carbamazepine. Screening for this allele should be undertaken in such individuals. Serum sodium levels should be examined before and during treatment in patients with pre-existing renal disease or in patients concomitantly treated with medicinal products which may lead to hyponatraemia. Serum sodium levels should be determined if clinical signs of hyponatraemia occur. If clinically relevant hyponatraemia develops, discontinue Zebinix. Use in primary generalised seizures is not recommended. Prolongations in PR interval have been observed. Caution in patients with medical

conditions or when taking concomitant medicinal products associated with PR prolongation. Monitor for signs of suicidal ideation and behaviours. Appropriate treatment should be considered. **Drug interactions:** In vitro eslicarbazepine is a weak inducer of CYP3A4 and UDP-glucuronyl transferases. In vivo eslicarbazepine may have an inducing effect on the metabolism of medicinal products which are mainly eliminated by metabolism through CYP3A4 or conjugation through the UDP-glucuronyl transferases. When initiating or discontinuing treatment with Zebinix or changing the dose, it may take 2 to 3 weeks to reach the new level of enzyme activity. Time delays must be taken into account when Zebinix is being used just prior to or in combination with other medicines that require dose adjustment when co-administered with Zebinix. Eslicarbazepine has inhibiting properties with respect to CYP2C19. Interactions can arise when co-administering high doses of eslicarbazepine acetate with medicinal products that are mainly metabolised by CYP2C19. Phenytoin: concomitant use may require an increase of Zebinix dose and a decrease of phenytoin dose. Lamotrigine and topiramate: no dose adjustments are required. However, clinical review should be considered. Valproate and levetiracetam: Concomitant administration with valproate or levetiracetam appeared not to affect the exposure to eslicarbazepine but has not been verified by conventional interaction studies. Carbamazepine: Concomitant treatment with carbamazepine increased the risk of the diplopia, abnormal coordination and dizziness. An increase in other adverse reactions caused by co-administration of carbamazepine and eslicarbazepine acetate cannot be excluded. Carbamazepine increases eslicarbazepine clearance. Zebinix slightly increases the clearance of carbamazepine. Oral contraceptives: Interacts with the oral contraceptive. Women of childbearing potential must use adequate contraception during treatment with Zebinix, and up to the end of the current menstruation cycle after the treatment has been discontinued. Warfarin: Zebinix has been shown to decrease exposure to S-warfarin. There are no effects on R-warfarin or coagulation. Monitoring of INR should be performed in the first weeks after initiation or ending concomitant treatment. Digoxin: no effect. MAOIs: an interaction between eslicarbazepine acetate and MAOIs is theoretically possible. **Side effects:** Adverse reactions were usually mild to moderate in intensity and occurred predominantly during the first weeks of treatment with Zebinix. Very common effects (≥1/10): dizziness, somnolence. Common effects (≥1/100, <1/10): Headache, abnormal coordination, disturbance in attention, tremor, diplopia, vision blurred, vertigo, nausea, vomiting, diarrhoea, rash, fatigue, gait disturbance. Uncommon (≥1/1,000 to <1/100): anaemia, hypersensitivity, hypothyroidism, increased appetite, decreased appetite, hyponatraemia, electrolyte imbalance, cachexia, dehydration, obesity, insomnia, apathy, depression, nervousness, agitation, attention deficit/hyperactivity disorder, confusional state, mood swings, crying, psychomotor retardation, stress, psychotic disorder, memory impairment, balance disorder, amnesia, hypersomnia, sedation,

aphasia, dysaesthesia, dystonia, lethargy, parosmia, autonomic nervous system imbalance, cerebellar ataxia, cerebellar syndrome, grand mal convulsion, neuropathy peripheral, sleep phase rhythm disturbance, nystagmus, speech disorder, dysarthria, hypoaesthesia, ageusia, burning sensation, vision disturbance, oscillopsia, binocular eye movement disorder, ocular hyperaemia, saccadic eye movement, eye pain, ear pain, hypoacusis, tinnitus, palpitations, bradycardia, sinus bradycardia, hypertension, hypotension, orthostatic hypotension, dysphonia, epistaxis, dyspepsia, gastritis, abdominal pain, dry mouth, abdominal discomfort, abdominal distension, duodenitis, epigastric discomfort, gingival hyperplasia, gingivitis, irritable bowel syndrome, melaena, odynophagia, stomach discomfort, stomatitis, toothache, liver disorder, alopecia, dry skin, hyperhidrosis, erythema, nail disorder, skin disorder, myalgia, back pain, neck pain, nocturia, menstruation irregular, asthenia, malaise, chills, oedema peripheral, adverse drug reaction, peripheral coldness, blood pressure decreased, weight decreased, blood pressure diastolic decreased, blood pressure increased, blood pressure systolic decreased, blood sodium decreased, haematocrit decreased, haemoglobin decreased, heart rate increased, transaminases increased, triglycerides increased, triiodothyronine (T3) free decreased, thyroxine (T4) free decreased, drug toxicity, fall, joint injury, poisoning, skin injury. For rare side effects see SmPC. When treated concomitantly with carbamazepine, diplopia, abnormal coordination and dizziness are reported more frequently. Use of Zebinix is associated with an increase in the PR interval. Adverse reactions associated with PR interval prolongation may occur. No second or higher degree AV block was seen in Zebinix treated patients. Rare adverse reactions such as bone marrow depression, anaphylactic reactions, severe cutaneous reactions (e.g. Stevens-Johnson Syndrome), systemic lupus erythematosus or serious cardiac arrhythmias did not occur during clinical studies. However, they have been reported with oxcarbazepine and their occurrence during treatment with Zebinix cannot be excluded. **Legal Category:** POM. **Basic UK NHS cost:** Zebinix 800 mg: pack of 30 £154.20. **Marketing authorisation numbers:** EU/1/09/514/012-020. **Marketing authorisation holder:** Bial-Portela & Cª., S.A. À Av. da Siderurgia Nacional 4745-457 S. Mamede do Coronado – Portugal. **Further Information from:** Eisai Limited, European Knowledge Centre, Mosquito Way, Hatfield, Herts, AL10 9SN, UK. **Date of preparation:** July 2009.

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and others explored clinical, physiological and pharmacological aspects of myoclonus. He was one of the pioneers of the clinical application of evoked potentials, and of electrical and magnetic stimulation of the brain and, with Peter Jenner, developed the MPTP marmoset model of PD. Parkinsonian disorders were the main thrust of his work, but he made his most important mark in the field of dystonia, bringing it out of the dark ages when so many cases were thought to be psychiatric, and placing it on a firm organic footing.

CDM's most critical interaction and collaboration, however, was with Stanley Fahn, Houston Merritt Professor of Neurology at the Neurological Institute in Columbia Presbyterian Hospital in New York. Together, in 1986, they founded the Movement Disorders Journal, of which they were both co-editors for its first ten years, and shortly later the Movement Disorder Society (MDS).

In 1987 Roger Gilliatt, the first Chair of Neurology at the Institute of Neurology at Queen Square, was to retire, and David was appointed to succeed him, so Peter Jenner and I organised a Festschrift* in recognition of his 17 years at Denmark Hill, little realising that another chance would not come.

At Queen Square in the late 1980's specialist clinics still tended to be frowned upon, but they began to thrive under David, and fellows continued to arrive from all corners of the world. The clinical and scientific field of neurogenetics was burgeoning, and we had the enormous good fortune to have Anita Harding, married to PK Thomas, to lead in this area. After eight years holding the Queen Square Chair of Clinical Neurology, David decided to step down and become Dean, and Anita was appointed, but tragically died of bowel cancer aged 42, just weeks before she was due to take up the Chair, which was then occupied by Ian MacDonald.

Anita's death was a terrible blow, particularly to David. He did not really enjoy being Dean, and when his term ended three years later he was looking forward to getting back to research – one of his plans at the time was to further unravel the mysteries of apraxia and to explain it to the world, but he never lived to complete this.

David was exceptional. He was highly intelligent and clearly 'driven' to be extraordinarily productive. One secret of his success was his attention to detail whilst at the same time clearly seeing the bigger picture. He had a rare ability to make complicated matters seem simple, and to share his thought processes with others. His teaching method was by example. He never acted as if his students should really already know through some osmotic process what he was deigning to teach them. Instead he revelled in taking them on a voyage of discovery. He did this best not in his lectures, which were of course outstanding models of clarity, but particularly in his clinics and ward rounds, and especially in his "book rounds". These weekly gatherings would bring together the junior staff on the firm, the clinical fellows, and the notes of the current inpatients. The SHO or registrar would begin the history and after several sentences David would say "Stop!" and ask one of the fellows what he or she thought of the story so far, and by iterating this process gave insight into the way he would approach the question of differential diagnosis, and imprinted the same analytical and teaching technique on his successors.

David was a complex personality, quite shy and private in some ways, so that few really felt they knew him really well personally. Yet he had an extraordinary ability to motivate people through charm, charisma, cajoling, and example. He could also be forceful in getting what he thought was important, although always relying first on the diplomatic route, but was always scrupulously fair. His long-term lieutenants were mainly from the UK, but almost all of his fellows were from abroad, which made for a cosmopolitan flavour, and has spread his influence around the globe.

David worked hard but also played hard, and had a legendary capacity to party late into the night when away at meetings, only to deliver a brilliant lecture the following morning. Although he gave up smoking for a few years in the 1980's, for most of his life he chain-smoked Malboro cigarettes, and was often to be found enveloped in a cloud of smoke together with Anita and Philip Thompson. His recreation listed in Who's Who was "the human brain", but he also enjoyed sailing, bird-watching and gardening.

In listing his professional achievements it is difficult to know where to start or to finish. His published work is extensive – 740 original papers, plus over 208 chapters, 76 reviews and 100 letters and notes – one publication every twelve days for over 30 years, covering clinical neurology, neuropsychology, neurochemistry, neuropathology, neuropharmacology and neurophysiology. He was Editor of *JNNP* for a decade, on the editorial boards of another 20 journals, member of 12 foreign societies, and held 36 visiting professorships, received 10 major awards, and gave numerous major invit-

ed lectures. He was awarded the MRCPsych in 1978, was elected FRS in 1983 and awarded a DSc from London University in 1984, and was on numerous advisory boards including the councils of the Royal Society, the MRC and the Royal College of Physicians. However, his biggest legacies to world Neurology have been his fellows, his Journal and his Society. ◆

Selected further reading

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> *I seem to be the only person here who has never written a paper with David Marsden!*
> (Gerald Stern at CDM's Denmark Hill Festschrift, June 1987)

Fitness to Fly

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The consideration of fitness to fly after neurological injury or disease is a wide ranging subject meriting a substantial chapter in the appropriate textbook (see Further Reading). As with all aspects of aviation medicine, an understanding of the physics of the flight environment coupled with a thorough knowledge of the pathological process will assist in assessing fitness to fly. The aeromedical disposition is concerned with the likelihood of sudden or gradual incapacitation during flight as well as the effect of the injury or disease on physical and cognitive function; this is obviously of importance for a pilot being able to perform the flying task, but it is also so for the well-being of the patient flying as passenger and the effect on the safe and expeditious conduct of the flight. The prediction of future events in a disease requires knowledge of the natural history and epidemiology, which is essential for assessing the flight safety risk in the hypobaric environment and the confines of an aircraft.

The hypobaric environment

The atmosphere is compressible and has mass. The air at the surface of the earth is supporting the mass of air above it and its molecules will therefore be pressed close together, causing the density of the air to be greatest at the surface. With increasing altitude, there is a fall in atmospheric pressure together with a decrease in density and temperature. Fortunately, the relationship between the oxygen saturation of haemoglobin and oxygen tension minimises the effect of the reduction in partial pressure of oxygen. Ascent to an altitude of 10,000ft produces a fall in the partial pressure of oxygen in the alveoli but only a slight fall in the percentage saturation of haemoglobin with oxygen. However, once altitude rises above 10,000ft the percentage saturation of haemoglobin falls quickly, resulting in the condition of hypoxia. The cabin of a commercial airliner is pressurised to maintain an equivalent altitude below 8,000ft irrespective of the aircraft's operating altitude. Occupants of light aircraft and gliders use personal oxygen equipment if flying at altitudes in excess of 10,000ft.

Mechanical effects of pressure change

In civilian passenger and transport aircraft, the climb to cruise altitude takes about 30 minutes and involves a maximum fall of about 200mmHg (26.6kPA) in cabin pressure (to the equivalent of 8000ft (2440m)). Descent to land takes much the same time. Body fluids and tissues generally are virtually incompressible and do not alter shape to any important extent when such pressures changes are applied. The same is true of cavities such as the lungs, gut, middle ear, and facial sinuses that contain air, provided that they can vent easily. Gas-containing spaces that cannot vent easily behave differently.

The thoraco-abdominal wall can develop transmural pressures of +100mmHg or so briefly, but is normally flaccid and has a transmural pressure of a few millimetres of mercury. Gas within will usually be at a pressure very close to that outside, and must follow Boyle's law. Ascent from ground level (760mmHg) to 8000ft (2440m) (565mmHg) will expand a given volume of trapped gas in a completely pliable container by about 35%. This may cause slightly uncomfortable gut distension in healthy people but it is not an important problem.

Even very diseased lungs can vent themselves over a minute or so. In consequence, the risk of lung rupture in normal flight is extremely rare.

The cavity of the middle ear vents easily, but sometimes fails to fill because the lower part of the Eustachian tube behaves as a non-return valve, especially when it is inflamed. As a result, the cavity equilibrates quite easily on ascent but does not refill on descent, and the ear-drum bows inwards, causing pain that can be severe (otic barotrauma).

Fitness to fly

Different medical requirements apply to the various classes of flying licence defined by the International Civil Aviation Organisation. Class 1 medical certification is required by airline transport and commercial pilots and Class 2 by private pilots. Standards are applied in the UK by the Aeromedical Section (AMS) of the Civil Aviation Authority on behalf of the European Aviation Safety Agency, using requirements originally formulated by the European Joint Aviation Authorities. In the UK there is another class of licence, the National Private Pilot Licence, for which the driving medical standards laid down by the Driver Vehicle and Licensing Authority are applied. This licence may be held by pilots of simple light aircraft, micro-lights and gliders, gyroplanes, balloons and airships. There are no statutory licence requirements for hang-glider or paraglider pilots or for parachutists, although supervision is carried out by their sport associations.

For passengers, the individual airline has a legal right to refuse carriage, with the ultimate authority resting with the aircraft captain. Many airlines employ a medical adviser, and the major companies provide website information on flying with, or after, medical conditions. The Aerospace Medical

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Table 1. Excerpt from JAR FCL-MED for Pilot Medical Requirements

FCL 3.210 Neurological requirements

(a) An applicant for or holder of a Class 1/2 medical certificate shall have no established medical history or clinical diagnosis of any neurological condition which is likely to interfere with the safe exercise of the privileges of the applicable licence(s).

(b) Particular attention shall be paid to the following (see Appendix 11 to Subpart B):

  (1) Progressive disease of the nervous system,

  (2) Epilepsy and other causes of disturbance of consciousness,

  (3) Conditions with a high propensity for cerebral dysfunction,

  (4) Head injury,

  (5) Spinal or peripheral nerve injury.

(c) Electroencephalography is required when indicated by the applicant's history or on clinical grounds [(see Appendix 11 to Subpart B)] .

Appendix 11 to Subparts B and C - Neurological requirements

1 Any stationary or progressive disease of the nervous system which has caused or is likely to cause a significant disability is disqualifying. However' in case of minor functional losses' associated with stationary disease the Aeromedical Section (AMS) may consider a fit assessment after full evaluation.

2 A history of one or more episodes of disturbance of consciousness of uncertain cause is disqualifying. In case of a single episode of such disturbance of consciousness' which can be satisfactorily explained' a fit assessment may be considered by the AMS' but a recurrence is normally disqualifying.

3 Epileptiform paroxysmal EEG abnormalities and focal slow waves normally are disqualifying. Further evaluation shall be carried out by the AMS.

4 A diagnosis of epilepsy is disqualifying' unless there is unequivocal evidence of a syndrome of benign childhood epilepsy associated with a very low risk of recurrence' and unless the applicant has been free of recurrence and off treatment for more than 10 years. One or more convulsive episodes after the age of five are disqualifying. However' in case of an acute symptomatic seizure' which is considered to have a very low risk of recurrence by a consultant neurologist acceptable to the AMS' a fit assessment may be considered by the AMS.

5 An applicant having had a single afebrile epileptiform seizure which has not recurred after at least 10 years while off treatment' and where there is no evidence of continuing predisposition to epilepsy' may be assessed as fit if the risk of a further seizure is considered to be within the limits acceptable to the AMS. For a Class 1 fit assessment a multi-pilot (Class 1 `OML') limitation shall be applied.

6 Any head injury which has been severe enough to cause loss of consciousness or is associated with penetrating brain injury must be assessed by the AMS and be seen by a consultant neurologist acceptable to the AMS. There must be a full recovery and a low risk (within the limits acceptable to the AMS) of epilepsy before a fit assessment is possible.

7 Assessment of applicants with a history of spinal or peripheral nerve injury shall be undertaken in conjunction with the musculo-skeletal requirements' Appendices and Manual Chapter.

8 The assessment of malignant conditions in this system is also explained in the Oncology Chapter of the Manual which provides information regarding assessment and should be consulted together with the Chapter specific to this system. All intracerebral malignant tumours are disqualifying.

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Association and the International Air Transport Association provide similar web-based information, as does the UK Civil Aviation Authority.

For pilots, aeromedical disposition following any injury or disease is predicated on the so-called 1% rule, which is an attempt to quantify risk assessment. By seeking to ensure that no individual with an incapacitation risk of over one per cent per annum operates as a pilot, it aims to achieve a target fatal accident rate of 0.1 fatal accidents per one million flying hours for commercial aviation. For non-commercial private aviation, the acceptable risk is greater and an arbitrary 2% risk of incapacitation may be acceptable. This rule is not used in assessing fitness for the UK National PPL.

Neurological Conditions

It is impossible in a short paper to provide a comprehensive guide to fitness to fly as affected by all neurological conditions. As in any clinical situation, the following questions should be considered:

1. Is the condition affected by reduction in ambient pressure or hypoxia?
2. Is the condition static? If so, what is the degree of functional incapacitation?
3. Is the condition progressive? If so, is the course predictable or unpredictable?
4. Can the condition be monitored successfully?
5. Can the condition result in sudden incapacitation?
6. Can the condition result in subtle incapacitation?
7. In the case of assessing fitness to fly as a passenger, does the condition impede mobility?

Pilots

The regulatory authority approves a network of aeromedical examiners (AMEs) who have undergone specialist training in aviation medicine, and are often pilots themselves. These AMEs perform the regular recurrent medical assessments required for maintenance of Class 1 and 2 licences, as well as the initial medical examination for Class 2 private pilots, and a bond of understanding and trust develops between the pilot and AME. Statutory licence holders have a legal duty to inform the Aeromedical Section (AMS) if they become unfit to exercise the privilege of their licence through injury or illness, and they frequently do this via the AME.

There is a partnership between the pilot, the AME and the AMS and in the event of illness or injury, the partnership extends to include the GP and/or the specialist. The AMS requires specialist reports from the treating clinician which assist in the assessment of fitness to return to flying. This decision is taken by the AMS after considering the clinical and operational factors affecting flight safety. It is the pilot's responsibility to ensure that the appropriate reports are sent to the AMS. An excerpt from the relevant medical requirements for neurological conditions is given in Table 1.

For recreational pilots holding a UK National PPL, the procedure is different. Medical assessment does not use the network of AMEs, but relies on a declaration of medical fitness by the pilot. To validate this declaration, and to prevent concealment of disease, it has to be endorsed by a doctor with access to the pilot's medical records, usually the GP. The paperwork is reviewed by the National PPL Medical Advisor at the CAA Medical Department.

Following neurological disease, the pilot's state of health is compared with the DVLA medical standards of fitness to drive. If the pilot wishes to carry passengers (maximum of three) then the standards for DVLA Group 2 professional drivers must be met. For solo flight, DVLA Group 1 standards will suffice. DVLA standards are available on-line via www.dvla.gov.uk/at_a_glance/content.htm

Pilots with disabilities

People with a wide range of disabilities may learn to fly. The British Disabled Flying Association aims "to get people with crutches

and wheelchairs into the air", for which they have some modified training aircraft and qualified instructors. A number of scholarships are offered annually, and individuals with severe disabilities have gone on to gain their private pilot's licence. Each case is assessed individually by an AME representing the CAA. The web site is http://www.bdfa.net/index.html

Cabin Crew

Cabin crew in the UK do not hold a statutory licence with an associated medical certificate. However they are required to be fit to carry out their safety function which includes the ability to open doors, operate fire fighting equipment, deploy escape slides, and control and evacuate passengers. They work in a dry hypobaric environment and experience sleep disruption and circadian dysrhythmia. The employer has a duty of care to ensure fitness for employment in the particular environment, and this function is normally discharged by the occupational health adviser in consultation with the employee's GP and/or medical specialist.

Passengers

Medical clearance is required when:

- fitness to travel is in doubt as a result of recent illness, hospitalisation, injury, surgery or instability of an acute or chronic medical condition;
- special services are required (e.g. oxygen, stretcher or authority to carry or use accompanying medical equipment such as a ventilator or a nebuliser).

Medical clearance is not required for carriage of an invalid passenger outside these categories, although special needs (such as a wheelchair) must be reported to the airline at the time of booking.

It is vital that passengers remember to carry with them any essential medication, and not pack it in their checked baggage.

Deterioration on holiday or on a business trip of a previously stable condition, or an accident, can often give rise to the need for medical clearance for the return journey. A stretcher may be required, together with medical support, and this can incur considerable cost. It is important for all travellers to have adequate travel insurance.

Assessment criteria

The passenger's exercise tolerance can provide a useful guide on fitness to fly; if unable to walk a distance greater than about 50m without developing dyspnoea, there is a risk that the passenger will be unable to tolerate the relative hypoxia of the pressurised cabin.

As well as the reduction in ambient pressure and the relative hypoxia, it is important to consider the physical constraints of the passenger cabin. A passenger with a disability must not impede the free egress of the cabin occupants in case of emergency evacuation. There is limited leg space in an economy class seat and a passenger with an above-knee leg plaster or an ankylosed knee or hip may sim-

The British Disabled Flying Association are a registered charity offering flight experiences and full flying training to PPL/NPPL, for disabled people, together with aircraft hire for disabled BDFA members. The aircraft fleet includes Piper PA28s adapted with hand rudder controls to allow pilots with spinal injury, lower limb weakness, amputation or spasticity to fly in safety. Pilots and student pilots with widely varying disabilities are catered for, enabling them to share the uniquely stimulating challenges provided by flying light aircraft. www.aerobility.net

Photograph: Francis Lees, and Nathan Doidge (seated) – student pilots.

ply not fit in the available space. The long period of immobility in an uncomfortable position must be taken into account, and it is imperative to ensure adequate pain control for the duration of the journey, particularly following surgery or trauma. Even in the premium class cabins with more available leg room, there are limits on space. To avoid impeding emergency egress, immobilised or disabled passengers cannot be seated adjacent to emergency exits, despite the availability of increased leg room at many of these positions. Similarly, a plastered leg cannot be stretched into the aisle because of the conflict with safety regulations. There is limited space in aircraft toilet compartments and, if assistance is necessary, a travelling companion is required. Cabin crew cannot provide individual personal assistance.

The complexities of the airport environment should not be underestimated, and must be considered during the assessment of fitness to fly. The formalities of check-in and departure procedures are demanding and can be stressful, and this can be compounded by illness and disability as well as by language difficulties or jet lag. The operational effect of the use of equipment such as wheelchairs, ambulances and stretchers must be taken into account, and the possibility of aircraft delays or diversion to another airport must be considered. It may be necessary to change aircraft and transit between terminals during the course of a long journey, and landside medical facilities will not be available to a transiting passenger. At London's Heathrow Airport, for example, transfer traffic accounts for more than 40% of all passengers.

There is often a long distance between the check-in desk and the boarding gate. Not all flights depart from or arrive to jetties, and it may be necessary to climb up or down stairs and board transfer coaches. It is thus important for the passenger to specify the level of

assistance required when booking facilities such as wheelchairs.

Guidance can be found on the websites of the Aerospace Medical Association (www.asma.org), the International Air Transport Association (http://www.iata.org/ps/publications/medical-manual.htm) and the British Thoracic Society (www.brit-thoracic.org.uk/docs/flyingguidelines.pdf), as well as individual airlines.

Training in aviation medicine

In the UK, aviation medicine is considered a sub-specialty of occupational medicine. The prime post-graduate qualification is the Diploma in Aviation Medicine awarded by the Faculty of Occupational Medicine of the Royal College of Physicians. Diploma is a misnomer for what is a high level qualification requiring six months full time study at King's College London (KCL) and the Royal Air Force Centre of Aviation Medicine (RAFCAM), prior to the academic examination. This is recognised by KCL with the award of an MSc in Aerospace Physiology & Health following satisfactory completion of a further six months research project.

KCL also offers a Basic and an Advanced Aviation Medicine course, each of two weeks duration, intended for medical practitioners wishing to be appointed as AMEs. These courses are ideal for those wishing to gain an understanding of the practical principles of aviation medicine. The website is www.kcl.ac.uk

Cranfield University offers a taught module in aviation medicine as part of the MSc in Human Factors & Safety Assessment in Aeronautics. The module is a two week taught course followed by a written examination in the Department of Systems Engineering and Human Factors. ◆

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ANOTHER OPTION IN YOUR FIGHT AGAINST ALZHEIMER'S DISEASE

Critchley Revisited:
Personification of a Neurologically Dysfunctional Limb

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Macdonald Critchley described personification of paralysed limbs in hemiplegics following an initial anosognosia over 50 years ago. He reported personal knowledge of patients who called their hemiplegic limbs "George", "Toby", "silly billy", "floppy Joe", "baby", "gammy", "the immovable one", "the curse", "lazy bones", and "the nuisance". He found it strange that this phenomenon had not been previously described in the literature.[1] A case of personification of a presumed functional neurological disability is presented.

A 30-year-old right-handed man was referred to the neurology clinic following attendance at A&E with an abrupt onset movement disorder affecting the right arm and leg. Asked what the problem was, he held up his shaking right hand and laughed, saying "This is Trevor". Present for about a month, the shaking had become less noticeable in the leg, varied from time to time, and was worse with reaching for, rather than holding on to, objects. It had occasioned the loss of his job as a graphic designer. There was no prior or family history of movement disorder, but the patient was treated for depression with paroxetine and had been investigated for joint pains with no explanation found. His examination showed no abnormalities, specifically no neglect, aside from a tremor of the right hand and arm which was reduced with distraction and could be entrained with contralateral fast finger movements. The patient's affect was ostensibly cheerful, jokey, and lacking in concern. A provisional diagnosis of psychogenic tremor was made based on the history of abrupt onset, positive entrainment, absence of finger tremor, and the history of depression and probable somatoform disorder.[2] Standard brain magnetic resonance imaging was normal and EEG showed no correlate with the shaking movement which was present throughout the recording.

Although most of the cases reported by Critchley occurred in the context of left hemiplegia, he noted at least one such case in a right-handed man with a right-sided paralysis. A number of other common features were also noted, particularly a detached attitude towards the deficit which was treated with insouciance and cheerful acceptance, reminiscent of the anosodiaphoria characterised by Babinski.[3] These features were shared by this patient, although since there was no history of prior anosognosia it may be a false generalisation to compare this case with personification of hemiplegia.

Critchley mentioned that personification might also occur in amputees with phantom limbs, as well as in hemiplegics,[1] but no previous accounts of personification of neurological deficits of presumed functional origin have been identified. Apparent anosognosia for a movement disorder (hemiballismus) was mentioned by Weinstein & Kahn.[4]

The neurobiological mechanisms in the current case are unknown, but presumably involve some form of dissociation or alteration of body image or schema. It might also fall under the rubric of motor conversion disorder. ◆

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Dancing Eye Syndrome

Mandy Caunter

mother to Ellie Marie Caunter, who was diagnosed with a very rare condition, Opsoclonus Myoclonus, in 2001. Ellie was just 13 months old when medics diagnosed her with the condition also known as Dancing Eye Syndrome. Ellie is now 9 years old.

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On Tuesday 10th July 2000, I gave birth to a healthy girl, Ellie Marie Caunter. Shortly after taking her home she never seemed to settle down. I took Ellie to see the GP, who diagnosed it as colic. This went on continuously for three months with constant crying throughout. After that period Ellie started to settle down, growing into a beautiful little girl. We celebrated Ellie's 1st birthday watching her take her first steps; it wasn't until shortly after this that her health started to deteriorate.

Our first concerns were at dinnertimes when Ellie would purge on her food, the second concern was that Ellie constantly wanted me holding her and would scream for hours on end, the only time Ellie seemed settled was when she was in my arms. Thirdly, when feeding Ellie her bottle, I noticed her eyes would roll to the back of her head showing the whites of her eyes. This caused me great concern as I thought she was having a fit. The final thing was when all Ellie's motor skills had gone, her speech had stopped, her ability to walk, sit and balance herself were lost.

I was so alarmed that I took her straight to the doctors. How could my daughter just wake up one morning and lose all her abilities? The GP informed me it was just a common cold; they booked an appointment to see a paediatrician who I was to see in a fortnight at Torbay hospital. Whilst waiting for my appointment date Ellie deteriorated so much so that we noticed her head was tilted to her left hand side. It was a mother's instinct this was no cold, so I took matters into my own hands and took Ellie to A and E. I explained all Ellie's symptoms to the junior doctor including Ellie's head constantly sitting to the left hand side, he suggested it was teething and was sending me home with paracetemol. I was adamant this was not a teething problem, after bringing up my other two sons I knew this was not normal behaviour for any child.

Therefore, I asked to see a paediatrician; they took one look at Ellie and admitted her. During the days ahead Ellie went through every test imaginable, this was very distressing for me and my husband to watch our little girl go through. After a week of tests ranging from blood test to brain scans etc, all results came back clear, no one could pin point what was wrong with her.

We met with Dr A, a paediatric consultant. She told me of one other case that she had seen before she was quite confident taking into account all Ellie's symptoms that it was the same diagnosis, a very rare condition, opsoclonus-myoclonus, also known as dancing eye syndrome. It took her only one week to diagnose Ellie.

Dr A told us that we would have to travel to Frenchay Hospital in Bristol for Ellie's medication. On arrival straight from Torbay hospital we were met by Dr B who had waited behind to see us as it was a late Saturday afternoon. We weren't to be seen till the Monday therefore Dr B felt it necessary to see Ellie on her first arrival. He tested Ellie straight away, noticing on first glance Ellie's eyes.

After taking a closer look he saw Ellie's abnormal eye movements and confirmed the erratic eye movement as dancing eye syndrome. He put Ellie on 10mg of steroid. We were left in the dark all weekend, devastated not knowing anything about the condition and what our poor daughter was going through. We were living a nightmare, my two sons were back in Torbay with family, too young to know what was going on and missing us, whilst our youngest child and only daughter was deteriorating right in front of our eyes. Her ability to sit and support her own bodyweight had just gone. She was constantly in our arms as she was screaming, her hands were shaking and she couldn't settle to go to sleep. We were so distressed just wanting to help her.

Monday arrived and we saw Dr B first thing at 9am. Once he started telling us about the dancing eye syndrome, we had the most devastating news any parent could hear, there was a possibility our 13-month-old daughter could have a tumour. We just couldn't believe what we were hearing. Ellie underwent a brain scan for the second time; this was a mistake on the hospital's behalf they were meant to be carrying out a scan on her abdomen to see if they could find a tumour. Our daughter had been put out unnecessarily and had to undergo the same procedure again this time to look for a tumour on her abdomen. After the surgery they confirmed they had found a tumour on Ellie's adrenal gland. We had the option for it to be removed and me and my husband thought it best to remove it.

During this time I also went to see an oncologist. They told me that Ellie was stable at the time but if purple spots were to appear anywhere on her body then this could be fatal. At that last word we went into shock, all the family rushed up the motorway to comfort us, we didn't know how much time Ellie had left. It was such an emotional time for the family. For three weeks we had to stay at Frenchay, monitoring her medication which was oral: steroids of 10mg daily and medication to help her sleep.

After Frenchay, we were allowed to take Ellie home with us until we were moved onto Bristol children's hospital. It was such a relief to be taking my daughter home to be back with the family and my two boys. Although this was only a short visit as in seven days time we had to be at Bristol children's hospital, this is where Ellie underwent surgery to have the tumour removed.

Whilst at Bristol hospital they took video footage to record Ellie's abnormal eye movement. The surgery went ahead and the outcome was a neuroblastoma capsulated so Ellie didn't have to have any follow-up treatment. We left the hospital a week later; at this stage Ellie's eyes were going absolutely ballistic. Ellie was very distressed at this time.

I would now like to talk about Ellie's behaviour when she was first diagnosed to the present day.

Behaviour was a huge issue; the constant screaming fits, the head banging, the aggressiveness in her and just her general frustration and distress. To calm Ellie's screaming I would constantly

have to have Ellie sat on my hip and keeping her moving. My husband would have to take her out in her pram, at all hours of the night just to calm her down. The head banging happened when I physically couldn't carry her any longer. I would place her on the floor and immediately she would start banging her head on the floor until she was back in my arms. Her aggressiveness was a problem to her older brothers, in her frustration she would pinch them and be very nasty towards them. For comfort she would play with her dad's ears, making them bleed. This was all due to frustration again. Ellie would be very distressed when around loud noises and sudden movements. Moving traffic and car journeys made her even worse. When in her car seat she would find the strength to release herself so that she could be on my lap. Her strength was abnormal. As every year went by slowly being weaned off her medication, her behaviour steadily improved. Ellie is now nine years old, she doesn't really have any major behaviour problems but when becoming ill we notice she can still be slightly aggressive. Also Ellie is very protective over her possessions and doesn't like change. She will notice the smallest of differences whether it is a new piece of furniture or something not being in its usual place.

The emotional side of things have been very hard for all the family. When Ellie was in the prime of her illness, the emotional strain was unbearable. The constant attention Ellie both wanted and needed was a massive strain for the immediate family. Ellie was very sensitive to everything. My husband had to give up work as it became impossible for me to care for Ellie 24hours a day as well as keeping a normal family environment. Our much loved family dog that had been with us for five years had to go as

we just couldn't look after him any longer. The strain got so bad on my two sons who were only 11 and 13 that they stayed with their grandparents. This was just for them to get peace and quiet as they were both at school. Myself and my husband's marriage was at breaking point due to the stress and strains of looking after a child with dancing eye syndrome. Sleep was a huge factor, as we were lucky to get 2-3 hours a night. Ellie would sleep in bed with us as this is the only place she would settle. This went on until the age of seven.

There were times when we couldn't see any light at the end of the tunnel. Ellie had been off steroids for six months where she was making really good progress. Then she had a virus and she lost all of her abilities again. At this stage I just couldn't take anymore, I became so low that I didn't really want to carry on. The doctor prescribed me anti-depressants which helped. As each year has gone by Ellie has improved slightly with her emotions. She is still very sensitive and shy. She finds it hard to play in a group and prefers to have one to one company. She has a very caring and gentle nature, to the extent that I have concerns especially with her school life which I will go into further now.

Ellie found starting school hard as she was so used to being with me 24hours a day. She went to playschool, where she had one to one support. The hardest part was separating her from me; I had to stay with her as it was impossible to leave her. After a year of being at play school she accepted me leaving her, although at times it was hard. She started mainstream school still with the problem of being away from me. They suggested that a statement wouldn't be needed as they didn't detect any learning difficulties at this stage. They wanted to concentrate more on settling Ellie into the

schooling environment as this was the main concern of the time. As Ellie progressed through the years it was evident Ellie had quite severe learning difficulties. It was quite evident that Ellie needed to be statemented in year three. I felt they had left it too late as Ellie was so far behind. I strongly believe that a child with dancing eye syndrome should be statemented as soon as they start schooling. She struggles with the academic pace as tests have proven that she is about two and half years behind her peers. She gets a lot of pressure from her peers as they notice she can't keep up as well as they do. She accepts now that she has to go to school but doesn't enjoy it. She has one to one help every morning at school with her maths and literacy and in the afternoons she is left to her own devices. Ellie is very behind with her reading and writing skills, hopefully she will be able to pick it up one day. Ellie is in year five now so in a year's time she will be moving onto secondary school. We have been advised by the senco at her school that Ellie would benefit more academically if she went to a special needs school. My husband and I are at the stage now where we are going to have to make the best decision for Ellie's future.

On a positive note, Ellie is a happy go lucky little girl. We never thought she would be able to ride a bike without stabilisers but she can. She is a very good swimmer and belongs to a swimming club which she enjoys very much. We feel very lucky as the dancing eye syndrome seems to have disappeared from her but unfortunately it has left her with severe learning difficulties. Life now is so much easier for the whole family unit, it's been a tough ride but things have definitely improved over time. ◆

BOOK REVIEWS

Oxford Handbook of Clinical Rehabilitation Second Edition

It is daunting to review an Oxford handbook, especially when written by colleagues whom I admire and who are experts in the field of rehabilitation. The handbook has the reputation for being an essential part of every rehabilitation clinician's bookshelf. It is primarily aimed at a wider multidisciplinary audience and not just at doctors in the field of clinical rehabilitation. I would like to emphasise that this review of the book is more from the perspective of a medic within the multidisciplinary team and specifically a trainee's viewpoint.

The book easily fits in the coat pocket with less than 500 pages of standard Oxford handbook size. The initial five chapters deal with the general concepts of rehabilitation like the ICF and multidisciplinary team. These are followed by chapters on management of some common clinical themes encountered in rehabilitation like spasticity, continence, sexuality, eating and swallow-

ing disorders, communication, technical aids, cognitive and behavioural problems. And then there are chapters dedicated to specific neurological conditions like multiple sclerosis, stroke, etc.

The ICF model and general concepts in epidemiology are brilliantly summarised. The chapters on the rehabilitation team and services are relevant and to the point. The chapter on assessment and outcome measures describes the types of scales and some scales relevant to common clinical problems. This is an area which is emphasised more in rehabilitation practice than in other clinical specialties, and which every rehabilitation MDT member (medic, physio, occupational therapist, speech and language therapist, etc.) should be well informed about. I think a brief description of the different psychometric properties like validity, reliability, and floor and ceiling effect could be included in this chapter for the benefit of junior clinicians. One
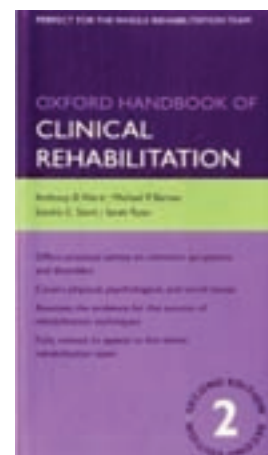
topic missing in the initial chapters is 'assessment of capacity' with reference to the Mental Capacity Act (MCA) and the recent Deprivation of Liberty Safeguards (DOLS).

Among the clinical theme chapters, the systematic approach to treating spasticity and urinary continence is very useful. The book rightly has a separate chapter dealing with sexual problems in complex neurological conditions. The chapters on behavioural disorders, psychiatric problems and cognitive dysfunction carefully define the role of psychological strategies/medication and the fine balance between the two needed in a rehabilitation setting. The flow chart on vocational rehabilitation and section on challenges during transition to adult life are impressive. It is a surprise not to find management of sialorrhoea in the chapter on swallowing disorders.

The chapters on specific neurological conditions deal excellently with the epidemiology, management and most importantly prognosis which are core essential facts needed when dealing with family and carers. The conditions covered are multiple sclerosis, stroke, traumatic brain injury, spinal cord injury, Parkinson's disease, MND, peripheral nerve disorders, epilepsy and dementia. There are two chapters dealing with common (non-inflammatory) musculoskeletal conditions and inflammatory rheumatologic conditions.

The practice of neurorehabilitation and musculoskeletal rehabilitation is very closely linked in countries outside UK because rehabilitation physicians are trained in both before they sub-specialise in their areas of interest. Oxford handbooks usually have substantial international readership and to maximise this, I feel the handbook should provide more room for musculoskeletal rehabilitation. For example, the latest evidence on different rehabilitation approaches for chronic back pain like functional restoration programmes could be added in the section on chronic back pain. The evidence for specific exercise regimens, steroid injections, autologous blood injections (approved by NICE) in the rehabilitation of tendinopathy could be included in the relevant chapters. Rehabilitation of concussion in sport could also be considered for inclusion.

The chapter on amputation is brief and could do with more facts on prostheses, it omits management of phantom pain altogether (in fact it does not feature anywhere in the book). Normal gait cycle (and abnormal gait patterns) is another important topic missing from the book. There is a section on 'chronic pain' in one of the earlier chapters but it lacks sufficient detail. A dedicated chapter on pain management among the initial chapters would have been ideal.

Overall, this is an excellent pocket guide on a par with other Oxford handbooks. A little more expansion in a few chapters and some additional topics would make the handbook more appealing to doctors in the field and give it a better international readership. There is already sufficient blank space in the book and such expansion can easily be made without increasing the volume of the book. I am aware the blank space is meant for reader's notes and observations, but frankly speaking how often does this happen? ◆

The Confabulating Mind. How the brain creates reality
Confabulation.
Views from neuroscience, psychiatry, psychology, and philosophy

Two books on confabulation published within a year by OUP: one thinks, perhaps, of London buses, but, by contrast, these books are an experience well worth waiting for. For example, did you know that in German, WIGAN is a non-word (Schnider, p 149)?

Schnider's monograph is suffused with his clinical experience of trying to rehabilitate confabulating patients: even in the midst of the science he acknowledges that this is a "gruelling experience" (p243). A review of the history of confabulation, including translations from the early works of Korsakoff, Kraepelin, Pick and others, is followed by the thorny issue of classification, with Schnider developing a 4-fold schema of intrusions, momentary confabulations, fantastic confabulations, and behaviourally spontaneous confabulations (p63-4), of which the latter form his main area of study. The aetiology is examined, with anterior limbic structures thought culpable, and the pathogenesis, including a wide variety of diseases, along with associated disorders (amnesia, disorientation, false recognition syndromes including the Capgras delusion, and anosognosia). Mechanisms are elucidated by means of psychophysical and neuroimaging studies, leading to the proposition that confabulators have reality confusion and a failure to integrate contradictory information due to the failure of a filtering process, 200-300 ms after stimulus presentation and before recognition and re-encoding, which normally permits suppression of currently irrelevant memories. This is a fascinating book, systematic in its approach. For those disinclined to battle through the detail, the conclusions to each chapter are excellent.

Hirstein's multi-author volume is, as expected, more diffuse than Schnider's but none the less stimulating. False memories, only briefly touched on by Schnider, are described at greater length here, in two chapters (from Loftus and Zaragoza) the import of which I found rather chilling: our brains have a surprising cognitive vulnerability to forced fabrication (I would be interested to know if this also applies to eidetics). Coltheart & Turner present evidence that the normal response to questions we don't know the answer to is not, as might be imagined, to admit ignorance with an "I don't know" response, but to indulge in confabulation, a tendency exacerbated in certain brain disease states (and by some clinicians?). Wheatley, in what is the best chapter (or worst, depending on your degree of concreteness) I have read in many moons, demolishes the notion of the brain as veridical. The book is more philosophically oriented than Schnider's, and perhaps more peripheral to clinical interests, though still grounded in clinical neuroscience.

In summary: in the human brain, memory is a construction, confabulation is normative, perception is illusion, and "meaning" is privileged over accuracy. A nihilist might conclude that life mediated through such a prism is an essay in futility, and aporia the only tenable neurophilosophy. ◆

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Developmental Delay – Causes and Investigation

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Introduction and definitions

This article provides a systematic approach to the causes of developmental delay and the importance of its rigorous investigation. It particularly highlights practical aspects relevant to adult neurological practice.

Delayed development most commonly follows the usual pattern of development where skills are acquired more slowly (e.g. Down's syndrome). Less commonly, skill acquisition can be disordered (e.g. autism). 'Delay' is a misnomer – children with developmental problems rarely 'catch up', and will usually have continuing difficulties with learning later in life.

Developmental delay is common, affecting 1-3% of the population.[1] Developmental delay is defined as significant delay (more than two standard deviations below the mean) in one or more of the following developmental domains:[2]

- Gross motor
- Vision & Fine motor
- Hearing, Speech & Language
- Social, Emotional & Behavioural

Developmental delay is a descriptive term used for children whose difficulties are apparent earlier in childhood where a cause is not yet established. It does not imply a particular organic or syndromic cause, and the term does not appear in ICD-10.[3]

Developmental Delay can be divided into:

Global developmental delay – delay in two or more domains (often delayed in all domains)

Specific developmental delay (e.g. Motor or Speech & Language) – delay in a single domain

The focus of this article is **Global Developmental Delay**.

Causes of Global Developmental Delay

Global developmental delay can be the presenting feature of a huge number of neurodevelopmental disorders (from learning disability to neuromuscular disorders). It is not possible to provide an exhaustive list; Table 1 gives an approach to aetiology.

Careful evaluation and investigation can reveal a cause in 50-70% of cases.[4,1] This leaves a large minority where the cause is not determined. It is still useful to investigate globally delayed development whatever the age of the child (occasionally older children with significant disability may not have been investigated adequately).

TABLE 1: Causes of global developmental delay (adapted from Forsyth and Newton 2007[5]).

Category	Comments
Genetic or Syndromic *Identified in ~ 20% of those **without** neurological signs, dysmorphic features or a family history*	• Easily identified syndromes e.g. Down's syndrome • Genetic causes that are less obvious in early childhood e.g. Fragile X, Velo-cardio-facial syndrome (22q11 deletion), Angelman's, Soto's, Rett's, maternal Phenylketonuria, Mucopolysaccharidoses, Duchenne Muscular Dystrophy, Tuberous Sclerosis, Neurofibromatosis Type 1, and subtelomeric deletions
Metabolic *Identified in ~1% of those **without** neurological signs, dysmorphic features or a family history*	• Nationwide universal neonatal screening for Phenylketonuria (PKU) and Medium-chain acyl-Co A Dehydrogenase deficiency (MCAD). • e.g. Urea Cycle disorders.
Endocrine	• There is universal neonatal screening for congenital hypothyroidism
Traumatic	• Acquired brain injury
Environmental Causes	• Children require their basic needs for food, clothes, warmth, love and stimulation to be met to develop normally. • Children in neglectful, abusive, fearful, under stimulated environments may not show normal development. • This can be a contributory factor co-existing with other pathology and where the child's needs are outside the parents' capacity to provide for them.
Cerebral Malformations	• e.g. Neuronal Migration Disorders
Cerebral Palsy and Developmental Coordination Disorder (Dyspraxia)	• Motor difficulties can prejudice development in general
Infections	• Perinatal e.g. Rubella, CMV, HIV • Neonatal meningitis
Toxins	• Fetal: Maternal alcohol or drugs in pregnancy • Childhood: Lead toxicity

Why is finding a cause important?

Establishing a cause has many benefits for the child and family and improves overall quality of life:[4]

- The family gains understanding of the condition, including prognostic information
- Lessens parental blame
- Ameliorates or prevents co-morbidity by identifying factors likely to cause secondary disability that are potentially preventable e.g. surveillance of other systems such as vision and hearing
- Appropriate genetic counselling about recurrence risk for future children and the wider family
- Accessing more support (e.g. within education services and specific syndrome support groups)
- To address concerns about possible causes e.g. events during pregnancy or delivery[1]
- Potential treatment for a few conditions

Investigation of Global Developmental Delay

Thorough history and examination are vital to produce a formulation of the child's problem and target investigations appropriately.[4,6] The diagnosis may occasionally be immediately obvious from history and examination. More often time is needed to review clinical features, case notes, prior investigations and to consult the literature, dysmorphology and neurogenetic databases.[4]

Transfer of a patient into your clinic from paediatric services is a good opportunity to review the diagnostic process. Most investigations are likely to have been performed early in the child's life; medical advances especially in genetic investigations and neuroimaging techniques may allow further diagnostic possibilities now. Clinical geneticists are an invaluable source of diagnostic acumen and suggestions for further suitable investigations.

The evidence base for investigation of developmental delay is poor and published work is mainly consensus opinion.[2] There is no one agreed recipe for the investigation of global developmental delay and there is much variation in practice. Historically, there has been patchy introduction of tests as they became available. This means it is well worth reviewing what investigations have actually been done.

A scheme illustrating the investigations considered for global developmental delay is shown in Figure 1. You should expect the first line investigations to have been done, and relevant second line investigations depending on clinical circumstances.

Practicalities:

The approach to performing investigations is influenced by:

- identifying treatable conditions
- identifying prevalent serious conditions (e.g. Creatinine Kinase for Duchenne Muscular Dystrophy)
- economic considerations (inexpensive, easy to perform tests for less common disorders, e.g. Fragile X)
- the practicalities of performing the investigations on young children

Figure 1: A scheme illustrating the investigations considered for global developmental delay (adapted from McDonald et al 2006[2] and 'A guide to investigation of children with developmental delay in East Anglia 2005')[1].

First Line
Chromosomes
Fragile X
U & E
Creatinine Kinase
Thyroid Function
FBC
Ferritin
Vision and Hearing assessments

Figure 1 Notes:
- MECP2 = gene for Rett's
- VLCFA = Very Long Chain Fatty Acids are for Peroxisomal disorders (e.g. Adrenoleukodystrophy)
- GAGs = Glycosaminoglycans are for Mucopolysaccharidoses (e.g. MPS type III Sanfilippo)
- WC enzymes = White cell enzymes. These and oligosaccharides are tests for lysosomal storage disorders (e.g. GM1 Gangliosidosis).
- Transferrins are for congenital disorders of glycosylation (CDG) e.g. type 1a
- 7-dehydrocholesterol is for Smith-Lemli-Opitz
- Paired CSF and plasma lactate are to investigate mitochondrial disorders where there are concerns about growth, multisystem involvement, visual and hearing impairments, and abnormal MRI brain.[1]

Second Line

Metabolic
Family History
Consanguinity
Regression
Organomegaly
Coarse Features
Seizures
Abnormal Head Size
Episodic decompensation
Congenital Ataxia
Sensory impairment Including
Glue Ear

Neuroimaging
Abnormal Head Size
Seizures
Neurological signs
 Cranial nerve abnormalities
 Cerebral palsy
 Neurocutaneous signs
Dysmorphic facies
Arthrogryposis
Severe visual impairment
 Optic atrophy
 Nystagmus

EEG
Seizures
Speech Regression

Genetics
Dysmorphism
Abnormal Growth
Sensory Impairment
Unusual Behaviours
Family History

Blood
Lactate (+/- CSF Lactate)
Ammonia
Amino Acids
Lead
VLCFA
Acyl Carnitines
Biotinidase
Homocysteine
Transferrins
WC enzymes
7-Dehydrocholesterol

Urine
Organic Acids
GAGs
Oligosaccharides

MRI
CT for bones, calcification

Consider 24hr EEG

Consider
Telomeres
Microarrays
Myotonic Dystrophy
Angelman's
Prader-Willi
MECP2

Simple blood tests can be achieved without too much difficulty.

MRI brain may require a general anaesthetic. This may have been delayed if the child was approaching an age (~ 5yrs or developmental equivalent) where they could manage an MRI without an anaesthetic.

If an anaesthetic is planned, consideration should be given to whether other invasive investigations can be done under the same anaesthetic e.g. blood tests, lumbar puncture, and skin or muscle biopsy.

Genetics

Chromosome analysis yields the highest number of abnormalities when investigating global developmental delay, even where there are no clinical features of a genetic problem.[2] Chromosomes and Fragile X testing are first line investigations if history and examination do not reveal an obvious aetiology. Fragile X is the commonest cause of inherited learning disability, but remains a rare disorder. Its dysmorphisms are difficult to recognise clinically in younger children and girls.

Subtelomeric rearrangements are karyotypically invisible and are traditionally looked for where the karyotype is normal but a genetic abnormality is still suspected. Specific tests for sub-microscopic microdeletions (e.g. for William's or Velo-cardio-facial syndrome) can be requested when clinical index of suspicion is high.[1]

The new advances in Microarray technology offer up to 15% more diagnoses than conventional karyotyping for global developmental delay. They are cost-effective and, although not yet used routinely, are likely to be adopted widely in the future.[7]

Neuroimaging

Cranial MRI in young children (≤5-6yrs) requires day case admission to hospital for sedation or general anaesthesia. It is a second line investigation performed in the circumstances outlined in Figure 1, in addition to global developmental delay. Neuroimaging performed in the first two years of life before cerebral myelination has been completed should be repeated after an interval of about a year.

The proportion of neuroimaging abnormalities found in children with delayed development varies widely between studies (9-80%).[8] Where high proportions are reported, some of the reported abnormalities are in children where the diagnosis would have been obvious clinically, not contributory to the diagnosis, or of uncertain significance. The yield of useful, diagnostic abnormalities is higher (60%+) using newer imaging techniques and in a population selected for global developmental delay with the clinical features outlined in Figure 1.[1,2]

CT scanning is only used where cerebral calcification is suspected (e.g. perinatal infection) or to look for an abnormality of skull bones.

Metabolic

Individual Inborn Errors of Metabolism (IEM) are a rare cause of global developmental delay (~1%). However, they can present with non-specific developmental delay and some are amenable to treatment. Metabolic investigations are targeted and selective (there is no such thing as a 'metabolic screen'). Useful metabolic investigations and the clinical circumstances in which they are considered are outlined in Figure 1.[1,2]

Biotinidase deficiency uncommonly presents with global developmental delay without other features, but early diagnosis and treatment improves outcome. This is not a universal first line investigation in many parts of the UK, but some authors argue that it should be.[2] Many countries screen for this disorder as part of universal neonatal screening; the UK does not.

Biochemistry
CK

Boys with Duchenne Muscular Dystrophy can present with delay in more than one domain of their development (e.g. language and motor delay); therefore Creatinine Kinase (CK) is measured as a first line investigation in boys with global developmental delay. CK measurement is considered in girls with severe global (and especially motor) developmental delay.

Renal, Bone

Electrolytes and Urea are first line investigations, and Calcium measurement can assist in the diagnosis of Velo-cardio-facial and Williams syndromes, and pseudohypoparathyroidism.

TFT

Thyroid Function tests are easy to perform and have historically been part of investigations for developmental delay. TSH is measured as part of universal neonatal screening. In addition, many chromosomal abnormalities are associated with an increased and ongoing risk of hypothyroidism (e.g. Turner's, Velo-cardio-facial syndromes). Thyroid function tests are worth repeating periodically in those at risk as the clinical diagnosis of hypothyroidism is more difficult in those with developmental difficulties.

Lead

Chronic lead toxicity has long-lasting developmental effects (developmental delay, behavioural change and poor coordination) and is potentially treatable by chelation. Despite evidence that children with developmental problems have higher blood levels of lead than the general child population;[9] interpretation of blood lead levels remains controversial.[10]

FBC

A Full Blood Count (FBC) and Ferritin identifies Iron deficiency which can cause global developmental delay and is easily treated.[2]

Neurophysiology

EEG should not be performed routinely, but reserved for those with seizures, or speech regression (looking for Landau-Kleffner) associated with global developmental delay.

Other Investigations

All children with global developmental delay should have Visual and Audiology assessments early on. An Ophthalmology opinion should be sought if there are concerns about visual function, abnormal appearance of the eyes or when looking for clues to the underlying diagnosis.

A TORCH screen for congenital infection is performed in children with Intrauterine Growth Retardation (IUGR), microcephaly, or sensory impairments. PCR for infective organisms can be performed retrospectively on the blood spots taken for the neonatal screening programme, even many years later.

Radiographs are performed primarily for suspected skeletal dysplasia, or lead toxicity. Subtle skeletal dysplasia can be difficult to diagnose on radiographs performed when most of the skeleton is not yet ossified and may need to be repeated at a later date.

Conclusions

- Global developmental delay is a common problem in paediatric practice and has a wide aetiology.
- Selective investigations are useful in determining the cause, but the cornerstone of the diagnostic process is careful clinical examination.
- Finding a cause confers many medical and social benefits for the child and family.
- Recent technological advances, especially in Genetics and Neuroimaging, make it important to review the need for repeat or updated investigations.
- The transfer of a patient to your practice from paediatrics is an opportunity to review the diagnosis (or lack of one), and to evaluate the need for further investigation. ◆

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Touting for Trade;
Attracting Future Neurologists

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Neurology in the UK has traditionally been a popular and competitive specialty, with no difficulty in attracting applicants from amongst the best medical graduates. Dramatic changes in neurology training have occurred in recent years.[1,2] Alongside this, it seems that neurology may be beginning to have difficulty recruiting trainees. Although neurology remained the second most competitive medical specialty nationally in 2007, there are now unfilled training posts in parts of the country. In one region, not a single ST2 trainee listed neurology as their first choice of specialty in 2009. This article will discuss possible reasons behind decreasing interest in neurology as a career choice and consider ways to combat this.

Future career choices are still strongly influenced by both experience of a subject as a medical student and a particular teacher and department.[3] Neurology has suffered from being perceived as a difficult specialty intellectually, causing many students and junior doctors to develop 'neurophobia'.[4] In a UK based survey of medical students, senior house officers and GPs, neurology was ranked as the most difficult of seven medical specialities and was the speciality in which they had the least knowledge and clinical confidence.[5] Knowledge of basic neuroscience was ranked as the most important factor for perceived difficulty in neurology, with poor teaching, reputation of neurology and complexity of examination also highlighted. It is perhaps not surprising that neurophobia develops when medical student teaching in neurology is only two weeks in the total medical course in some centres.

Exposure to medical specialties prior to entering specialty training also influences future career choices. In more than 55% of junior doctors surveyed one and three years after graduating, experience and enthusiasm for the job was shown to have influenced future career choice in medical hospital specialties 'a great deal'.[6] The recent change in training for foundation doctors and core medical trainees may be impacting on entry to neurology training. Foundation posts in neurology are rare compared to other medical specialities and are often reported as being linked to less attractive posts. In the past, stand-alone neurology SHO posts attracted post-membership trainees with a clear interest in the specialty, but today's core medical trainees have less control over the specialties they are exposed to. Changes in working patterns may also have reduced the opportunities for neurology SHOs to take part in clinics and other useful training opportunities.

Are the revolutions in neurological training discussed by Fuller 2007[1] now having downstream impact on applications to the speciality? In the annual report from the JRCPTB to the PMETB 'acting down' of specialist trainees to cover gaps in rotas from reduction in core medical trainee numbers was identified as a key concern.[7] The ABN trainees' committee is aware this is still a major issue, exacerbated by rota demands from the European Time Working Directive. This could easily result in trainee dissatisfaction resulting in negative publicity of the specialty to future trainees. However, despite these difficulties, overall satisfaction among neurology trainees still remains at over 70%.[8]

We are now entering a stage where neurologists need to compete with their fellow specialties to attract applications to specialist training. As a specialty we are in a good position to do this. British neurology has retained its strong academic record whilst now giving greater opportunity to those wanting to be involved in front line acute neurology.[9,10] It seems vital to encourage potential neurologists from the very earliest stages of their careers. Changes in teaching style at medical schools can alter the perception and knowledge base of neurology in medical students. This has been shown by the teaching program at Guy's, King's and St Thomas' Medical school[11] which concentrates on teaching core neurology skills and common neurological conditions as stipulated in the ABN curriculum. The use of multimedia has been expounded by Singapore neurologists, using video clips as well as a neurolocalisation computer game to try to demystify neurology.[12]

The initiative of the ABN to host a roadshow for medical students and foundation year doctors at the 2010 ABN Meeting is a positive step in raising the profile of neurology (see box below). As trainees we are working on compiling a national CD of interesting neurological video clips to try to provoke interest at local career fairs. Updating the ABN website, with more open access areas may also encourage interest in our speciality. We need to nurture and encourage our SHOs, making sure that their training needs are not lost amid the pressures of service delivery. Finally, the power of the individual teacher in trainees' career choices should not be forgotten: inspiring individuals have influenced the careers of many current neurologists, who we hope can now go on to inspire the next generation. ◆

For more information and support to participate in a local careers fair contact Christine Burness (librarian of the ABNT chrissieburness@doctors.org.uk).

The medical student and foundation year roadshow, will be held before the main ABN conference in Bournemouth, on the morning of the 11th May. Contact Josie Shew (josie.shew@theabn.org) for more details.

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My neurology training includes an SHO post in King's college and registrar posts in Wolverhampton, Singapore, Nottingham and now Sheffield. I am preparing for my Phd viva on the glial cell involvement in Motor neuron disease. It has taken me an extra two years after leaving the lab to write up and submit.

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The Research Series

In this, the last issue of the research series, we have come full circle. A year ago we started the series with a review of the first annual research forum which took place at the Association of British Neurologists (ABN) conference in Liverpool. Set up with the aim of inspiring and facilitating young neurologists to pursue research in their career, the review started the research series well. The inspiration behind the research forum, Dan Blackburn, talked about his vision for the research forum in the future, a vision which has now been taken up by the Clinical Research and Academic Committee (CRAC) chaired by Patrick Chinnery, with Beth Mallam as the trainees representative.

Since then, in the intervening issues, we have travelled along the academic pathway, from medical student to principal investigator, with guides along the way to point out the path. In this final issue, we consolidate this route finding. Dan Blackburn, the inspiration behind the research forum, talks of his sense of wonder at the start of the path and provides us with the fuel to start our journey. Beth and Patrick show how CRAC have provided us with a team of guides, in the form of the research forum in Bournemouth and the ABN research network, who are available to show us how to pass treacherous parts of our journey ahead, if we only ask. Finally, we are lucky to have one of the most influential neurologists of our time, Alastair Compston, to show us what lies ahead from his high vantage point above.

The research forum inspired the trainees committee of the ABN (ABNT) to help those trainees interested in research to get involved. We hope that we have gone some way to doing this. We hope that for anyone stuck at the fork, uncertain of the way, that this series will help you to choose the route that is right for you. ◆

Boyd Ghosh, Series Editor.

Seeing the Wonder in Research

"Any sufficiently advanced technology is indistinguishable from magic"
Arthur C Clarke

"In the expanding field of knowledge we but increase the horizon of ignorance"
Henry Miller

The quotes above are the reasons why I chose to do research. As I prepare to submit, these are the same reasons why I would like to carry out more research and ponder over my results from the last five years. The horizon of ignorance is slighter wider and there is more mystery than ever about what astrocytes and microglia do in motor neuron disease. What is more, there are scientific experiments, such as real-time imaging of glial function in animals running around in a cage, which seem to me, like magic.

I started my research as ignorant as any. I had done a BSc in psychology, so had no experience in basic science research. I had no idea what I was letting myself in for.

There are many reasons why we choose to do research, from thinking it will make us a better clinician, to wanting to become a professor. How do we start a research project? What should we do? Who should we choose to be our supervisor? I struggled with these questions. The strategies we usually use to answer these questions are usually straightforward, if slightly limited in scope. We can find a supervisor and ask them what project they have, or we can ask the deanery to see if they can advise what is available.

During my research, I travelled to America to present a poster at the American academy of Neurology. At this conference, there was a research forum where scientists at different stages of their careers gave brief talks and took questions. Most importantly, scientists were identified from different groups with different research topics. Anyone interested in those research topics or willing to live in that geographical location were encouraged to approach these scientists, not just to ask about potential research posts, but also to ask for general advice, support and mentorship. Having struggled with these issues myself, I recognised that a research forum would be invaluable in the UK. After some planning we had a research forum in Liverpool. There were researchers from different levels giving talks and taking questions. However this first forum was in a lecture theatre and there was no opportunity to ask informal questions.

What next?
Reading this is a good start. As Patrick Chinnery and Beth Mallam have highlighted, there is a website with information on who is doing what and where. There is also a second research forum at Bournemouth, with ample opportunity to have informal discussions with researchers.

Please look at the website when it goes live and please come to the second research forum in Bournemouth. Try to find a mentor, ask questions that may seem silly, but come and join the quest to expand the field of ignorance and perform magic. ◆

Patrick Chinnery

is chair of the Clinical Research and Academic Committee of the Association of British Neurologists. As a Wellcome Trust Senior Fellow in Clinical Science and Professor of Neurogenetics in Newcastle upon Tyne, he runs the clinical neurogenetics service closely linked to a translational research programme in genetic neurology, with a particular interest in mitochondrial disorders.

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Beth Mallam

is the ABNT Research Representative. She is currently working towards a PhD with Professor Scolding's team at Frenchay Hospital, Bristol. Her research is looking at the potential of mesenchymal stem cells as a therapy for Multiple Sclerosis.

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The ABN Research Network and the Second Annual ABN Research Forum

The Clinical Research and Academic Committee (CRAC) has recently introduced two long-lasting resources for those interested in advancing their career in neurological research. The first is an interactive database of information, the 'ABN Research Network', to be found on the ABN website; the second is the Annual ABN Research Forum, which will take place at the ABN Meeting in Bournemouth in May 2010. These resources will benefit trainees embarking on their careers in research, clinical academics who are looking to recruit new trainees or colleagues and more senior Principal Investigators seeking to extend their time in research or dovetail research with their clinical work.

The ABN Research Network on the ABN website

The aim of this network is to assist neurology trainees and consultants to find their ideal research opportunity. The Network will consist of three main sections:

- a guide to getting involved in research (with links to the articles in this ACNR series on careers in research)
- a database of funding opportunities
- an electronic compendium of UK academic neurology departments, including links to current vacancies

This network will be an easily accessible, one-stop source of information, where people can find all the information necessary to move their career in research forward.

More than 85% of the research centres invited to be represented in the compendium have responded and we hope that the remainder will do so once they see the site up and running! In order to keep the network straightforward and easily navigable, information for each department has been standardised: browsers are directed to departmental websites for more detailed information.

It is envisaged that the network will 'go live' before May 2010, and will be clearly sign-posted on the ABN website.

The Annual ABN Research Forum

In 2010, the Annual ABN Research Forum will be in the form of a poster fair. This will take place alongside the main poster session, allowing those interested in research to browse posters, illustrating what is happening in neurology across the UK. Perhaps more importantly, it creates an ideal opportunity for informal discussions with those presenting the posters. Trainees interested in research are specifically invited to attend (with their CVs), in order to take full advantage of this unique opportunity to meet key investigators in a relaxed environment. ◆

> Further information, including poster abstracts, about this year's Research Forum will be available in the ABN Meeting Welcome Packs.
>
> If you would like any further information about becoming involved with either of the above, please email Beth Mallam (bethmallam@doctors.org.uk) or Josie Shew (josie.shew@theabn.org)

Patrick Chinnery

is chair of the Clinical Research and Academic Committee of the Association of British Neurologists. As a Wellcome Trust Senior Fellow in Clinical Science and Professor of Neurogenetics in Newcastle upon Tyne, he runs the clinical neurogenetics service closely linked to a translational research programme in genetic neurology, with a particular interest in mitochondrial disorders.

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New Opportunities for Clinical Research Training in Neurology

The restructuring of clinical academic training following the "Walport Report" has opened up new opportunities for trainees to begin a clinical academic career at different levels. In addition to the traditional route, typically involving nationally funded pre- and post-doctoral fellowships, there are now NHS-funded academic foundation programmes, clinical fellowships, and clinical lectureships throughout the UK. The expectation is that trainees will use these NHS-funded posts as a spring-board towards nationally competitive fellowships. This is intended to restore and even enhance the number of trainee neurologists seeking nationally funded fellowships, and as a result, both the Medical Research Council and Wellcome Trust have dramatically increased the number of fellowships on offer to aspiring clinical academics.

In recent years, neurology and neuroscience have done extremely well in the national competition, managing to secure a greater proportion of clinical research training fellowships (CRTFs) than would be expected given the size of the clinical specialities – but resources will undoubtedly become stretched given the current economic crisis, placing greater emphasis on alternative sources of funding.

In neurology we are fortunate to have a healthy number of disease-specific charities, each contributing to the massive research effort. However, charity has tended to operate its own selection process. This situation is not ideal. For trainees, there are many organisations, each with its own procedures active

at different times of the year. Each charity has to organise and co-ordinate an expert panel. This in itself is challenging, and there is usually little in the way of feedback to unsuccessful applicants. Anecdotally, the quality of the proposals submitted to disease-specific charities can be of a lower standard that that seen at MRC or Wellcome Trust review panels, giving the perception of a reduced kudos, despite the often highly productive research training programme in an excellent environment.

There is also a group of clinical trainees who do not initially aspire to an academic career, but do seek a more limited period of research exposure. At present these individuals usually join a local research group on 'soft' funding, often engage in routine clinical trials work, and do not study for a higher degree (PhD, MPhil, or MRes). This arrangement offers little in the way of research experience, and it is likely that some clinical academics of the future will be lost to the system through such exposure. More generally, without developing a genuine understanding of the research process, future clinical neurologists are less likely to be effective contributors to the increasingly numerous and important local and national research networks which are now firmly part of the NHS fabric.

In response to these concerns, the Clinical Research and Academic Committee (CRAC) of the Association of British Neurologists (ABN) approached the major UK neurological charities and charitable trusts to offer assistance in co-ordinating a centralised Clinical Research Fellowship Application process. The initiative was designed to benefit applicants and charities alike, allowing shared funding between generic and disease-specific sources, and providing a simple "one point of entry" for applicants. The proposal was very well received, and as a result, a number of charities have committed substantial funds to the scheme, including Ataxia UK, The Patrick Berthoud Trust, The Guarantors of Brain, The Multiple Sclerosis Society and The Parkinson's Disease Society.

In the spring of 2010, applications will be invited for fully-supported Clinical Research Training Fellowships of up to three years duration, with a closing date of 31st May 2010. Shortlisted candidates will be interviewed on 29th July 2010, with final confirmation of funding in early September 2010. ◆

Further details are available from p.f.chinnery@ncl.ac.uk. Application forms are available from josie.shew@theabn.org

Route Finding for Tomorrow's Neurologist

Alastair Compston
is Professor of Neurology and Head of the Department of Clinical Neurosciences in Cambridge; President of the Association of British Neurologists (2009-2010); and Editor of Brain (from 2004). He is a foundation Fellow of the Academy of Medical Sciences, and Foreign Member of the National Academy of Sciences of Germany. His research on the clinical science of human demyelinating disease has been recognised by award of the Sobek Foundation International Research Prize (2002), the Charcot Award of Multiple Sclerosis International Federation (2007), and the Zülch Prize of the Max-Planck Society (2010).

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Interested in finding research fellows and collaborators?
The ABNT is collating information to create an interactive research networking database on the ABN website. This will include cross-referenced lists of Academic Neurologists, research groups and research posts available in the UK.

If you would like to find out more, or ensure that your group is represented, please contact the ABNT Research Rep, Beth Mallam: bethmallam@doctors.org.uk.

Training as a specialist serves several purposes. It ensures that the quality of care provided to any member of the public through the National Health Service (NHS) is excellent. It establishes in the trainee the means for life-long learning that sustains interest in the subject, keeps us safe and addresses issues of clinical governance. And it reduces the risk of professional arrogance by making doctors sensitive to our limitations, responsive to the challenges of not knowing enough and, through research, motivated to advance the subject. In short, training serves not only the vocational principles of medicine as a profession, but it also imprints the ethic and standards to which we aspire.

Neurological training in the UK
Like the Norfolk countryman asked for directions ("if I was going to Norwich, I wouldn't start from here"), trainees suffer a system that they did not design and may wish to change for themselves and their successors. Once, neurology was patrician. Its practitioners considered the laying-on of diagnosis to be a sufficient activity, ideally delivered as fleeting visits from Harley Street whilst the Rolls Royce was kept gently purring in the hospital car-park. Later, and especially following the NHS reforms of the early 1990s, establishment improved, commitment increased and regional deployment became more evenly distributed. Although the model remained essentially centre-based, networks of care developed in response to the imperative of delivering care close to where people live and become ill. For neurology, the impact of this expanded infrastructure was mainly reflected by increased out-patient activity and participation in the management of chronic neurological disorders. Now, neurologists are also negotiating more active involvement in acute care. However, the facilities and expertise needed to practice neurology at the highest level cannot sensibly be reproduced in each and every hospital where neurology has a presence. Therefore,

tomorrow's service must allow rapid access for the patient at any point along the continuum of community, district hospital and tertiary centre; and thereafter to permit traffic effortlessly in either direction according to need. That basic principle requires the service to be well led, coordinated and fully integrated within any one geographical region or city, and delivered by a team that includes staff trained in professions allied to medicine.

One size will not fit all. Neurology needs to accommodate several styles in response to the model of responsibility and care distributed across a spectrum that ranges from primary care to ivory tower. The generalist in the district retaining meaningful links to the centre; the sub-specialist who is nonetheless competent in general neurology; the super-specialist who rarely strays outside a particular area of expertise (previously parked safely through placement on the Specialist Register but without a Certificate of Specialist Training); and the medically qualified full-time research scientist who occasionally sees patients. It follows that training must adapt to reflect these changing patterns of neurological practice, and the need to work efficiently and comfortably at the various locations where services are to be delivered.

The reverberations on training of the notorious proposals for Modernising Medical Careers (MMC) can still be felt. Is it overly cynical to conclude that MMC was designed entirely to support a political manifesto that promised no more absentee consultants doing private practice or out on the golf course whilst trainees did all the work; now, medicine was to be led and delivered by consultants? No-one would challenge the merits of that principle. Since specialists, including neurologists, could not be cloned overnight, and expansion within medical schools would take a generation to increase the number of consultants trained according to existing structures, the only medium-term solution was to designate doctors as specialists at the earliest possi-

ble stage in their careers. Therefore, the duration of training had to be curtailed; and luxurious items such as grounding in general medicine and experience of research rapidly sidelined. Concerns were expressed by trainers and trainees alike with respect to whether this cut-price system would equip newly appointed consultants to manage the diversity of neurological illness confidently and without having to learn a great deal 'on-the-hoof'. Patients understand that doctors need to 'practice' but preferably not on them. Furthermore, since most clinical research is carried out by trainees on behalf of consultant supervisors, academic neurology was particularly challenged by these and related changes to the career pathway. Those threats were real not perceived and, despite the apparent demise of MMC, have had profound influences on training in neurology.

The changing face of academic neurology

As others in this series have commented, until recently a period of research was a non-negotiable rite of passage for higher training as a specialist registrar. The aspiring neurologist was stacked for a few years, carrying out research for which not every individual necessarily had an appetite, pending clearance to land for clinical training in a given deanery. At the same time, the academic aspirations of medical schools submitting to the Research Assessment Exercises (RAE), needing a portfolio in which neurology and all the other main medical specialities were represented, became too dependent on support from the pharmaceutical industry given the stiff competition for grants awarded by the Research Councils or major Charities. But with much tighter pharmaceutical regulation, realisation that the dividend for knowledge from these investments was often small, and changing models of industry research and development strategy, the support from Big Pharma has contracted, leaving some vulnerable research active neurology (and other) departments badly exposed. Trainees in research were unevenly distributed when MMC, proposing alterations not only in the schedule for training but also placing restrictions on geographical migration between deaneries, was introduced; and many were caught out when the shutters came down. Centres that had overloaded the system with researchers who could not subsequently be placed in local training posts were seen to have acted irresponsibly by inflating the research market. With this newly acquired pariah status, we hung our heads in shame at having wantonly promoted research. Articles in the present series reiterate the advice to avoid expanding the pre-specialist registrar (ST3) post-core medical training (ST2) cohort merely to suit 'professors looking for research fellows'.

Were these changes altogether a bad thing? In the main 'yes'; for the simple reason that, in medicine, academic is an adjective not a noun. It reflects a style and interest in acquiring new knowledge, and is fundamental to clinical education. The exposure to uncertainty equips the trainee to sift the available information and make judicious decisions in situations where the evidence is ambiguous or incomplete. Therefore, over and above the potential for acquisition of new knowledge – an uncertain dividend – the academic component matters purely from the training perspective. It creates the sense of confidence needed to challenge the subject throughout the neurologist's career without feeling daunted; to manage complex situations decisively without resorting to the protective armour of endless and repeated investigation; to know what are the strategic directions for our subject, through being able to assess the significance for clinical practice of emerging discoveries; and - not necessarily a bad thing – it does indeed serve as rite of passage to appointment as a consultant neurologist in a competitive environment.

In the run-up to MMC and its aftermath, some organisations responded to the threats for academic medicine with initiatives that provided complementary or alternative routes to training. By way of example, the Guarantors of Brain introduced a flexible entry scholarship scheme that continues to support clinical trainees across transitional career gaps at stages where the next step on the ladder is competitive, success unpredictable, and opportunity limited by availability. The Eastern Deanery established 7 year Clinical Neuroscience Training Fellowships with (4 year) clinical training linked to a fully funded (3 year) period of research. Later this year, the Association of British Neurologists will introduce 'ABN Fellowships'. These fellowships will bring together the resources of several Charities who feel that the interests of their donors are best served by a generic clinical research fellowships scheme, which enables trainees to work on the right project for the trainee and in the most suitable place, ensuring high quality and careful assessment of applications and thereby matching the '3Ps' (Person, Place and Project) in the interests of all concerned. But these domestic activities, introduced on the small scale, are merely papering over the cracks. On a grander scale, new Academic Training Fellowships and Clinical Lectureships have been introduced; the Department of Health and the Academy of Medical Sciences have supported Clinician Scientist Fellowships; and the Higher Education Funding Council for England awards Senior Lectureships through the National Institute for Health Research and its Integrated Academic Training Pathway. Recognition that the interest of potential career academics needs to be captured early led to the introduction of academic Foundation Year programmes that include a research attachment as a taster for longer-term commitment to research. To some extent, these initiatives have been targeted at subjects that seemed especially threatened by the changing landscape and neurology was not perceived to be a particular casualty of the system. One stricture on these schemes is the requirement for the host insti-

tution to contribute between 25% and 75% of the salary costs. Therefore it has proved difficult to integrate these parallel track positions within programmes without sacrificing existing training posts or finding alternative sources of collateral funding; and some departments elected not to bid for additional academic posts, sensing that their ability to recruit and keep the wheels of the research engine well oiled would continue undiminished.

Overall, however, the perceived threats have proved to be real. It would astonish our predecessors to learn that training posts in neurology are unfilled; and that the Association of British Neurologists is organising the first road-show for medical students and Foundation Year doctors designed to capture interest in the specialty. Expectations on trainees have changed. Being on call no longer replays scenes from Doctor in the House: propping up the bar in the hospital mess and wandering down to casualty at closing time. More active involvement in acute medicine, including stroke, means routine management of acute thrombolysis. Many hospitals now organise acute triage systems requiring early input from specialists including neurologists so that, rightly, patients are managed quickly and by the most appropriate teams. Complying with European Working Time Directives threatens the specialist registrar grade with the same fate that befell senior house officers required to work shifts. Under-staffing and the lack of individuals wanting locum appointments for training (LATS) makes it much more difficult to arrange out of programme experience. And the attrition on research training posts has been especially noticeable. Topics that offer a predictable dividend from time in research remain popular, as do posts in those regions where the number of training posts is high and entry into clinical training beyond research more predictable. But the take-up of more challenging experimental laboratory studies is low. One senses a growing feeling amongst trainees that the interest in research must be declared early. Not to obtain an academic Foundation Year post is to distance oneself from research. Subsequent de-differentiation down an academic track, if so desired, is then considered something of a reversal of tactic and a retrograde step. As a result, research activity is again starting to be mal-distributed – geographically and by topic; and trainees are forced to commit to a research style training, or not, at too early a stage in their careers. These trends will shape the development of neurology in terms of the topics that receive most attention - emphases that may not suit society or the long-term professional interests of the future neurologist, nor ones that leave the discipline alert and responsive to unexpected developments.

Finding the path for tomorrow's academic neurologist

Quite what tomorrow's neuroscience and its clinical applications will bring remains speculative. Self evidently global changes in demog-

raphy and economics will impinge on neurology. Epidemics of novel infectious diseases will continue. Neurodegenerative diseases will become more prevalent as the population ages. That much is obvious. More generally, descriptions of disease will change as eponymous nosology is replaced by classifications that reflect disease mechanisms - Parkinson's disease and fronto-temporal dementia being examples of the alpha-synucleinopathies and tauopathies, respectively. Empirical therapeutics will be refined by treatments that target defined molecular pathways. Diagnosis will be anticipated on the basis of biomarkers derived from the many '–omics' that screening provides, shifting the concept of disease from pathology to risk. Behaviour will no longer be studied exclusively in the individual nervous system, but rather as interactions that form social neuroscience networks, and impact on decision-making and cultural activity in all realms of human endeavour and social organisation. How will these trends affect the training needs of tomorrow's neurologists?

Because opportunities are narrowed yet the number of trainees who aspire to medium- or long-term academic posts also reduced, that market is currently neither a buyer's nor seller's, but generally in recession. For those who are attracted to research, timing can be problematic. Establishing a relationship with a department known to be experienced and having a reasonable track record in mentoring sooner rather than later makes good sense, even if these provisional arrangements require research interests to be shaped slightly earlier than is ideal. After all, with a dynamic subject such as neurology, the longer the interval between committing to a particular research topic and developing a clinical sub-specialty interest, the greater the risk that the two will end up not closely aligned. This is the down-side of the early higher degree such as that embodied in MB PhD programmes that are common in the United States and increasingly adopted by Universities in the United Kingdom. Because the MB PhD student has recently been exposed to basic neuroscience, the subject matter for research that appeals may be clinically remote and this can widen the gap between skills acquired early and the eventual clinical sub-specialty focus. Therefore, whilst a basic neuroscience project may provide an excellent grounding in laboratory methods, that choice makes it all the more sensible for the potential clinician scientist to establish a relationship, maintain continuity and negotiate re-entry links to a host department well in advance of clinical training. For those who come to research later, looking around in terms of place and topic of interest and acquiring clinical experience as a specialist registrar before embarking on research is sensible and most certainly does not thwart the process. Often, this is an appropriate caution, so that one may sample enough of the subject to sense

what will prove to be a specialist area of lasting interest. And although it should be remembered that research is time consuming and the commitment relatively inflexible towards the end of training, when the priority may be appointment to a consultant post, once the right opportunity arises, it is almost never too late to start.

Choosing where to do research involves assessing the extent to which the preferred department is capable of accommodating individuals who are clinically inactive at times during their attachment and used to moving trainees on and off the wards without encouraging two cultures – research fellows and real doctors – who do not interact. Having a pool of clinical trainees based either in research or clinically active at any one time, and all of whom experience both aspects of training during their attachment, offers an ideal environment in which academic (the 'adjective' and the 'noun') neurologists are nurtured and can flourish. Furthermore, programmes that are regionally coordinated and offer diversity of clinical training both in the district and centre, with supervision when needed and freedom when wanted, best equip the trainee to work in the future health service.

Can one map the ideal training today for tomorrow's world, especially for neurologists with an interest in research? It makes good sense to sample research and perhaps make initial overtures with a future sponsor through an academic Foundation Year appointment. But this is of less importance than obtaining experience in the general medical disciplines that impinge on neurological practice. An Academic Training Fellowship provides right of access to a training programme, if the intended transition to a Clinical Training Fellowship does not materialise. Protected time for research and the default position of clinical training are clearly advantageous to the trainee, but they do not remove the need to be in the right place, with experience of the right research topic. Appointed before entry to specialist training, the Academic Training Fellowship endorses the run-through principle that neurology has otherwise argued against – the discipline preferring to filter applicants through competitive entry at ST3 with a further curriculum of five years in training (with one off for good behaviour if time is spent in research). Even so, choosing the most appropriate academic environment should count for more than merely obtaining one of these early-career Fellowships. For the remainder, because the channel through which the academically-minded trainee must subsequently pass at ST3 is relatively narrow and competitive, any opportunity to decorate the curriculum vitae with something that stands out and distinguishes one from another is bound to help. This matters more in a system where applications are increasingly anonymous and centralised making personal knowledge and preference somewhat more difficult to manage, both for the trainee and host department. The current arrangement for appointing specialist registrars, with and with-

out research experience, will – until the next invention supervenes – involve national application for a single annual round of regional appointments, specifying two preferred locations and ranking the remainder. Short-listing and interview will be local but standardised and scored so that, in the event of unfilled posts and individuals whose applications are not successful, a clearing system can operate that is calibrated and does not require re-application or re-interview. Local interview panels may add questions that reflect the style and flavour of their programmes but must focus on the structured components. It is rumoured that only one deanery has indicated that it will ask about research interests as part of this bolt-on menu to the standardised interview. Appointments are timed for the autumn, with much of the year a closed season for local recruitment in order to protect posts for the national round. Only for a couple of months in the pre-Christmas period may deaneries manage their own affairs outside the national recruitment scheme. Presumably, with only a single annual round of appointments, gaps will appear in rotations pending arrival of the national juggernaut. These will not be filled by LATS, for there are none; and research staff may find themselves frog-marched on to the wards at crucial periods in their research. Although this ritualised system may prove efficient during the clearing phase, it disadvantages the applicant who has developed a career strategy early, based on a specific vision for training in a place that suits that person's interests and abilities. The cynical view is that once again, the motivation seems not to be protection of those for whom discrimination and disadvantage were perceived to exist but rather the need to move trainees through the system fast and with built-in delays avoided so that each person graduates as a clinical consultant at the earliest possible opportunity. In neurology at least, trainers and trainees do not support this arrangement for appointment and it seems that enormous trouble has been taken to fix something that was not bust. Beyond the acquisition of clinical experience as a specialist registrar, for the trainee seeking a long-term academic post, the secondary phase of research is the defining period. Here, an independent profile and experience of writing successful grant applications are established, work is delegated and led within a group, and the curriculum vitae acquires all the characteristics predicting long-term and sustained success. All that remains is to become a professor and join the local golf club.

Even in the present climate, the only thing that stops someone realising ambitions for a career in neurology is uncertainty about what you want. That applies equally to a purely clinical post and one that carries research responsibilities. The pathway for training in each may diverge in the years ahead so it is worth giving the matter careful thought at a relatively early stage in your career. Clinical activity is important and rewarding; discovering new things is sustaining and thrilling. ◆

EDITOR'S CHOICE

Neurogenetics: Making a diagnosis by whole-genome sequencing

As neurologists, at least in the UK, we tend to approach the patient with a probable inherited neurological disease in a fairly structured way. Following a careful history and examination, the search for the precise genetic abnormality begins. For certain monogenic neurological conditions, the likelihood of achieving a genetic diagnosis is favourable; for example, Huntington's disease in a patient with chorea, dementia and a relevant family history. However, we now know that many neurological conditions can present with identical phenotypes but be caused by a wide variety of underlying genetic defects. Charcot-Marie-Tooth disease (CMT), the commonest inherited neuromuscular disorder, is a familiar example. While a number of excellent clinical and neurophysiological algorithms exist to help request the appropriate gene test in CMT, logistical reasons dictate that most patients will have the commonest mutations tested first, leaving many without a precise underlying genetic diagnosis. This may change following the publication of a paper by Lupski et al. describing their approach to genetic diagnosis in a patient with demyelinating CMT, deemed to be autosomal recessive.

Instead of taking the traditional 'one gene at a time' approach, Lupski et al. decided to take advantage of the advances seen in DNA sequencing in the past 10 years and sequence the whole genome of their patient and extended family members. This included both coding and non-coding regions of DNA. Using reference genome sequences and the sequences obtained from unaffected family members, the precise genetic mutations in the known CMT-associated gene,

SH3TC2, were identified. While one could argue that the clinical details, family history and neurophysiological data available would have pointed towards the SH3TC2 gene using the traditional approach to genetic diagnosis, Lupski et al. show that whole-genome sequencing is now not only possible, but can also be applied to the clinical setting. The impressive advance that whole-genome sequencing provides is its ability to identify all DNA changes in each haplotype (exons, introns and copy-number variants), making it a potential powerful tool when applied to diseases with complex genetic aetiologies.

Nevertheless, there remain a number of cautionary notes. First, the diagnosis was possible due to the fact that the SH3TC2 gene was already known and characterised. Second, the accuracy of the genetic disease databases is questioned as the patient also displayed a mutation in the ABCD1 gene reported to cause X-linked adrenoleukodystrophy, without showing any clinical features of this disease. And the price? Lupski et al. estimate that their whole experiment would now cost less than $50,000. In comparison, a clinical-testing panel looking at the copy number variant that commonly causes CMT along with mutations in 15 other genes associated with CMT currently costs $15,000. We should not put away our tendon hammers and tuning forks just yet.

– *Rhys Roberts, Cambridge University.*
Lupski JR, et al. **Whole-Genome Sequencing in a Patient with Charcot-Marie-Tooth Neuropathy.**
THE NEW ENGLAND JOURNAL OF MEDICINE
2010 Apr 1;362(13):1181-91. Epub 2010 Mar 10.

FTLD genetics: progress through collaborative splitting

The frontotemporal lobar dementias (FTLDs) are a clinically, pathologically and genetically heterogeneous group of diseases. Although frequently described as "the second commonest cause of presenile dementia", FTLD remains an uncommon disease (incidence 3.5, prevalence 4-15, cases per 100,000 in 45-64 year olds; Mercy et al 2008). It has therefore taken a large collaborative study using samples from North America, Europe and Australia to identify the first association of common genetic variants with FTLD. Van Deerlin et al identified association with single nucleotide polymorphisms on chr 7p21 surrounding the TMEM106B gene, which encodes an uncharacterised 274 amino acid transmembrane protein. Functional studies suggested that risk alleles could result in increased brain expression of TMEM106B and a more aggressive disease course.

Genome-wide association studies (GWAS) in general are used to identify association in common diseases, such as diabetes, and require many thousands of cases to generate the power to determine true associations. Nevertheless, Van Deerlin et al appear to have succeeded with an n of just 515. Their success stems partly from preparation of a homogeneous group of cases made up only of patients with TDP-43 pathology (FTLD-TDP). By excluding those with tau inclusions and other less common pathological subtypes of FTLD, they appear to have distilled the

genetic pool under scrutiny, reducing the chances that a true association would be lost. It must be noted, however, that the majority of the chr 7p21 association appears to be due to a sub-population of their cohort already identified to have autosomal dominant FTLD due to GRN mutations. A further interesting observation is that the most significant SNPs Van Deerlin et al identified on chromosome 9 are in a region of great interest in another 'TDP-43 proteinopathy', amyotrophic lateral sclerosis (Van Es et al 2009, Vance et al 2006).

– *Jemeen Sreedharan, Guy's and St Thomas' NHS Trust, London.*
Van Deerlin VM et al. **Common variants at 7p21 are associated with frontotemporal lobar degeneration with TDP-43 inclusions.** **NATURE GENETICS 2010 Mar;42(3):234-9. Epub 2010 Feb 14.**
Mercy L, et al. **Incidence of early-onset dementias in Cambridgeshire, United Kingdom.** **NEUROLOGY 2008 Nov 4;71(19):1496-9.**
van Es MA, et al. **Genome-wide association study identifies 19p13.3 (UNC13A) and 9p21.2 as susceptibility loci for sporadic amyotrophic lateral sclerosis.** **NAT GENET. 2009 Oct;41(10):1083-7.**
Vance C, et al. **Familial amyotrophic lateral sclerosis with frontotemporal dementia is linked to a locus on chromosome 9p13.2-21.3. BRAIN 2006;129(Pt 4):868-76.**

Memory: A name for forgetting

When considering memory it is easy to neglect forgetting. Over the centuries, forgetting has continued to represent the dark side of memory, often portrayed as a passive process of memory fading, or an 'overwriting' by competing memories. Modern science too has dwelled more on the mechanisms of memory than on those of forgetting. The authors in this study now take steps to redress this deficiency by directly examining the molecular mechanisms of forgetting. They define a molecular pathway which, when activated, causes memories to fade faster; conversely, inhibiting the pathway makes memories more lasting and more resistant to change. The study uses fruit flies expressing mutated versions of a molecule called Rac in defined adult neurones, analysing them with standard behavioural memory tests. The authors firstly demonstrate that memory fades more rapidly in the presence of a constitutively active version of Rac, and less rapidly if an inactive version is used (crucially, they also confirm that the differences are not because of an alteration in the strength of the initial memory). They go on to look at reversal learning, where the conditioned stimulus in a learning task is reversed on a second trial, forcing the flies to relearn; the reversal turns out to be easier in the presence of active Rac, showing that the initial memory is now less durable. Conversely, in the presence of inactive Rac the flies stick more stubbornly to their original memory, relearning the new association less readily. Finally, the authors show in wild type flies that levels of active Rac fall as learning is consolidated by repeated trials, but are raised in reversal learning paradigms, correlating with an increased need to 'remove' or overwrite inappropriate associations.

That active Rac seems to promote forgetting comes as something of a surprise. Conventional understanding has it that memories, and molecular correlates such as long-term potentiation, rely on glutamate receptor clustering and increases in polymerised actin within strengthened synapses; both of these changes are driven by active Rac (and its downstream target PAK1). On this background, the idea that Rac activity promotes forgetting seems counter-intuitive. One solution to the paradox may be that Rac is key to a forgetting mechanism that is effectively integral, 'built in as standard', to each new memory, and which wanes as the memory matures with repeat exposure. Rac activity then becomes a marker of the recency of memories, with newer memories being more susceptible to forgetting than consolidated ones – a useful feature in case fresh memories need to be overwritten before they become too established. Such insights are clearly relevant to diseases such as Alzheimer's, where forgetting is the rule, and where dysregulation of Rac pathways may well be involved. These questions are not directly addressed in this paper, but a central message stands out: forgetting has a mechanism, and it needs to be understood.

– *Philip Buttery, Cambridge Centre for Brain Repair and Queen Elizabeth Hospital, King's Lynn.*
Shuai et al. Forgetting Is Regulated through Rac Activity in Drosophila. CELL 2010;140(4):579-89.

Stimulating the brainstem in Parkinson's Disease   a step in the right direction?

The use of deep brain stimulation (DBS) to treat patients with movement disorders is now well established and this is perhaps most obvious in advanced Parkinson's Disease (PD) with DBS of the subthalamic nuclei. However, whilst this treatment works well for many features of PD, it does not improve all aspects of the disorder, especially those that involve more axial features and this includes gait. As a result modifications have been sought that can help this disabling aspect of PD, and one approach has been to target brainstem nuclei involved with locomotion such as the pedunculopontine nucleus (PPN).

The PPN is a small structure within the brainstem that has widespread connections throughout the CNS, receives from the basal ganglia output nuclei, and has been thought for many years to be a vital relay station in the initiation and generation of gait. It has been found to be affected in PD, having pathology itself as well as being in receipt of a disordered basal ganglia output. As such it became the target for the stimulating electrode of curious neurosurgeons! The initial open label studies sug-

gested that benefits could be seen using low frequency stimulation of the PPN in patients with PD. However, such studies are hard to interpret given the placebo problems inherent in small open label studies and the different criteria used to select patients for this treatment in these trials. Thus better controlled studies are needed although what constitutes a good control arm is difficult when the treatment under scrutiny involves invasive neurosurgery. Nevertheless with DBS, one does have the opportunity to switch on or off DBS without the patient knowing the activation status of their stimulator. This strategy has now been exploited in two recent studies reported in Brain.

First, Ferraye et al took 6 patients with PD and severe freezing of gait that was unresponsive to L-dopa or DBS of the subthalamic nucleus. These patients all had bilateral electrodes placed in the PPN with the primary outcome being the improvement in gait, freezing episodes and falls at 1 year. There was a period between 4-6 months when a double blind cross over study was done with the stimulator being on or off. The main finding was that at one year the number of freezing episodes and falls was reduced, although none of the other outcomes were improved nor was there any clear consistent effect seen in the double blind period. In the second study by Moro et al, 6 patients with advanced PD and significant gait and postural abnormalities were recruited and treated using a unilateral PPN stimulator (the side chosen for stimulation being contralateral to the most severely affected side of the body). In this case the patients had to have failed medical therapy but had not had DBS of the subthalamic nucleus. These patients were then subject to a double blind treatment with the stimulator being either switched on or off, and again some benefit was seen with respect to falls but no other measures using subsections of the UPDRS motor examination.

So what are we to make of all this? I think the studies have suggested that the PPN may be a useful target in helping treat axial features of PD - especially issues of gait and falls. This is important because these features are often resistant to L-dopa therapies and carry significant morbidities and impact on quality of life. Thus being able to offer something useful in this domain is worth pursuing, but bigger studies are needed to know the extent to which this stimulating approach really works and benefits patients with PD.

– *Roger Barker*
Ferraye MU et al. **Effects of pedunculopontine nucleus area stimulation on gait disorders in Parkinson's disease. BRAIN 2010; 133: 205-214.**
Moro E et al. **Unilateral pedunculopontine stimulation improves falls in Parkinson's disease. BRAIN 2010; 133:215-224.**

Parkinson's Disease: earliest diagnosis

Neurologists strive to differentiate early idiopathic Parkinson's disease (PD) from its mimics in order to properly advise patients about prognosis and treatment options. Clinical diagnosis alone will get it wrong about 15% of the time, and accuracy improves as disease progresses. Tang and colleagues at The Feinstein Institute for Medical Research in New York used fluorine-18-labelled-fluorodeoxyglucose-PET to differentiate idiopathic PD, multiple system atrophy and progressive supranuclear palsy in 167 patients with parkinsonism of unknown cause. They used an automated voxel-based classification procedure to map characteristic pattern abnormalities in these three conditions. The patients were scanned at an early stage of their disease, and followed-up for a mean of 2.6 years by a blinded movement disorder specialist to ascertain the final diagnosis. When the accuracy of the initial image-based classification was compared with the final diagnosis, the positive predictive value was greater than 90% for each condition. The imaging categorisation was reproducible on repeat scanning and confirmed in nine patients on postmortem examination.

The fact that 32 patients had to be excluded at the outset because the final clinical diagnosis was unclear should not be forgotten, as this was the gold standard in the study. Further, patients with structural brain abnormalities that could potentially account for their symptoms (including white matter and ischaemic lesions which are commonly seen in the clinic) were excluded. The utility and cost-effectiveness of PET in the early differential diagnosis of parkinsonism needs to be proven further, but the desire to identify suitable candidates for novel drug trials and sur-

gical procedures (such as stem cell transplantation) means that there is bound to be considerable interest in this approach.

– David Breen, Cambridge University Centre for Brain Repair.
Tang CC et al. Differential diagnosis of parkinonsim: a metabolic imaging study using pattern analysis. LANCET NEUROLOGY 2010;9(2):149-58.

Parkinson's Disease: Reckless Generosity

Here is another phenomenon to add to the growing collection of impulse control disorders (ICDs) in Parkinson's disease. O'Sullivan et al describe three cases of "excessive and inappropriate philanthropy". All three were taking dopamine agonists and the behaviour improved or ceased when the agonist was reduced or discontinued.

The authors speculate as to the pathophysiological basis in dysfunctional dopaminergic reward pathway stimulation, an interaction between increased oxytocin release and dopaminergic reward systems, and impaired decision making, with an insensitivity to the negative consequences of a particular action. As with all impulse control disorders, their presence should be screened at each clinic visit, and patients warned. As one can imagine, the behaviours may be associated with profound consequences for the patients and carers, both financially and socially.

– Wendy Phillips, Norfolk and Norwich University Hospitals NHS Trust
O'Sullivan S et al. Reckless generosity in Parkinson's disease. MOVEMENT DISORDERS 2010;9999.

Rehabilitation: the importance of prior depression in surgical outcome

Although the relationship between disability, depression and pain is a complex one, is there a case to be made for attempting to optimise psychological as well as physical health prior to complex surgical procedures? The existence of the term "failed back syndrome" to describe patients who have had poor outcomes from spinal surgery illustrates the chronic and disabling consequences of adverse results for this intervention. It is obvious that optimising general health improves outcome, and high risk patients will be assessed from an anaesthetic perspective well in advance to minimise their physical co-morbidities. This paper looks specifically at outcomes following lumber spinal stenosis surgery in relation to depressive symptoms in the pre-operative and post-operative period. Rather than focussing solely on pre-operative depressive symptoms, the authors have looked at "depressive burden" across the pre-operative, post-operative and late (3 and 6 months) periods. Depressive symptoms were evaluated with the Beck Depression Inventory and disability was assessed by walking capacity, back and leg pain, and the Oswestry Disability Index. Perhaps not surprisingly, late depression had a strong association with pre-operative depression although depressive symptoms generally improved following surgery. There is a clear relationship between pre-operative depression and post-operative outcome, in terms of disability, however. This is true for both younger and older patients. There are serious clinical, economic and social consequences of a "failed back" and whether these could be attenuated by rigorous pre-operative screening and intervention for psychological issues remains to be seen.

– Lloyd Bradley, Western Sussex Hospitals Trust
Sinikallo S et al. Depressive symptoms predict postoperative disability among patients with lumbar spinal stenosis: A two-year prospective study comparing two age groups. DISABILITY AND REHABILITATION 2010;32(6):426-68.

Dementia: motor predictions

Mild parkinsonian signs (MPS) are common in the elderly, and two previous studies (including the Washington Heights Inwood Columbia Ageing Project, WHICAP) have suggested that MPS is a risk factor for developing dementia. The authors of this paper have studied a new cohort from 1999-2001, an extension of the original WHICAP cohort (1992-1996). Again, these prospective population based data show that MPS in elderly people

(>65 years) is associated with a greater than two-fold risk of developing dementia, mainly (86.4%) Alzheimer's disease (AD). A cohort of 1851 randomly sampled elderly people underwent a neurological examination, abbreviated unified Parkinson's disease rating scale (UPDRS) evaluation and a standard neuropsychological battery; mean follow up was 3.7 years. MPS was defined as ≥ 2 UPDRS rating of 1 or one rating of ≥ 2 (PD was defined as ≥ 2 UPDRS rating of ≥ 2). People with MPS were more than twice as likely to develop dementia as those without MPS, particularly in the domains of language and memory. Furthermore, with each point increase in the UPDRS score, the risk of dementia increased by 15%. Patients with MPS were older and more had diabetes and stroke- but the increased risk of dementia still held after adjusting for these confounders (hazard ratio, HR = 1.98), and also when the 408 participants with mild cognitive impairment (MCI) were removed from the analysis. Those with axial dysfunction and tremor (rather than rigidity) were more likely to develop dementia. The risk of dementia with MPS was not compounded by other known risk factors (including education, family history, stroke, apoE). There was no interaction between MCI and MPS - so MPS cannot be used as a predictor of MCI progression.

MPS have been thought to be relatively benign, but this study underlines a substantial risk of dementia. Although the majority of patients developed AD, it would have been interesting to know what other dementias were diagnosed - particularly PD dementia, vascular dementia and Lewy body disease; and, the progression of MPS to frank Parkinsonism. This is particularly relevant given that the distinction between MPS and PD is relatively subjective (only one point on the UPDRS could make the difference). The basis for MPS as a risk factor for dementia is unknown but one possibility is that MPS represents basal ganglia tangles (and patients with AD often have MPS). It is perhaps surprising that those with tremor, rather than rigidity, were more likely to develop dementia given that tremulous PD is relatively benign. Neurologists do not tend to see the very frail elderly, so it is helpful to have a reminder that MPS are very common among this population, and that MPS are not necessarily 'normal for age'.

– Wendy Phillips, Norfolk and Norwich University Hospitals NHS Trust
Louis E et al. Mild parkinsonian signs are associated with increased risk of dementia in a prospective, population-based study of elders. MOVEMENT DISORDERS 2010;25:172.

Cognition: finding where we keep track of when

It has been established for a long time that temporal perception, the ability to perceive the passage of time, is influenced by attention, and thus the neural systems underlying temporal perception and attention might include similar structures. This study used repetitive transcranial magnetic stimulation (rTMS) to test the a priori hypothesis that the right parietal lobe plays an important role in both orientation of attention and temporal perception. Previous studies using rTMS have established the role of the angular gyrus (AG) in temporal perception but the role of the supra marginal gyrus (SMG) had not previously been tested. A two stage experiment was designed in which healthy volunteers had to compare the duration of a visual stimulus presented in different durations with and with out rTMS to three brain areas (Right SMG, left SMG and vertex). The difference between the two stages of the experiment was in rTMS timing. In the first stage, rTMS was delivered during presentation of the first sensory stimulus whereas in the second stage this happened during presentation of the second stimulus. This was to establish whether memory and decision making processes, which are more prominent in the latter part of the test, impose any significant effect on the temporal perception. Analysis of the results revealed that rTMS delivery to the right SMG consistently led to increased temporal perception compared to the left SMG, vertex stimulation and no rTMS delivery. These findings reinforce the existing theories regarding importance of the right parietal lobe in temporal perception, and for the first time highlight the particular role of right SMG in this process.

– Seyed Sajjadi, Herchel Smith building and Neurology Unit, Addenbrooke's Hospital.
Wiener et al. Fast Forward: Supramarginal Gyrus Stimulation Alters Time Measurement. J COG NEUROSCI. 2010 Jan

Challenges Ahead

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The role of neurology in our ever-changing health service is uncertain. Evidence supports the importance of neurologists, particularly in the acute treatment of patients. In Britain, neurological involvement in acute care, including stroke, continues to be low, despite the fact that 15-20% of acute medical admissions are neurological, and of these, stroke constitutes one-quarter. Early involvement of neurologists impacts on diagnosis and management, this effect occurring no matter the ratio of neurologists to population.[1] This works both ways – neurologists reduce overdiagnosis as well as highlighting life-threatening diseases. For example, one study found significant misdiagnosis of seizure and stroke; in benign conditions such as migraine, syncope or peripheral vertigo.[2] In presentations with possible epilepsy, neurological consultation increased the diagnostic rate by 50%,[3] while absence of neurological input led to significant misdiagnosis of epilepsy in both community and hospital based groups. The view that neurologists should focus largely on outpatients undermines some of the proven strengths of neurology.

This has major implications for neurologists at all stages of our careers. We need to continue attracting keen medical students to neurology. Trainees need a broad base of medicine and a diversity of experience if they are to be good at dealing with emergency care. 'Jobbing' neurologists working hard in busy general hospitals must have the protected time to keep up-to-date and inspired. Probably most crucial, we need to persuade others in Britain of the importance of a paradigm shift in thinking about neurological services. This will take considerable energy and drive, as in cash-strapped times, we may be seen to be fighting for scarce resources, and in competition with other specialties.

And what is the Association of British Neurologists (ABN) doing about this? We have added the first roadshow to the ABN Meeting in Bournemouth, to pass on the excitement of neurology to medical students. We are thinking about future directions of the ABN, and how to protect high standards of training, with enough flexibility to allow people to come to neurology from different angles. As for all of us, the domestics of life take up a huge amount of energy for the ABN. We want to make sure we are using our time wisely (which is the membership's time). The membership at large; as well as Charles Warlow, our Non-Executive Officer; the President, Officers and Council, all put in a massive effort to meet tight deadlines for comment on a variety of neurological topics. We will be auditing the huge number of guidelines and commentaries requested from us. We need to know whether the effort we put into these is heeded. The ABN must have a role in protecting valuable supporting activities which are vital to excellence in practice; and academic and teaching contacts; just as important for clinicians as for academics. There has been a focus on broader ethical issues in medicine of particular importance to neurology, and how to draw commentary and consensus from our members on these.

Almost all neurologists in Britain, from training onwards, are members of the ABN. This is the greatest strength of the organisation. We are diverse, and should reject stereotypes which never fitted anyway. If we are going to make the most of our organisation, then members' views on the political role of the ABN are crucial and we want your voice on a variety of day to day and large scale ethical issues. And most importantly, on the shape of our political involvement. Should the ABN be a politically neutral organisation? There is a strong argument that political neutrality is a misnomer, that neutrality means acceptance of the status quo without question. When we exercise our political muscle, life is more complex. Many issues will raise hackles, as well as lively and constructive debate. An organisation that says anything of vigour will tread on toes, even with the most robust attempts at consultation and balance.

My bias is obvious. I think that the ABN should be actively involved in politics, and making a noise. But the ABN is all of our members, and decisions about our political profile need to come from the membership. The Annual General Meeting, next at Bournemouth in May, is a forum for the views of membership. Council want, and need, your active involvement and your opinions. ◆

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3. Angus-Leppan H. *Diagnosing epilepsy in neurology clinics: a prospective study.* Seizure 2008;17:431-436.

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E. aguven@symcon.com.tr

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E. mohamed@icnc2010.com
www.icnc2010.com

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OZC - Cognitive Assessment and Rehabilitation
11 May, 2010; Ely, UK
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E. Rachel.everett@ozc.nhs.uk

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E. info@theabn.org

Neuroscience: Epilepsy Conference
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14th International Neuroscience and Biopsychiatry Conference "Stress and Behavior"
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Brain Injury Awareness Week
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Management of Spasticity in MS
18 May, 2010; London, UK
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E. education@mstrust.org.uk
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E. mohamed.sakel@ekht.nhs.uk

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E. Rachel.everett@ozc.nhs.uk

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www.physiouk.co.uk

20th Meeting of the European Neurological Society
19-23 June, 2010; Berlin, Germany
www.ensinfo.org

NCORE: Assessment & Treatment of a client with Perceptual and Cognitive Dysfunction
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www.ncore.org.uk

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T. 01724 290065
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3 July, 2010; Essex, UK
www.physiouk.co.uk

European Life Science meeting: Cytokines in translational research: bench to bedside
8 July 2010; Hertfordshire, UK
E. enquiries@euroscicon.com
www.regonline.co.uk/cytokines10

The Society for Research in Rehabilitation Summer Meeting
7-8 July, 2010; Shefiield, UK
T. 01142255336
E. conference21@shu.ac.uk or srr_secretary@srr..org.uk

7th International Congress on Neuroendocrinology
10-15 July, 2010; Rouen, France
T. +33 149 284 676
E. william.rostene@st-antoine.inserm.fr

6th National Autism Today Conference
12-13 July, 2010; London, UK
E. anne.haylock@markallengroup.com

Warwick University Short Course.Techniques and Applications of Molecular Biology: A Course for Medical Practitioners
12-15 July, 2010; Warwick, UK
T. 024 7652 3540
E. charlotte.moonan@warwick.ac.uk
www.warwick.ac.uk/go/bioscienceshortcourses

XII International Congress on Neuromuscular Diseases
17-22 July, 2010; Naples, Italy
www.icnmd2010.naples.org

3rd INBR Congress
24-30 July, 2010; Abuja, Nigeria
E. polycarpnwoha@yahoo.com

August

4th Migrating Course on Epilepsy
15-22 August, 2010; Sercock, Poland
E. petra@epilepsy-academy.org
www.epilepsy-academy.org

15th World Congress of Psychophysiology - the Olympics of the Brain - IOP2010
30 August – 4 October, 2010; Budapest, Hungary
Mark Molnar, T. 61 350 1854
E. worldcongress2010@world-psychophysiology.org

September

3rd International Congress Biotechnologies for Spinal surgery
1-4 September, 2010; Amsterdam, Netherlands
E. meisel@bergmannstrost.com
www.biospine.org

Cambridge Memory Disorders Workshop
2-3 September, 2010; Cambridge, UK
T. 01223 217557
E. fiona.aschmann@addenbrookes.nhs.uk
www.ozc.nhs.uk

XVIIth International Congress of Neuropathology
11-15 September, 2010; Salzburg, Austria
Brigitte Millán-Ruiz, T. 43 1 404 005 573
E. brigitte.millan-ruiz@meduniwien.ac.at

Parkinson's Disease SpR Masterclasses
13-17 September, 2010; Central England, UK
T. 01872 225552
E. info@redpublish.co.uk
www.redpublish.co.uk/courses

Congress of Neurological Surgeons Annual Meeting
16-21 September, 2010; San Francisco, USA
T. +847 240 2500, F. +847 240 0804
E. info@1CNS.org
www.neurosurgeon.org

OZC – Understanding Brain Injury
17 September, 2010; Ely, UK
T. 01353 652173
E. Rachel.everett@ozc.nhs.uk

Evolving MS Services
17 September, 2010; Maidstone, UK
T. 0208 438 0809
E. pcrossman@mssociety.org.uk

Understanding and Dealing with Behaviour Problems following ABI
17-18 September, 2010; Gatwick Airport, London, UK
E. enquiries@braintreetraining.co.uk
www.braintreetraining.co.uk

Clinical Reasoning in Soft Tissue Repair: Using the evidence to maximise recovery using manual therapy, exercise and electrotherapy
18 September, 2010; Bath, UK
www.physiouk.co.uk

Second Meetingof the European Societies of Neuropsychology
22-24 September, 2010; London, UK
E. dana.samson@nottingham.ac.uk

14th Congress of the European Federation of Neurological Societies (EFNS 2010)
25-28 September, 2010; Geneva, Switzerland
T. 41 229 080 488
E. efns2010@kenes.com

Fifth Meeting of the UK PD Non Motor Group:
Non Motor Symptoms of PD: Treatment & Quality of Life

Conference details: 20 March 2010, Royal Society of Medicine, London, UK. *Reviewed by:* Miss Chandni Chandiramani, Kings College and Institute of Psychiatry, London, UK and Mr Kartik Logishetty, Kings College, London, UK,

The fifth meeting of the Parkinson disease Non-Motor Group (PDNMG) was held at the Royal Society of Medicine, London. This year the international faculty sought to look deeper into issues surrounding treatment and quality of life in Parkinson's disease (PD).

Professor K Ray Chaudhuri (UK), the PDNMG chairman and meeting organiser, welcomed the delegates by presenting an overview regarding the recognition and prevalence of non motor symptoms (NMS) of PD. Professor AHV Schaipra (UK), formally began the meeting by shedding light on neuroprotection approaches for PD. He discussed recent evidence which encourages early initiation of treatment, highlighting the results from ADAGIO, TEMPO and DATATOP trials which suggest that PD patients who started on early treatment had better outcomes with more symptomatic relief. He postulated that drugs such as selegiline, rasagiline and levodopa are able to promote brain plasticity and compensation. Prof Schapira emphasised preclinical non-motor markers of PD, including olfaction and constipation. He concluded that the decision of starting treatment should be based upon weighing treatment side effects and effects on quality of life with symptom control and disease progression. However, with questions surrounding the conclusiveness of the data and the power of the studies, further robust trials are required to further understand the possible disease-modifying properties of PD drugs.

Next, Prof DJ Brooks (UK) discussed the role of neuroinflammation in PD. He explored the evidence suggesting a pathogenic role of microglia in PD. Microglia are most highly concentrated in the substantia nigra, and most highly active and clustered around dystrophic dopaminergic neurones. Cytokine release leads to microglial and macrophage activation and subsequent dopaminergic and cholinergic cell death and brain remodelling. Prof Brooks outlined the uses of FDG-PET, FP-SPECT, F-Dopa PET, acetylcholinesterase imaging and PET amyloid plaque imaging in PD. These neuroimaging strategies provide biomarkers of the ongoing disease activity. Finally, he examined the correlation between Braak-staging of PD with clinical manifestations, imaging the substantia nigra and the non motor symptoms including olfactory disturbances, autonomic symptoms and disorders in the cognitive domain.

Prof Chaudhuri provided a succinct review of pain in PD. As well as outlining a classification of pain in PD (symptomatically grouped into musculoskeletal, radicular/neuropathic, dystonic, central or primary pain, and

Standing: Graham Macphee, Pablo Martinez-Martin, Peter Fletcher, Per Odin, Kieran Breen
Seated: Alison Forbes, Fabrizio Stocchi, K Ray Chaudhuri, Cristian Falup-Precariu.

Per Odin, Alexandra Rizos, K Ray Chaudhuri, Dag Aarsland, Pablo Martinez-Martin.

akathisia) he highlighted that depression may contribute to the intractability of a chronic pain syndrome. Orofacial pain is a poorly understood NMS but highly detrimental to quality of life. It encompasses headaches, burning mouth syndrome, temporomandibular joint pain and compromised trigeminal reflexes. He emphasised that most painful symptoms could occur during 'off periods', particularly early in the morning. Prof Chaudhuri discussed the generic pain evaluation tool - McGill Pain Questionnaire (MPQ) . The MPQ, used judiciously, is useful for defining the prevalance and characteristics of pain according to its location, intensity and temporal pattern, thus enabling a pain specialist to tailor management plans and monitor treatment response.

Professors P Martinez-Martin (Spain) and P Odin (Germany) discussed the impact of NMS on quality of life, and non-declaration of NMS in PD, respectively. Particular NMS including depression and autonomic, sexual and gastrointestinal dysfunction are under-reported by patients and as a result under-treated by health care professionals. This could be attributed to patients' lack of awareness between their NMS and PD or perhaps a reluctance to reveal embarrassing problems to a stranger. The recently published study recommends the

use of the patient-completed 'Non-Motor Symptom Questionnaire' (NMSQuest) to provide an early screen of NMS.

Professor A Antonini (Italy) offered an appraisal of drug therapy for motor and non-motor symptoms. He began with reviewing results from the recent PRIAMO study – a large Italian cross-sectional observational study which described epidemiology and evolution of NMS. NMS in the psychiatric domain were most frequent, with apathy being most associated with reduced quality of life scores. NMS are closely associated with cognitive impairment, with the number of NMS per patient increasing with age and disease severity. Finally, the PRIAMO study highlighted the high prevalence of NMS in the PD population (98.6%). For the treatment of NMS, Prof Antonini went on to discuss pramipexole, which has negative effects on daytime sleepiness but may significantly alleviate depression. The clinical benefit of DBS in NMS is relatively much higher than that of apomorphine. However, while DBS may improve dyskinesias in late PD, it does not seem to have any effects on sexual aspect of NMS in PD. Lastly, intrajejunal infusion of levodopa is a more invasive treatment than apomorphine. Levodopa infusion not only replaces oral medication but also helps in avoiding swallowing problems that may be commonly experienced in PD.

In recent years, dementia has been recognized as a common albeit highly variable feature of PD. Professor D Aarsland (Norway) outlined the clinical and neuropathological differences between PD dementia (PDD) and Alzheimer's disease (AD) pathology with or

without dementia. Old age, visual hallucinations, and more marked motor symptoms are established risk factors for PDD, with at least 75% of PD patients developing dementia within 10 years. Differentiating PDD with Alzheimer's disease (AD) pathology remains difficult, since half of dementia patients have enough pathology to be diagnosed with AD while PDD can develop without any AD pathology at all. However, a shorter duration of PD symptoms before onset of dementia in an older patient may suggest PDD+AD pathology. Sufferers are prone to experience cognitive impairment, psychiatric fluctuations and sleep disturbances. There are a wide range of treatment approaches for dementia in PD. Prof Aarsland reviewed cholinesterase inhibitors and memantine (specifically licensed for AD) as possible treatments for PDD. Statins, anti amyloid strategies, anti inflammatory treatments and anti psychotic therapies were also briefly discussed .

Dystonia is not classically regarded as one of the non motor symptoms of PD but it seems to share analogous features with NMS in PD. Like NMS, dystonia is under-recognised as well as under-treated. Professor T Warner (UK) discussed the multiple factors which may induce dystonia before reviewing the diverse treatment strategies for dystonia in PD. Purported links between dopa-responsive dystonia and exercise-induced dystonia with PD remain unclear. Dystonia in PD seems to have a genetic connection - autosomal recessive inheritance, involving mutations in PARK2 and PARK6 genes. He recommended anti-dyskinetic drugs like amantadine, continuous levodopa infusions, botulinum toxin to treat this troublesome, albeit rare, problem in PD.

Professor F Stocchi (Italy) examined the correlation between gastrointestinal problems in PD and quality of life. Dribbling of saliva, swallowing abnormalities, nausea, vomiting and constipation are some of the most common NMS seen in PD. Prof Stocchi outlined that constipation could precede the motor symptoms and be regarded as one of the pre-clinical markers of PD. There are many therapies that have been advocated for the treatment of gastrointestinal symptoms in PD, including botulinum toxin as a solution for dribbling of saliva and even constipation.

Dr Graeme MacPhee (UK) examined the aetiology, prevalence and the various assessment tools and treatment strategies for depression in PD. Depression is a key neuropsychiatric NMS and can affect up to 45% of PD patients. Dysfunctions of dopaminergic, serotonergic and noradrenergic pathways in the limbic system of depressed PD patients have been implicated. He recommended the use of the Hamilton depression scale (HAD Scale) to identify depression. The treatment should be tailored to symptom severity, in addition, recent SIGN guidelines examining the treatment of depression in PD identified that tricyclic antidepressants showed the best efficacy but that these agents often came at the expense of adverse effects. SSRIs are often used in routine practice.

The meeting ended with video case presentations of PD patients facilitated by Prof Chaudhuri, Prof Stocchi and Professor G Macphee (UK). The interactive session examined the sometimes puzzling and atypical presentation of parkinsonism and was buoyed by enthusiastic audience contribution.

Non motor symptoms have a significant impact on quality of life – more so than their motor counterparts. The search for a therapy that adequately addresses motor and non-motor symptoms continues. In the meantime, clinicians must adopt a holistic approach to their treatment, and place the patient's individual perception of their symptoms at the core of any management strategy. On reflection, it is clear that since its genesis 6 years ago, the PDNMG has gone some way in achieving its initial mission statement. Thanks in part to the widespread use of the group's internationally validated assessment tools, non motor symptoms are now a widely recognised feature of PD. It is likely that from 2011 onwards, meetings will take place under the banner of 'EUROPAR', a group dedicated to the advancement of non-motor research in PD.

Sixth World Congress for Neurorehabilitation 2010

Conference details: 21-25 March 2010, Vienna, Austria *Reviewed by:* Louise Blakeborough, on behalf of the World Federation for Neurological Rehabilitation.

The 6th World Congress for Neurorehabilitation was held between the 21st and 25th March in Vienna. Over 1600 health professionals from 71 countries met in the historical Congress Centre in the Hofburg, Vienna's former imperial palace.

There was an extensive programme of workshops, lectures and symposia on clinical practice and research covering topics from basic science to practical applications. The breadth of content attracted neurorehabilitation clinicians and therapists from all disciplines. Just a few highlights follow.

In the Opening Ceremony, Heinrich Binder, President of the Austrian Society of Neurorehabilitation welcomed delegates to Vienna. The President of the World Federation for Neurorehabilitation (WFNR), Michael Selzer, then introduced the first Michael P Barnes Lecturer in Neurorehabilitation, given by the eminent Alberto Juan Aguayo. This Lecture will now be the highlight of each WFNR World Congress, in recognition of the visionary leadership of the WFNR's founder, Michael P Barnes.

Alberto Aguayo gave an historical overview of axon regeneration in the central nervous sys-

tem (CNS), beginning with Santiago Ramón y Cajal's 'Degeneration and Regeneration of the Nervous System,' which was published in 1914 and anticipated many of the current ideas in the field. Beginning in the 1980's, Dr Aquayo and his colleagues at McGill University carried out pioneering studies that showed injured axons of the central nervous system were not intrinsically incapable of regenerating after injury, as had been assumed. Aguayo rediscovered an old finding by Cajal and his students that these axons could grow for long distances into grafts of peripheral nerve. In a long series of elegant experiments in the spinal cord, brain and optic nerve, Aguayo showed that the extracellular environment of the CNS is an important factor in limiting the regenerative ability of axons. These studies laid the groundwork for the subsequent discovery of molecules found in the CNS that are inhibitors of axon regeneration.

Later in the congress, Dr Selzer introduced two of the most prominent scientists in the field, who focused on the molecular mechanisms that underlie Aguayo's findings. Dr James Fawcett of Cambridge University described how perineuronal nets containing chondroitin sulphate proteoglycans and other inhibitory molecules suppress axon regeneration and sprouting, a form of plasticity, in the brains and spinal cords of rats. Enzymatic digestion of chondroitin sulphate proteoglycans increased sprouting in the injured spinal cord, but this did not automatically result in functional improvement, unless the treatment was combined with behavioural reinforcement (physical therapy). This demonstrates what neurorehabilitation researchers have long suspected, that restored anatomical connections will have to be sculpted by physical therapy in order to achieve optimal restoration of function. Dr Marie Filbin of the City University of New York focused on another group of inhibitory molecules, those contained in CNS myelin. These molecules bind to the Nogo receptor, part of a receptor complex present in the membranes of axons that triggers inhibition of their growth. Dr Filbin has discovered many of the steps in the intra-neuronal signalling cascade that leads from binding to the Nogo receptor to shut-down of axon growth. Clinical trials still ongoing are aimed at neutralising these inhibitory molecules in patients with spinal cord injury.

Although actual cures for serious nerve injuries have not yet been achieved and there are many challenges ahead, multiple strategies are now converging to manipulate the nervous system at many levels in order to promote axon sprouting and regeneration.

A session entitled Cell Therapies: Hope or Illusion? introduced by Dr Bruce Dobkin encapsulated the acceleration of neurological research in the field of stem cells for conditions such as stroke, multiple sclerosis, Parkinson's and Huntington's disease. The session began with an audience vote on whether they believed that cell therapy interventions would eventually improve life for the most severely impaired patients. The majority of the

audience voted yes. However, Dr Dobkin cautioned against the selling of hope to vulnerable people and families by 'for-profit stem cell organisations' and strongly advocated the conduct of prospective, randomised, multicentre controlled trials as ethically and scientifically necessary.

A very encouraging development was reported by Dr Wise Young, who has worked with research communities around the world, including the Peoples Republic of China, to adopt the use of standardised frameworks to guide future pre-clinical and clinical research. This session was attended by several disabled young people who asked the speakers and audience to encourage "partnerships with the spinal cord injury community" and ensure that patients understand the basics of this exciting science.

As with any meeting about neurorehabilitation, the use of robotics provided lively discussion and debate. There is no doubt that rehabilitation robotics is a highly promising technology that has demonstrated benefit in several disabling neurological illnesses. Dr Hermano Igo Krebs reported results of a prospective, randomised, multicentre controlled trial of robotic-assisted physical therapy for upper limb recovery after stroke, carried out in the US Department of Veterans Affairs. While conventional physical therapy resulted in almost as good recovery, this was only true if the intensity of therapy was equal. It is possible that robotics will allow a greater intensity of therapy.

The key problem faced by this technology is our uncertainty about the appropriate way to use these devices and their potential limitations. Maybe, as Dr William Rymer said "the problem is not with robotics but with us and our way of using them". The key to successful use of robotics may be their simplification and adaptation to home use.

Another symposium focused on the potential use of brain-computer interfaces to permit totally paralyzed patients to control assistive devices and even their own paralyzed muscles. Dr John Donoghue explained that evidence from multielectrode microchips implanted in paralysed human patients shows that command neurons in the cerebral cortex survive despite the neurodegenerative nature of amyotrophic lateral sclerosis and trauma to axons in spinal cord injury.

But with all the high-tech advances in regenerative medicine and robotics, perhaps the most interesting theme of the congress related to the notion of simplicity in research design. A poster by Dr Bruce Dobkin and colleagues presented the results of a clinical trial designed to allow participation by investigators who have no access to specialised equipment. In the SIRROWS study, providing inpatients recovering from stroke with feedback on how quickly they walked improved their ultimate walking speed over ten metres and how far they could walk in three minutes. The improvement persisted at least as long as a three month follow-up.

Several sessions addressed evidence-based

neurorehabilitation, an area that has been slow to progress, partly due to the constraints of randomised controlled trials. Matching the right intervention for a patient's deficits can prove to be extremely difficult, with a lack of treatment protocols available. An overview of guideline preparation was presented by Dr Lynne Turner-Stokes and Dr Thomas Platz who outlined guidelines for arm treatment after stroke.

Recent neuroscience research suggests that the neural systems underlying music also serve non-musical functions, such as linguistic processing, motor control, attention, memory and other functions. Dr Michael Thaut postulated that music can affect general cognitive and motor functions subserved by these brain systems via mechanisms of neural plasticity. There is now a new treatment model of Neurologic Music Therapy with considerable evidence for its effectiveness in rehabilitating disorders of the human nervous system.

When do you start neurorehabilitation? This key question was discussed by Dr Heinrich Binder and followed by Dr Anthony Ward who showed that the outcomes of brain injured patients were improved by interventions that took place in the intensive care unit rather than waiting until the patient has been transferred onto a rehabilitation ward. But perhaps the most impressive example of the application of simplicity to research design was given by Dr Gert Kwakkel of the Netherlands. Using multivariate analysis he showed that within a few days after a stroke, recovery of hand and arm coordination could be almost perfectly predicted by two findings on very simple bedside tests; a small amount of finger extension, and a small amount of shoulder abduction. Similarly, recovery of walking could be predicted by whether the patient could sit up over the side of the bed.

There were over 400 interesting and diverse poster presentations throughout the week. The prize for the best poster by a student or fellow went to Dr Johan Gaverth of Sweden for developing a biomechanical model that can quantify spasticity and distinguish it from contracture. The prize for the overall best poster went to Dr D Cinteza of Romania for a study that showed the superiority of training to step over obstacles over treadmill training for recovery of gait after stroke.

The meeting ended with a special lecture by Dr Henry Markram of Lausanne, Switzerland. He gave a spectacular demonstration of the Blue Brain Project, a combination of experimental work and computer modelling that is developing an accurate representation of the cerebral cortex down to the finest details of synaptic connectivity and molecular mechanisms.

The next World Congress for Neurorehabilitation in 2012 will take place in Melbourne, Australia.

For further information please visit the WFNR website www.wfnr.co.uk

Positive Steps in Parkinson's Disease

Conference details: 5-6 March 2010, London UK   *Reviewed by:* David Burn, Professor in Movement Disorder Neurology, Newcastle University and Dr Doug MacMahon, Consultant Physician, Camborne-Redruth Hospital, Cornwall.

The third Positive Steps in Parkinson's Disease meeting, sponsored by Teva Pharmaceuticals Ltd and Lundbeck Ltd, was held on March 5th-6th in London. The presentations and discussions covered both cutting edge clinical research and aspects of daily practice that, although sometimes overlooked, have significant impact on patient quality of life. Although the presentations were varied in content, it was striking that a common theme was the recognition that Parkinson's disease (PD) is no longer considered solely a motor disorder, and that treatments and research strategies need to address the issues of non-motor problems suffered by the majority of people with PD.

Dr Doug MacMahon began the programme by giving an update on clinical trials reported in the past year. New genome-wide association studies have recently shown two strong association signals in genes coding for alpha-synuclein and Tau proteins. Importantly, these new studies were not conducted in relatively small populations with familial PD, but in patients with "sporadic" idiopathic PD, thus demonstrating a clear role for common genetic variants in the aetiology of this disease, and also recent speculation of the possible role of prions. Dr MacMahon highlighted that recent research has tended to focus on the recognition and treatment of early disease in the hope of a treatment that will slow or halt the inexorable progression of PD. The recognition that non-motor symptoms (such as hyposmia and constipation) can often emerge before motor symptoms or signs has given rise to the notion of diagnosing prodromal PD. Dr MacMahon stressed that the early recognition of PD becomes more crucial as we begin to review the role of early treatment. Last year saw the publication or release of data from a number of large clinical trials in early disease and although some of the results were disappointing, some have indicated that more strategic use of currently available drugs may help maintain patient function for longer. While discussing the results of the ADAGIO (rasagiline) and PROUD (pramipexole) delayed-start studies, Dr MacMahon noted that physicians must now be able to interpret data from complex trial designs and understand the rationale that effects of drugs given in early disease may not always be clinically obvious as the patients only display mild symptoms, but may modify the progress thereafter.

A hot topic in PD is the association of dopaminergic therapy with impulse control disorders (ICDs) and Dr Graeme Macphee gave a presentation covering the large amount of work recently conducted in this area. Although they have only been recognised relatively recently, ICDs (including compulsive buying, pathological gambling, binge eating, hypersexuality) are not uncommon. A recent large observational study conducted in the United States and Canada found that 13.6% of patients with PD had at least one ICD, and 36% of these had more than one disorder. ICDs are often associated with dopamine agonists, but patients receiving both levodopa and a dopamine agonist appear to be at highest risk. Dr Macphee suggested that ICDs can be viewed as a continuum of reward-based behaviours; the earliest signs being the emergence of atypical behaviours that the patients often try to hide. Notably, there is often a lack of pleasure associated with the behaviours, the patient needing rather than liking the feelings associated with the activities. Pathologically, it appears that degeneration in the ventral striatum and nucleus accumbens is more closely associated with problems with impulse control than degeneration in the dorsal striatum. Dr Macphee suggested that non-physiological stimulation of dopamine receptors in the ventral striatum might underlie the development of ICDs; the analogy later suggested by the panel was that ICDs may be regarded as a form of 'limbic dyskinesia'.

Dr Peter Fletcher continued the theme, looking at non-motor problems in elderly patients with PD. People in the western world are now fitter and living longer, so more people are surviving other diseases to achieve older age, when PD becomes more prevalent. Added to this, improvements in the care of patients with PD mean that they are now surviving longer and this brings a new aspect to care; the elderly PD patient is no longer just the patient who developed PD in later life, but also includes patients who have lived with PD for a long time. In addition to the core motor symptoms, the typical elderly patient with PD will suffer from a multitude of non-motor symptoms, particularly autonomic dysfunction, sleep disorders, dementia and depression – often with considerable impact on caregivers and family. The risk of falls and associated fractures can start early, but the average time to first fracture is 9 years from diagnosis and is the number one cause for admission of people with PD to A&E. As more patients are surviving longer in the complex and palliative care phases of PD management, Dr Fletcher stressed that physicians need to take the long view and that treatment should target the needs of the whole patient and not just motor symptoms and that our training and support systems need to change in recognition of this.

The problems of dementia were reviewed in further detail by Professor David Burn who highlighted the high cumulative incidence of PD dementia (PDD) and its significant neuropsychiatric burden (including psychotic features and mood disturbances). The people most at risk for PDD are older with more severe disease. They will often have the PIGD phenotype and might have REM sleep behaviour disorder. Professor Burn discussed that diagnosing cognitive impairment is not always easy and that a collateral history from caregivers and relatives is essential in teasing out the slow progression of cognitive decline that is associated with PDD. Though a wide variety of cognitive tests are available for daily practice, physicians should no longer rely on the MMSE for assessing PDD. Tests such as the Montreal Cognitive Assessment (MoCA) and the Addenbrooke's Cognitive Examination (ACE-R) are relatively short and are better for picking up problems with executive function. Treatment with cholinesterase inhibitors remains the mainstay of treatment (only rivastigmine is licensed for PDD), and although the atypical antipsychotics can be useful they are not licensed for the treatment of PDD. Despite the association of cholinesterase inhibitors with increased tremor in the titration phase, this doesn't appear to be troublesome enough for the patients to withdraw from treatment. However, physicians should be aware of the increased risks of fractures and bradycardia before giving a cholinesterase inhibitor. In addition, Professor Burn stressed that if one cholinesterase inhibitor doesn't work, it is always worth trying another as they each have specific efficacy and tolerability profiles that may suit different patients.

Another problem associated with PD is poor oral health, and Dr Helen Roberts surprised the audience by giving one of the first talks on this topic at a national meeting. Although physicians who treat PD are very familiar with the problems of drooling and dysphasia, most are less aware of the problems of xerostomia (dry mouth), burning mouth

and dental caries. Dr Roberts pointed out that the common practice of reducing salivary flow (by atropine or botox) to control drooling has the adverse effect of impairing the normal buffering role of saliva, leading to an acidic environment, demineralisation of the teeth and ultimately tooth decay. Similarly xerostomia, which can be caused by treatments such as levodopa, can affect up to 55% of the PD population and also carries an increased risk of dental caries and periodontal disease. The few dental studies which have been carried out have all shown that PD patients have more missing teeth, swollen gums and denture discomfort, all of which can impact on the patient's ability to eat. Dr Roberts urged all attendees to question their patients about their oral health, and to coordinate care with dentists where possible to give advice on the specific dental problems associated with PD.

The question of who is a good candidate for neurosurgery was tackled by Dr Tom Foltynie, who stressed that patient selection is the key to a successful outcome. Accepted indications include severe motor fluctuations, dyskinesia and tremor, and more recently patients who are intolerant to medication (for example due to ICDs) are increasingly being considered. The benefits of deep brain stimulation (DBS) can be dramatic and studies have shown that the effects are relatively long lasting, but the 'fitness' of the patient should always be considered, as surgery is not without risk. Aside from

the immediate risks of an invasive procedure (the overall rate of surgical complications is 3%), patients should be cognitively intact and have good speech as DBS can affect verbal fluency. Weight gain can also be a problem for some patients. Advances in the technology include changes in the electrode, for flexibility in targeting, and rechargeable batteries. There is also evidence that although earlier rather than later DBS treatment may optimise its benefits, there are logistical and financial obstacles to adopting this theoretical approach.

Looking to the future, Dr Roger Barker discussed the role of stem cells as a neurorestorative treatment. Recent advances in developing Induced Pluripotent Stem (IPS) cells now allow the generation of stem cells from the patient's own skin, thus avoiding many of the ethical problems of embryonic stem cells. Indeed, it has been reported this year that it is now possible to convert fibroblasts directly to neurones by using appropriate growth factors. However, numerous technical problems have meant that this technology is currently best used as a way to model the disease rather than as a treatment. Furthermore, experience with foetal grafts into the striatum tells us that we should again pay close attention to patient selection and timing of the graft. Younger patients with localised nigral pathology have been reported to do extremely well, whereas older patients who suffered from postural instability and gait dysfunction tended to have

a more widespread pathology throughout the CNS and experienced minimal benefit and dyskinesia. Similarly, significant benefits motor function were only seen in patients with a UPDRS score of <49.

Professor Peter Jenner closed the meeting by looking at upcoming drugs in the PD pipeline. A number of potential non-dopaminergic drugs have recently failed in Phase III studies, although a few candidates such as the adenosine A2A antagonists remain in clinical development as adjunct therapies. Similarly, research into neuroprotective and neurorestorative therapies have yet to produce any real candidates for treatment. However, the introduction of new delivery systems for older drugs (including levodopa and a number of dopamine agonists) and revised treatment algorithms have already made a significant impact on patient care. For example, evidence is now accumulating that early intervention may increase the amount of time that the patient remains stable and delay the onset of motor complications. Professor Jenner ended the meeting by stressing that in order to meet the developing needs of people with PD, physicians should take a long-term strategic approach to treatment.

The lively discussions and debate were all supplemented with workshops and interactive sessions and participants left eagerly looking forward to the next meeting planned for 4-5 March 2011 in Newcastle upon Tyne.

Review of the Third Biennial Meeting of the UK Swallowing Research Group

Conference details: 4-5 February 2010, London, UK. ***Reviewed by:*** Sophie Puritz CT1, Medicine, University Hospital of Wales and Tom Hughes Consultant Neurologist, University Hospital of Wales.

The UK Swallowing Research Group held a conference on Thursday 4th & Friday 5th February 2010 in UCL Institute of Child Health, London. This was the third meeting of the group following its first meeting in Manchester four years ago. The attendees were from a range of backgrounds but speech therapy was the best represented profession. Although it may seem anomalous to some to arrange a conference around a single function or ability, the relevance of a clinical appreciation of swallowing problems and the complications of defective swallowing soon became apparent during the presentations.

Swallowing was the subject of some of Sherrington's revealing experiments in the early 1900s. In 1916 he demonstrated the deglutition apnoea and the expiration that (usually) precedes and follows it. He described various phagetic agents and their effectiveness in eliciting reflex swallowing in decerebrate cats; whiskey was the most effective and viscous oily liquids the least.. His insights into the basics of swallowing are still the subject of discussion today as reflected in presentations in this conference about the integration of respiration and deglutition in health and disease and the differences in opinion regarding the extent to which swallowing is voluntary or reflex.

The conference started with a comprehensive review of dysphagia research (Dr. Paula Leslie, University of Pittsburg USA), demonstrating how far the field has expanded over the past twenty years. The future of dysphagia research was also considered, serving as a reminder of the need for clinically relevant research to inform the development of evidence based practice.

Following on seamlessly from this opening was a series of talks demonstrating the effect of dysphagia research on clinical practice, including the use of fibreoptic endoscopic evaluation of swallowing (FEES) in adult and paediatric patients (Ms Sarah Wallace, Manchester, Ms Sophie Frey, Germany, Ms Rebecca Harris and Ms Martina Ryan, London.)

Towards the end of the morning, we heard about swallowing problems in two very different populations of patients; those with neuromuscular disorders such as Duchenne muscular dystrophy and patients who have suffered a stroke (Dr.Anita Simonds, London). It became apparent how ideas are changing about the mechanism and management of dysphagia in these patients and how different approaches are required to reduce morbidity and mortality. The relationship between swallowing and breathing was explored (Dr. Katie Ward, London), offering a further opportunity to consider dysphagia in a different context.

During the lunch break, while we all checked the integrity of our own swallowing mechanisms, there was a display of high quality posters, some of which were also platform presentations during the afternoons. Some of the notable presentations included: Promoting the recovery of swallowing after stroke by stimulation of the motor cortex (Dr Andrew Barritt, Kent,); Reduction in rates of aspiration pneumonia after stroke (Dr. Soenke Stanschus, Germany); and a pilot study into the effectiveness of thickened fluids in preventing pneumonia (Dr. Sue Pownall, Sheffield), which won the prize for the best free paper.

The following day, there was an emphasis on assessment

tools and rating scales, starting with an in-depth five-year research project carried out in the USA (Prof. Bonnie Martin Harris) using the modified barium swallowing study. We were also introduced to the pitfalls of rating scales (Dr. Stefan Cano, Plymouth), many of which, although commonly used, are based on weak scientific theory and questionable arithmetic.

Later in the afternoon, we had our focus brought back to patients with an overview of the holistic approach to swallowing problems and a reminder to view dysphagia in context, as an 'oral feeding' problem (Dr. Tom Hughes, Cardiff). The conference was closed with two talks concerning the regeneration of voice and swallowing using various methods including tissue replacement and neuromuscular electrical stimulation (Prof. Martin Birchall, UCL, Ms Emilia Michou, Salford) .

After such a variety of topics within this highly specialised field had been covered, I (SP) certainly felt that my knowledge of the swallowing mechanism and related pathology had increased. The importance of the multidisciplinary team was made more apparent to me; complex problems require input from several different sources. I was also amazed by the volume and depth of dysphagia related research that has been going on worldwide over the past few years, and the different approaches to the dysphagic patient it has opened up. A highly specialised, niche field it may be, but as the third meeting of the UKSRG has shown, dysphagia research continues to influence and guide the management of our patients with the common aim of improving quality of life.

Carl Zeiss increases Fluorescence Sensitivity by 100%

Carl Zeiss is setting new standards for image quality in fluorescence microscopy with the launch of the LSM 780. The new microscope features radical, high quantum efficiency, GaAsP detector technology, which increases sensitivity by 100% compared to the class-leading Zeiss LSM710.

The LSM 780 will be of particular value to cell- and neuro-biologists, enabling weakly fluorescent or bleach-sensitive specimens or specimens with fine structures to be visualised more rapidly and with higher image quality. It also permits specimens that could not be satisfactorily examined in the past to be imaged at high resolution for the first time.
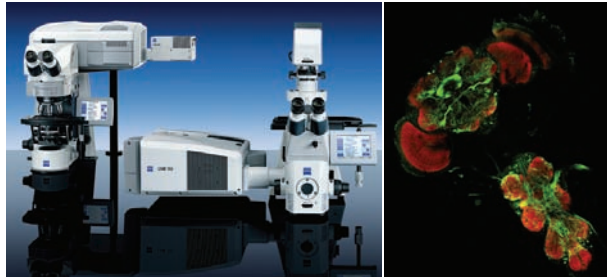
Zeiss offers three versions of the GaAsP detector technology: a 32-channel detector in the LSM 780 laser scanning microscope, an internal detector upgrade for

existing LSM 710 systems and an external LSM BiG upgrade module. All versions of the 32-channel GaAsP array permit traditional spectral imaging, photon counting with maximum sensitivity, and single molecule visualisation through fluorescence correlation spectroscopy (FCS) with one to six signal channels. The LSM BiG module gives LSM users a substantial increase in the flexibility of their imaging system and is a considerable advantage in multiphoton microscopy when fitted to the LSM 780 NLO or 710 NLO systems.

For more information E. micro@zeiss.co.uk

Training future physiotherapists with SonoSite MicroMaxx® ultrasound systems

The SonoSite MicroMaxx point-of-care ultrasound system is being used for musculoskeletal visualisation to train undergraduate and postgraduate physiotherapists in the School of Health and Rehabilitation at Keele University.

Kim Major, a clinical physiotherapist and lecturer at the school, said, "We chose the MicroMaxx system to illustrate our lectures, showing muscles and soft tissue in action and how everything interrelates inside the body, instead of relying on two-dimensional textbooks. For our purposes, being able to delineate muscle is the key element and the MicroMaxx's image quality has allowed us to see almost everything we need. Its portability is a real boon because we need to be able to move the system from room to room, and it is easy to set up. We now use

the MicroMaxx in several undergraduate research projects when we effectively hand it over to the students, and the system's fairly indestructible nature is very reassuring. The five-year warranty is important in that respect, too. The image storage facilities have also been very useful for these projects." Kim concluded, "Ultrasound gives the students a much better understanding and it really speeds up the learning process for many of them."

For information and to register on SonoSite structured training courses, log on to www.sonositeeducation.co.uk
For more information about SonoSite products
T. 01462 444 800, E. uk-sales@sonosite.com

Epilepsy – I think my patients take their medication!

In discussions with those that treat epilepsy we often find a general belief that their patients adhere to the prescribed regimen of AED's. Further discussion often reveals that this belief is not based on careful questioning of the patient. It therefore raises the question as to whether it is safer to assume that patients' adherence is poor rather than good. Indeed, non-adherence has been shown to be a common problem with several studies showing that adherence to AED's typically ranges from 27% to 59%. It is not surprising that this can be an important factor in the effectiveness of the medication and studies report that seizure frequency is higher when adherence is poor. It is clear that a medication cannot be expected to work if the patient does not take it. Other studies show a preference towards a simpler once daily regimen. NICE suggest that, where appropriate, clinicians should consider the preferences of the patient and/or carers when individualising AED regimens. Once daily controlled release versions of valproate have, for example, been shown to be preferred by patients, improve adherence, reduce seizure frequency and improve clinical outcomes. There is an argument that to get the most out of an AED the prescriber should aim for a convenient presentation that makes it as easy as possible to gain concordance in order to help ensure an effective outcome.

For more information contact Beacon Pharmaceuticals on T. 01892-600930

EPDA and PAI launch Parkinson's Decision Aid

Deciding on drug treatments and how to manage the life of a person with Parkinson's (PWP) is not easy. Choosing the best way to live with the disease – in terms of both mental attitude and physical health – can be confusing for both the person with Parkinson's (PWP) and their healthcare professional. It requires excellent communication between both parties.

As a result, the EPDA and the Parkinson's Association of Ireland (PAI) have worked together to launch the Parkinson's Decision Aid (PDA), an online educational toolkit that seeks to put the PWP in the best possible position to make the right choices so they themselves can actively work with their healthcare professional to improve their quality of life and make informed choices together.

It is hoped the PDA will be rolled out in other parts of Europe over the next few years. It provides a wealth of up-to-date information about Parkinson's that has been researched and reviewed by European Parkinson's experts, and has been written in an easy-to-understand style for everyone.

The website has three core sections:

PD Essentials: Questions a PWP can ask their doctor and other healthcare professionals that will enable them to receive the right answers.

PD In depth: A huge library of researched and reviewed information to help PWPs live a better life as well as providing answers to the many questions they might have.

Later in Life: This section provides information for people who have lived with Parkinson's for some considerable time. The information provides answers to many complex issues they may have experienced, for example surrounding palliative care, end-of-life issues and a different life.

For more information see www.parkinsonsdecisionaid.eu.com

Nikon introduces new colour camera to Digital Sight series

Nikon has added the high speed DS-Vi1 colour camera to its market-leading range of Digital Sight cameras for microscopic imaging. The DS-Vi1 offers high frame rates and increased sensitivity for both multiple live image and sharp still image capture, making it ideal for high end biological research, clinical analysis and documentation as well as medical teaching use.

The DS-Vi1 features a 2-megapixel colour CCD with outstanding SXGA video display rates of up to 27 frames per second possible and effortless fast focusing. In addition, the DS-Vi1 offers high sensitivity and a wide dynamic range of more than 600:1, enabling the capture of clear, sharp images.

The DS-Vi1 can be combined, via a USB 2.0 interface, with either the stand-alone Nikon DS-L2 control unit or the DS-U2 PC control-based unit. The DS-L2 features a large 8.4 inch high-definition LCD monitor and allows live observation, camera control and image capture via simple on-screen menus without connection to a PC. In addition,

the DS-Vi1 can be controlled by Nikon's NIS-elements software. With the DS-U2 PC control unit, live images can be viewed, recorded, measured, processed, and analysed with integrated control of the camera and microscope peripherals.

*For further information contact Nikon Instruments Europe, T. 0208 247 1718,
E. info@nikoninstruments.eu*

SonoSite supports regional anaesthesia training in the South West

The South West Regional Anaesthesia (SoWRA) Group runs a popular regional anaesthesia course, and is supported by SonoSite through the loan of equipment and training aids. This initiative is helping Trusts in Devon and Cornwall to expand their use of ultrasound for regional nerve blocks, as Dr Matthew Grayling, a consultant in anaesthesia at the Royal Devon and Exeter Hospital and secretary of SoWRA, explained, "Our aim is to promote local interest in regional anaesthesia techniques, using local expertise to provide cost-effective training and establish a good foundation in high quality anaesthesia care in the region. SonoSite and other manufacturers have been very generous by loaning equipment and teaching us to use their instruments, helping us to invest more in developing the course and providing a forum to improve regional nerve blocks in the South West."

*For information and to register on SonoSite structured training courses, log on to
www.sonositeeducation.co.uk
For more information about Sonosite products
T. 01462 444 800.*

Carl Zeiss VivaTome makes Optical Sectioning Fast and Easy

Optical sectioning is the technique of choice for fluorescence imaging of biological specimens, providing highly-resolved, contrast-rich images even from thick living cells. However, its appeal has been limited by the cost and complexity of the systems and the sophisticated software and time-consuming processing required.

VivaTome, from Carl Zeiss, cuts through these barriers, combining the imaging speed of a spinning disk system with the light efficiency of structured illumination, pioneered by Zeiss with the award-winning ApoTome. Designed for life science applications where temporal resolution is a priority, VivaTome provides developmental and cell biologists with a fast, cost-effective tool to examine the dynamics of living specimens without extensive prior knowledge of optical sectioning.

VivaTome's structured illumination technique is one of the easiest and most efficient ways to implement optical sectioning capabilities into a white-light widefield system. Fast frame rates of up to 30 frames a second capture highly-dynamic processes in living samples, something only possible until now with advanced microscope systems.

For more information see http://bit.ly/cSUcqr

The new INFINITY 1.4 Megapixel Ultra-Sensitive CCD Microscopy Camera from Lumenera Corporation

Vision Source has announced the release of a new ultra sensitive high colour fidelity CCD scientific camera from Lumenera Corporation. This newest USB 2.0 offering from the popular INFINITY family of microscopy cameras is an ideal solution for low light applications such as fluorescence, and where precise color reproduction is needed.

The INFINITY3-1U offers large 6.45μ x 6.45μ pixels in a 2/3" format with a maximum resolution of 1392 x 1040. It employs the Sony ICX285 1.4 megapixel CCD sensor – the market leader for fluorescence and other challenging low light applications. In addition, the cameras near-perfect colour rendition makes it an excellent addition to any clinical laboratory. Suitable for both fluorescent and brightfield imaging, this camera offers an excellent price-to-performance ratio.

The camera's adaptability to vary resolution and frame rate requirements, combined with low noise performance and 8- or 12-bit pixel data mode, make the INFINITY3-1U an ideal camera for both live and fixed cell imaging. Live video preview allows for real-time focus; while auto exposure and auto/manual white balance efficiently capture your optimal image. This complete solution includes Lumenera's INFINITY CAPTURE and INFINITY ANALYZE software, and is offered with both colour and monochrome capability. Advanced camera control is available through a Software Developers Kit, while TWAIN and DIRECTX drivers ensure integration and compatibility with a variety of 3rd party software applications.

For more information see www.visionsource.co.uk

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