

ACNR

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ADVANCES IN CLINICAL NEUROSCIENCE & REHABILITATION

In this issue

Alex J Mitchell

The Prognosis of Mild Cognitive Impairment - Is it Better than Expected?

Geraint Rees and Rimona Weil

How Does the Brain Fil-in the Visual World?

James M Gilchrist and George M Sachs

Longitudinal Neurophysiologic Assessment of Disease of the Peripheral Nervous System





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

Magstim Young Investigator Award and Poster Prizes



Pioneering research into the diagnosis and treatment of a number of neurological conditions through magnetic stimulation was recently celebrated at the 3rd annual Magstim TMS Summer School. The event, held in conjunction with University College London (UCL), saw the announcement of the Magstim Young Investigator Award and Poster Prizes.

Dr Charlie Stagg of the University of Oxford received the Young Investigator Award for her work in exploring the potential use of TMS and tDCS as post stroke rehabilitative therapies, whilst the 2009 Poster Prize was awarded to Marius Moisa of the Max Planck Institute for Biological Cybernetics, Germany. Mr Moisa and colleagues developed a novel method which combines TMS and continuous arterial spin labelling (CASL) for the first time as an alternative to more traditional imaging methods to assess the effect of TMS on brain connectivity. This new combination enables the measurement of both blood oxygenation level-dependant (BOLD) signal and blood perfusion, an important advantage when studying the effects of TMS on brain connectivity.

For more information E. andrew.thomas@magstim.com

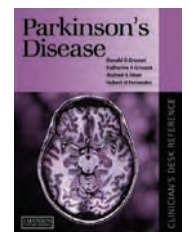
Professor Rossor wins 2009 Bengt Winblad Lifetime Achievement Award

Professor Martin Rossor has been recognised by the The Alzheimer's Association for his achievements in advancing Alzheimer's research. The 2009 Bengt Winblad Lifetime Achievement Award was awarded to Martin Rossor, MD, Head of the Division of Neurology and Director of the Dementia Research Centre at the UCL Institute of Neurology and the National Hospital for Neurology and Neurosurgery, Queen Square, London. Dr Rossor's research includes studying familial Alzheimer's disease and familial frontotemporal lobar degeneration. Longitudinal studies of at risk individuals from affected families has helped identify the first clinical and imaging changes that signal the onset of disease.



Competition Winners

Congratulations to the two winners of our competition, who each win a copy of Parkinson's Disease – Clinician's Desk Reference from Manson Publishing. The winners were Tessa Bennett from Farnham Hospital, and Claire Robinson from the Birmingham Learning Disability Service. Thank you to Manson Publishing for providing the prizes.

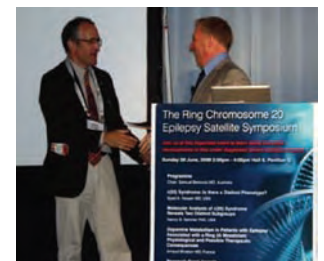


New research grants for Research on Ring Chromosome 20 Syndrome

The first international symposium dedicated to the treatment of genetic epilepsy condition ring chromosome 20 syndrome took place at the 28th International Epilepsy Congress. Medical professionals from around the world specialising in the treatment of r(20) gathered with over 250 delegates to share new research findings and learn about upcoming research.

Three new research grant awards were presented to Antonio Gil-Nagel MD from Spain, Franck Semah MD from France, and Nancy B. Spinner PhD from the USA. Ring chromosome 20 syndrome, r(20), is a chromosomal anomaly resulting from the joining of each end of chromosome 20 resulting in ring formation. This syndrome is characterised by medically intractable epilepsy, nocturnal subtle seizures, behavioural problems and mild mental impairment. Dysmorphism is rarely reported. Unfortunately, diagnosis is missed or delayed due to under-utilisation of chromosomal testing in epilepsy patients. The symposium was filmed and will be available at www.ring20.org

For more information contact Donald Gordon on 07976 244007.



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Cover picture: Scenes from Bangkok, venue for the World Congress of Neurology. See preview on page 45. Picture by Niko Guido.

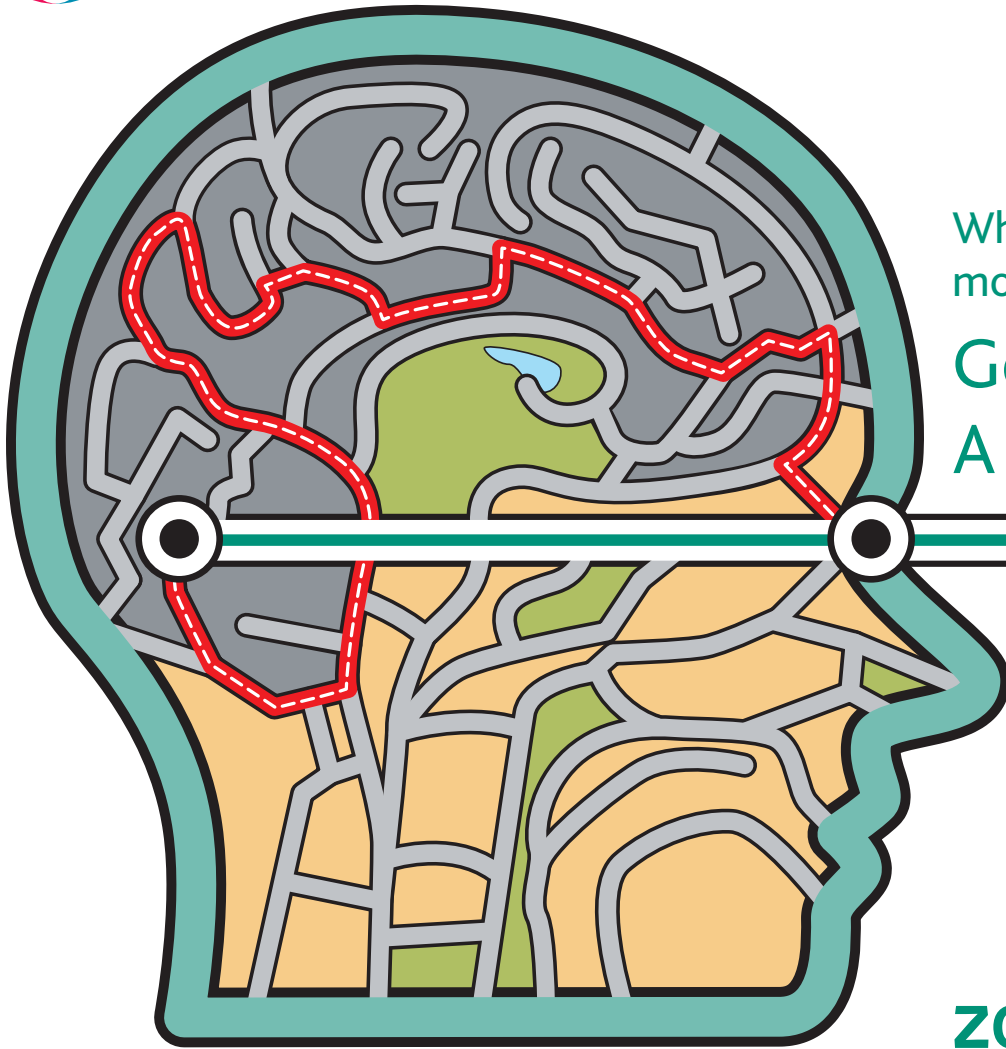
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prior stone formation, a family history of nephrolithiasis and hypercalcaemia. Evaluate and monitor serum bicarbonate levels in patients who have: underlying conditions which might increase the risk of metabolic acidosis; increased risk of adverse 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 ($\geq 1/10$): anorexia, agitation, irritability, confusional state, depression, ataxia, dizziness, memory impairment, somnolence,

diplopia, decreased bicarbonate. Common effects ($\geq 1/100$, $< 1/10$): 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 ($\geq 1/1000$, $< 1/100$): 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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Neurology Digest

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cognitive dysfunction
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Join ACNR's editors **Roger Barker** and **Alasdair Coles** to discuss key reviews in Movement Disorders and Multiple Sclerosis published in the past 12 months.

A unique opportunity for discussion and debate, reviewing basic and clinical science, as well as a rehabilitation perspective from Diane Playford.

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It is strange, when you think about it, that we see the visual world as complete – there are no gaps or missing pieces of information where the vessels and optic nerve fibres cross and disappear through the retina. The ability of the visual system to fill-in for this missing information is very successful, and in their article Rimona Weil and Geraint Rees explain how this may occur. In addition they provide a series of figures which allow you to experiment on yourself with this fill-in phenomena.



What does it mean to have mild cognitive impairment (MCI) in terms of the risk of developing dementia in the immediate and short term future? In the review article by Alex Mitchell we learn that "MCI is not a uniform prodromal condition but rather a collection of disorders united by a propensity towards modest memory (and to a lesser extent non-memory) cognitive difficulties." As a result most studies now show that only the minority of patients with MCI go on to dement. The challenge therefore is in better identifying this subgroup of individuals with the hope that we can delay or arrest the degenerative process that underlies their emerging cognitive dysfunction.

Alexander Jeans and Olaf Ansorge in their article offer a useful complimentary account to that of Jemeen Sreedharan and Chris Shaw (ACNR 9.2), covering the neuropathology of motor neurone disease. They highlight how the new genetic causes of some forms of familial MND have changed our perspectives on the pathology and the nature of the pathogenic pathways leading to the demise of these cells.

Geophagia is the main symptom (and sign?) discussed by Andrew Lerner in his ongoing series of articles entitled Neurological signs. The consequences of such a habit are not good, as Dr Livingstone commented when he was the first to observe and comment on this phenomena! Indeed Andrew and his colleague Dr Ford also treat us to an interesting tour of neurology as seen on the big screen.

Boyd Ghosh has kindly taken on editing a new series of articles, discussing the challenges of research for those in training and how this can best be accommodated in the changing landscape of the NHS and the expectations placed on the next generation of Consultant Neurologists. In the first of the series, Boyd lays out how the series came about and how it will evolve, and includes an article by Geraint Fuller discussing "Doing Research in the post MMC world". This series should help those planning to do, or those actually doing, research, explaining how this can best be achieved – and this includes achieving it within the new European Working Time Directive! This is the topic that Biba Stanton takes as the theme for discussion in the ABNT section. Talking of which, Paul Morrish has responded to an earlier article in this series and discusses his views on how neurology and neurologists can best plan for the future demands that will be increasingly placed in this field of medicine.

Continuing in a similar vein we are also seeking to have the occasional article written about leading neurologists of the last century, who have now passed away. In the first of these, Alastair Compston gives a very personal account of the late Anita Harding. A neurologist who sadly died at the age of 42 and who had done so much to change our understanding of many neurological conditions - especially hereditary neuropathies and cerebellar ataxias, as well as introducing us to mitochondrial disease. Who knows what Anita could have achieved, but even in her short life, Alastair reveals much about her as a person as well as summarising all she did academically.

In our Personal Perspective, we are fortunate to have a most eloquent account by a patient who suffers from a Congenital Insensitivity to Pain (CIP) due to problems in the SCN9A gene. This article summarises the traumas (literally) of living with this condition and how she has learnt to cope with it, along with the frustrations of trying to explain her condition to the medical community, most of whom have never heard of it, and thus don't believe it exists! The account that the patient gives us should make us all sit and think about how much we listen to patients and their problems. She prefers to remain anonymous for personal reasons.

In our Neurophysiology series, Professor James Gilchrist and George Sachs discuss how neurophysiology can be used not just for diagnosis, but also in the longitudinal assessment of patients and then how this can be used to help guide decisions on management.

We have in addition a short article in which there is a discussion on whether the Department of Health should reconsider drug substitution plans for epilepsy and we also have our usual book reviews along with our eclectic mix of conference summaries and journal reviews. Finally, we have some more great case reports, some in the journal, but more on the web edited by Alastair Wilkins. See www.acnr.co.uk for more information. ♦

Roger Barker,
Co-Editor, Email. Rachael@acnr.co.uk

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to lacosamide or to any of the excipients. Known second- or third-degree atrioventricular block. In addition for tablets, hypersensitivity to peanuts or soya. **Precautions:** Lacosamide has been associated with dizziness. Use with caution in patients with known conduction problems, severe cardiac disease or in elderly. Excipients in the syrup may cause allergic reactions (possibly delayed), should not be taken by those with fructose intolerance and may be harmful to patients with phenylketonuria. Monitor patients for signs of suicidal ideation and behaviours. Advise patients and carers to seek medical advice should such signs emerge. **Interactions:** Prolongations in PR interval with lacosamide have been observed in clinical studies. Use with caution in patients treated with products associated with PR prolongation and those treated with class I antiarrhythmic drugs. Strong enzyme inducers such as rifampicin or St John's Wort may moderately reduce the systemic exposure of lacosamide. No significant effect on plasma concentrations of carbamazepine and valproic acid. Lacosamide plasma concentrations were not affected by carbamazepine and valproic acid. No clinically relevant interaction with ethinylestradiol and levonorgestrel. No effect on pharmacokinetics of digoxin. **Pregnancy and Lactation:** Should not be used during pregnancy. For precautionary measures, breast feeding should be discontinued during treatment with lacosamide. **Driving etc.:** Patients are advised not to drive a car or operate other potentially hazardous machinery until they are familiar with the effects of Vimpat on their ability to perform such activities. **Adverse Effects:** Very common (≥10%): Dizziness, headache, diplopia, nausea. Common (between 1%-10%): Depression, balance disorder, abnormal coordination, memory

impairment, cognitive disorder, somnolence, tremor, nystagmus, blurred vision, vertigo, vomiting, constipation, flatulence, pruritus, gait disturbance, asthenia, fatigue, fall, skin laceration. Adverse reactions associated with PR prolongation may occur. Consult SPC in relation to other side effects. **Pharmaceutical Precautions:** Tablets: None. Syrup: Do not store above 30°C. Use within 4 weeks of first opening. **Solution for infusion:** Do not store above 25°C. Use immediately. **Legal Category:** POM. **Product Licence Numbers:** 50 mg x 14 tabs: EU/1/08/470/001; 100 mg x 14 tabs: EU/1/08/470/004; 100 mg x 56 tabs: EU/1/08/470/005; 150 mg x 14 tabs: EU/1/08/470/007; 150 mg x 56 tabs: EU/1/08/470/008; 200 mg x 56 tabs: EU/1/08/470/011; Syrup (15 mg/ml) x 200 ml: EU/1/08/470/014; Solution for Infusion (10 mg/ml) x 20 ml: EU/1/08/470/016. **NHS Cost:** 50 mg x 14 tabs: £9.01; 100 mg x 14 tabs: £18.02; 100 mg x 56 tabs: £72.08; 150 mg x 14 tabs: £27.03; 150 mg x 56 tabs: £108.12; 200 mg x 56 tabs: £144.16; Syrup (15 mg/ml) x 200 ml: £38.61; Solution for Infusion (10 mg/ml) x 20 ml: £29.70. **Name and Address of PL Holder:** UCB Pharma SA, Allée de la Recherche 60, B-1070 Bruxelles, Belgium. **Further information is available from:** UCB Pharma Ltd, 208 Bath Road, Slough, Berkshire, SL1 3WE. Tel: 01753 534655. Fax: 01753 536632. Email: medicalinformationuk@ucb.com. **Date of Revision:** March 2009 (09VPE0122) Vimpat is a registered trade name. **References:** 1. VIMPAT[®] Summary of Product Characteristics. 2. Beyreuther BK et al. CNS Drug Rev 2007; 13(1): 21-42. 3. UCB Data on file. **Date of preparation:** April 2009. 09VPE0142

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For further information please visit www.vimpat.co.uk



The Prognosis of Mild Cognitive Impairment - Is it Better than Expected?



Alex J Mitchell

is consultant in liaison psychiatry at Leicester Partnership Trust and honorary senior lecturer at the University of Leicester. In 2004 he published the BMA award winning book, *Neuropsychiatry & Behavioural Neurology Explained*. His research and clinical interests are listed at www.psych-oncology.info

Correspondence to:
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There is much misinformation about the natural history of people with subjective memory complaints (SMC) who do or do not have objective evidence of cognitive decline. The combination of the two, where insufficient to meet criteria for dementia, is essentially mild cognitive impairment or MCI (Table 1).¹ From these criteria it is evident that MCI is not a diagnosis based on specific cognitive tests, neuroimaging or neuropathology but is a descriptive syndrome of convenience likely to represent many possible underlying causes. Yet MCI is still important and common, more common than dementia itself. For example in a primary care sample of 3,327 individuals aged 75+ the prevalence of MCI was 15.4% to 25.2% depending on definition used.²

The main role of MCI has been its ability to predict later dementia as it has been assumed (perhaps wrongly) that most with MCI are not functionally impaired. Many authors have suggested that MCI is an inescapable intermediate stage between normal ageing and dementia.³ This is because numerous short term studies have generated a view that the annual conversion rate (ACR) averages 10 to 15%⁴ and logically if this rate held true in a linear fashion then within 10 years of diagnosis all surviving MCI suffers would have developed dementia (cumulative conversion rate CCR = 100%). However, most very large studies dispute this. In The Three Cities community study, which followed 2882 individuals with MCI for four years only, 6.6% progressed to dementia.⁵ In a 10 year community study Ganguli and colleagues found a low ACR of only 2.75%.⁶ Even in the multicentre memory clinic-based Descripa study the CCR was only 29.7% after three years.⁷ What might explain this discrepancy in risk? It is most likely due to sampling effects. Thus where individuals with definite memory

complaints (and other risk factors) seek help from specialist centres there is indeed a typical 10% ACR, according to a recent meta-analysis (95% CI 6.3% to 13.4%).⁸ However, if data are limited to the longest studies lasting at least 5 years (including six long term clinical studies in hospital settings and nine community studies), the mean ACR to dementia is 4.2% (95% CI 3.9% to 4.6%) and the CCR 31.4%. Risk is appreciably lower outside of hospital settings and for those not spontaneously reporting SMC. Remarkably, the ACR also diminishes according to the length of follow-up suggesting a bias in shorter studies from recruitment of individuals at highest risk.⁹

For the clinician the take home message is that MCI has low sensitivity but high specificity which means a modest positive predictive value for predicting dementia especially when the prevalence is low but conversely high negative predictive value. For example, in the large and clinically representative Cache County study, sensitivity (Se) was 34% and specificity (Sp) 98% for prediction of later decline (Table 2).¹⁰ In the previously mentioned meta-analysis of 41 studies, the predictive power of MCI averaged 32.3% for those with Mayo clinic defined MCI (that is MCI with SMC) and 24.1% for those with non-Mayo criteria.⁸ To increase accuracy additional risk factors must be measured. For example in several countries CSF is routinely sampled and CSF phosphorylated tau appears to be a promising biomarker. In a new meta-analysis soon to be reported, p-tau was able to separate MCI from healthy individuals with a Se of 79.6% and Sp of 83.9% (PPV 85.9%, NPV 76.9%).¹¹ Of even more interest, p-tau was reasonably successful in predicting progression to dementia in MCI (separating progressive from stable MCI) with a Se of 81.1%, a Sp 65.3%, a PPV 63.0% and a NPV of 83.0% and thus showing

Table 1: Consensus Criteria for MCI from Portet et al 2006

A. Moderate cognitive deficits, short of dementia
B. Self-reported and/or informant reported cognitive complaints
C. Impairment on objective / clinical cognitive tests
D. Preserved basic activities of daily living and minimal impairment in complex instrumental functions

Table 2. Predictive Accuracy of MCI from Cache County

Cache County Results	Dementia	Non-Dementia	Predictive Value
MCI	55	65	PPV 45.8%
Healthy Elderly	104	3042	NPV 96.7%
	Se 34%	Sp 97.9%	



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the pharmacodynamics and pharmacokinetics of oral contraceptives (0.03 mg ethinylestradiol, 0.15 mg levonorgestrel). Switching to another dopamine agonist may be beneficial for those patients who are insufficiently controlled by rotigotine. **Pregnancy and lactation:** Rotigotine should not be used during pregnancy. Breast-feeding should be discontinued. **Driving etc.:** Rotigotine may have major influence on the ability to drive and use machines. **Adverse Effects:** Very common (>10%): nausea, somnolence, dizziness and application site reactions. Common (between 1%–10%): hallucinations, confusion state, insomnia, abnormal dreams, headache, dyskinesia, orthostatic hypotension, vomiting, constipation, diarrhoea, dry mouth, dyspepsia, hepatic enzyme increase, rash, hyperhidrosis, erythema, pruritus, asthenic conditions, peripheral oedema, decreased weight, fall. Consult SmPC in relation to other side effects. **Pharmaceutical Precautions:** Store in a refrigerator (2°C–8°C). Store in the original package. **Legal Category:** POM. **Marketing Authorisation Numbers:** EU/1/05/331/001-012. **NHS Cost:** 2 mg Continuation Pack of 28 patches: £77.24. 4 mg Continuation Pack of 28 patches: £117.71. 6 mg Continuation Pack of 28 patches: £142.79. 8 mg Continuation Pack of 28 patches: £142.79. **Marketing Authorisation Holder:** SCHWARZ PHARMA Ltd, Shannon, Industrial Estate, Co. Clare, Ireland. **Further information is available from:** UCB Pharma Ltd, 208 Bath Road, Slough, Berkshire, SL1 3WE. Tel: 01753 534655, Fax: 01753 536632. Email: medicalinformation@ucb-group.com. **Date of Revision:** October 2008 (08NE0225). Neupro is a registered trademark.

Adverse events should be reported. Reporting forms and information can be found at www.yellowcard.gov.uk
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References: 1. Braun M et al. 2005; Poster presented at 9th Congress of the European Federation of Neurological Societies; September 17–20, Athens, Greece. 2. LeWitt PA et al. *Neurology* 2007; 68: 1262–7. 3. Giladi N et al. 2006; Poster presented at 10th Congress of the European Federation of Neurological Societies; September 2–5, Glasgow, UK. 4. Poewe WH et al. *Lancet Neurol* 2007; 6: 513–20.

Date of literature preparation: January 2009.



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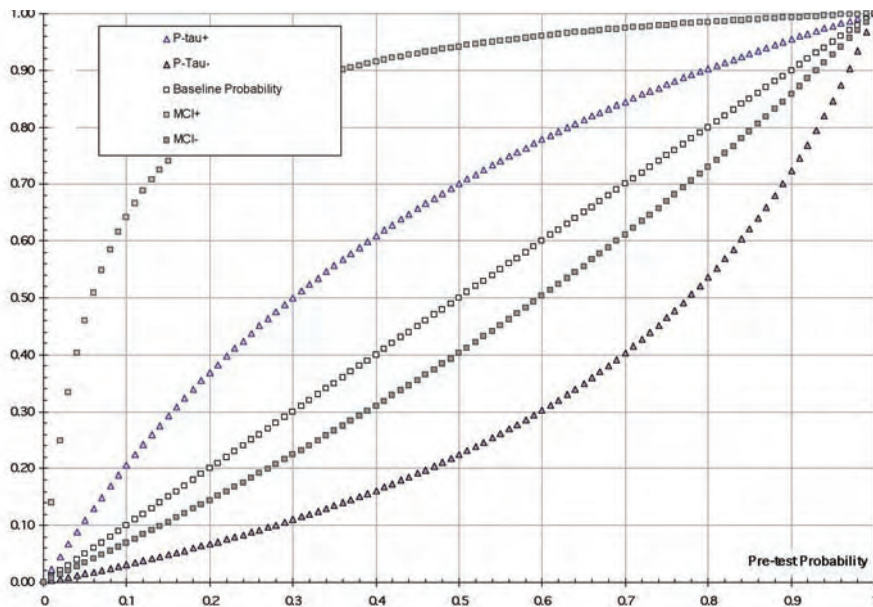


Figure 1. Bayesian Pre-Post Test Probabilities of Dementia; MCI Status vs P-tau Status.

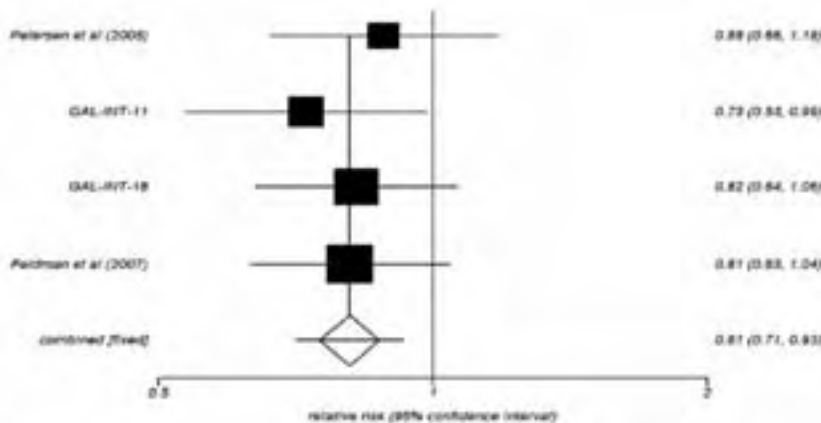


Figure 2. Relative risk of Progression of MCI, Acetylcholinesterase inhibitors vs Placebo.

reasonable value as a screening (or “rule-out”) test. The predictive abilities of MCI alone vs P-tau alone for predicting dementia are plotted in Figure 1. Unfortunately no single risk factor appears sufficient for wholly accurate prediction and a complex panel (such as age + neuropsychological status + function + ApoE + MRI + CSF p-tau + vascular risk) may be required akin to the predictors in cardiovascular settings.

From the patient’s perspective the take home message is that MCI is not an inescapable condition that is always a prodrome of dementia. In the large AD Anti-inflammatory Prevention Trial of 2528 individuals who developed incident dementia over 3 years, only 63% had a prodromal phase of MCI or a related condition.¹² Non-degenerative, potentially treatable causes of cognitive decline are found in 10-30% of people with MCI.¹³ Equally importantly, many people do not deteriorate. Wolf and colleagues (1998) demonstrated that over 3 years 20% of MCI sufferers had recovered and an additional 60% neither improved nor deteriorated.¹⁴ Later

Ganguli et al (2004) also found that, of those with MCI at baseline, 55% no longer met criteria for either MCI or dementia after 6 years of follow-up,⁶ and similarly in the Three Cities Study over four years 56.5% of those with MCI remained stable and 37% actually improved.⁵

Finally, let’s address the question of whether treatment alters the progression of the condition. Most research has been conducted on the acetylcholinesterase inhibitors but new data is emerging on non-pharmacological strategies. The first meta-analysis of three published and five unpublished trials (three on donepezil, two on rivastigmine, and three on galantamine) did not find significant differences compared with placebo groups although analysis was incomplete.¹⁵ Our own re-analysis of the four largest studies involving 1701 individuals (one donepezil, one rivastigmine, and two galantamine) does indeed show a reduced risk of progression in the short term (RR 0.81; 95% CI 0.71-0.93) for those taking an acetylcholinesterase inhibitor which is statistically significant (Figure 2) but really requires fur-

ther confirmation from much longer trials which are of course expensive to complete.

In conclusion, only recently has sufficient data accrued to say with confidence that MCI is not a uniform prodromal condition but rather a collection of disorders united by a propensity towards modest memory (and to a lesser extent non-memory) cognitive difficulties. Surprisingly, most individuals with MCI do not develop dementia within the first 10 years although a caveat is that no studies have yet to exceed that period. A substantial minority remain stable for some years and a significant proportion actually improve which means we may need to moderate what we tell individuals and families with MCI and related conditions. ♦

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advised and dose adjustment may be needed when treating patients with severe hepatic impairment. **Children and adolescents:** Not recommended. **Treatment discontinuation:** If treatment is to be withdrawn, it should be gradually reduced, in steps of 1 mg/24 h with a dose reduction preferably every other day, to avoid the possibility of developing neuroleptic malignant syndrome. **Contraindications, Warnings, etc:** **Contraindications:** Hypersensitivity to rotigotine or to any of the excipients. Neupro® should be removed prior to Magnetic Resonance Imaging (MRI) or cardioversion to avoid burns. **Precautions:** Literature reports indicate that treatment of RLS with dopaminergic medicinal products can result in augmentation. External heat should not be applied to the patch. Dopamine agonists are known to cause hypotension, and monitoring of blood pressure is recommended. Where somnolence or sudden sleep onset occurs, or where there is persistent, spreading or serious skin rash at the application site, consider dose reduction or termination of therapy. Rotate the site of patch application to minimise the risk of skin reactions. In case of generalised skin reaction associated with use of Neupro®, discontinue treatment. Avoid exposure to direct sunlight until the skin is healed. Compulsive behaviours and hallucinations have been reported in patients treated with Neupro®. **Interactions:** Do not administer neuroleptics or dopamine antagonists to patients taking dopamine agonists. Caution is advised when treating patients taking sedating

medicines or other depressants in combination with rotigotine. Co-administration of rotigotine (3 mg/24 h) did not affect the pharmacodynamics and pharmacokinetics of oral contraceptives (0.03 mg ethinylestradiol, 0.15 mg levonorgestrel). **Pregnancy and lactation:** Rotigotine should not be used during pregnancy. Breast-feeding should be discontinued. **Driving etc.:** Rotigotine may have major influence on the ability to drive and use machines. **Adverse Effects:** **Very common (>10%):** Nausea, application and instillation site reactions, fatigue, headache. **Common (between 1%–10%):** Vomiting, dyspepsia, irritability, hypersensitivity, somnolence, sleep attacks, sexual desire disorder, insomnia, sleep disorder, abnormal dreams, pruritus, hypertension. Consult SmPC in relation to other side effects. **Pharmaceutical Precautions:** Store in a refrigerator (2°C–8°C). Store in the original package. **Legal Category:** POM. **Marketing Authorisation Numbers:** 1 mg x 28 patches: EU/1/05/331/040; 2 mg x 28 patches: EU/1/05/331/002; 3 mg x 28 patches: EU/1/05/331/049. **NHS Cost:** 1 mg x 28 patches: £77.24; 2 mg x 28 patches: £77.24; 3 mg x 28 patches: £97.48. **Marketing Authorisation Holder:** SCHWARZ PHARMA Ltd, Shannon, Industrial Estate, Co. Clare, Ireland. **Further information is available from:** UCB Pharma Ltd, 208 Bath Road, Slough, Berkshire, SL1 3WE. Tel: 01753 534655. Fax: 01753 536632. Email: medicalinformationuk@ucb.com. **Date of Revision:** March 2009 (09NE0059). Neupro® is a registered trademark

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References: 1. Braun M et al. 2005; Poster presented at 9th Congress of the European Federation of Neurological Societies; September 17–20, Athens, Greece.
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09NE0113c

How Does the Brain Fill-in the Visual World?



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Our awareness of the visual environment comes to us from the pattern of light on the retina. But this pattern is an incomplete record of the visual scene, because many pieces of the scene fall on the blind spot or are obscured by retinal vessels. This loss of information can be worsened by disease-induced retinal damage, or when cortical injury following stroke damages areas of visual cortex corresponding to parts of the visual field. Yet healthy people and most patients are largely unaware of this missing or incomplete information. Instead, we see the visual scene as though it were complete because the brain ‘fills-in’ the missing information. The neural mechanisms involved in such perceptual ‘filling-in’ can tell us a great deal about normal visual processes, and are also likely to be involved when parts of the visual system are damaged and more extensive filling-in takes place.

Filling-in at the blind spot

Although the blind spot is devoid of photoreceptors and carries no visual information from the corresponding region in visual space, when we view the world through one eye, we don’t see a blank patch: the visual system fills-in the missing information from the surrounding colour or pattern (Figure 1). Behavioural studies in healthy people suggest that filling-in at the blind spot is a rapid, preattentive process that occurs early in the visual system. For example, if several rings are viewed, but with one positioned in the visual field so its retinal projection lies just around the blind spot, then this particular ring will ‘pop out’ of the group as it is perceived not as a ring, but as a filled-in disc among the other rings that do not lie over the blind spot.¹ Even an extremely narrow border (0.05 deg) surrounding the blind spot, will generate the appearance of uniform colour filling-in the blind spot,² consistent with the theory that such filling-in depends on local processes generated at the edge of the blind spot representation in primary visual cortex. Single cell recordings

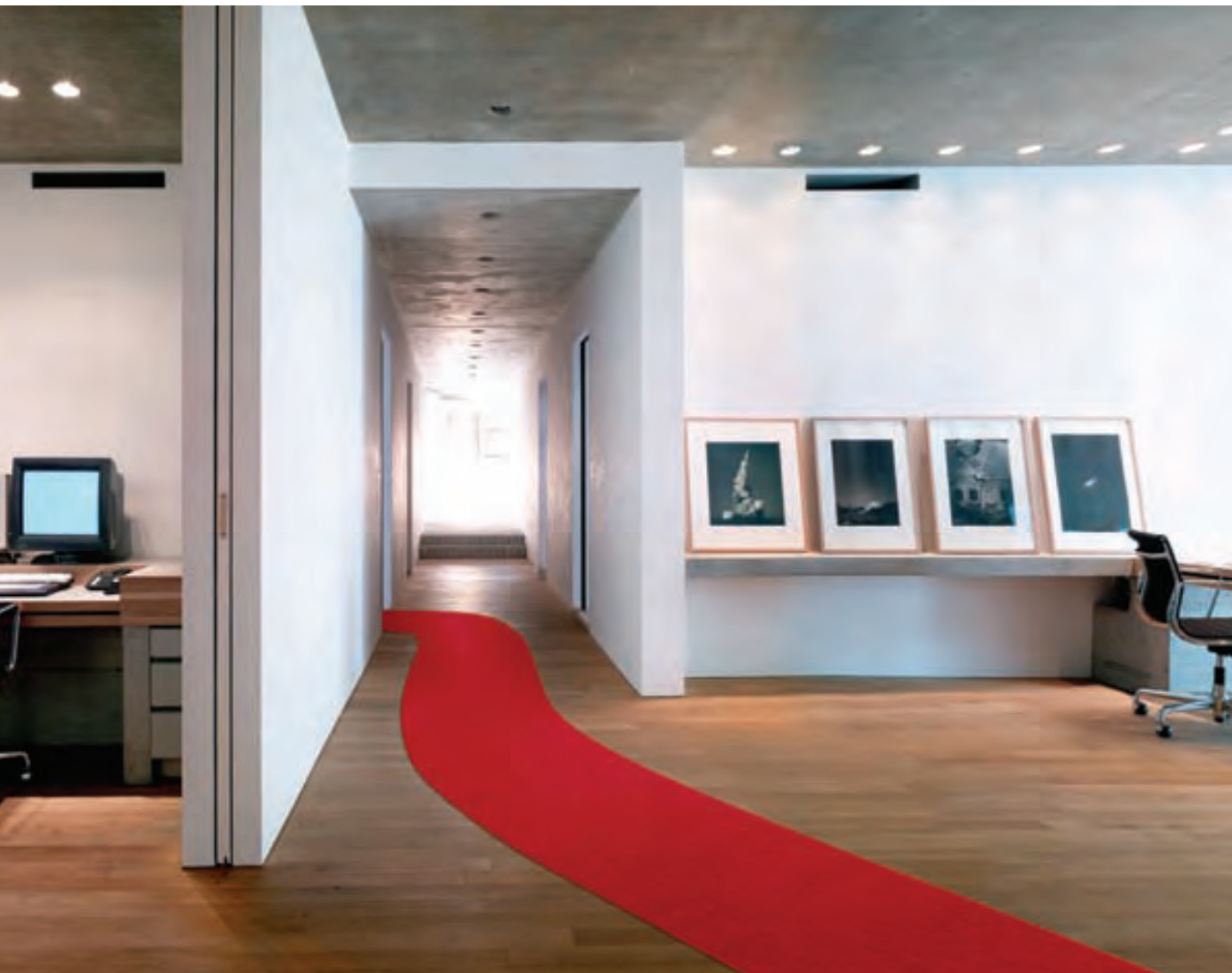
from anaesthetised monkeys show that when filling-in takes place at the blind spot, neural responses are generated at the retinotopic representation of the blind spot in primary visual cortex.^{3,4} However, the precise mechanism by which perceptual filling-in across the blind spot occurs is still unknown. The two main theories are that it involves lateral propagation of signals from the edge of the blind spot, or is due to remapping of receptive fields of surrounding neurons into the blind spot region.⁵

Filling-in after prolonged fixation

Filling-in also takes place in normal vision during prolonged fixation. For example, a figure viewed in the periphery on a bland and featureless background will seem to disappear after a few seconds of prolonged fixation, to be replaced by the background (see Figure 2a). This type of filling-in is known as Troxler fading.⁶ A similar but more striking effect is seen if the featureless background is replaced by a dynamic texture, similar to the static on a television set. This dynamic background promotes rapid filling-in of even quite salient figures placed on top of the background, and the resultant effect is described as an ‘artificial scotoma’ because the figure becomes invisible and ‘filled in’ by the textured background⁷ (see Figure 2b). These ‘artificial scotomas’ may be associated with similar neural processes that lead to the filling-in which takes place when targets are stabilised on the retina, as eye movements disrupt the artificial scotoma.⁸ Behavioural studies suggest that the filling-in associated with an artificial scotoma takes place in early retinotopic cortex as it is influenced by low-level sensory factors such as eccentricity and boundary length of the figure that ‘fills-in’.^{9,10} This is consistent with single cell studies in monkeys¹¹ and neuroimaging reports in humans.^{12,13} However, recent work suggests that higher cognitive factors may also play a role, as directing spatial attention to the peripheral figure makes it



Figure 1: Examples of perceptual filling-in at the blind spot. Hold the page approximately 15 cm from your face, close your right eye and fixate the cross with your left eye while attending to the horizontal bars. Move the page gently closer and/or further away from you until the green disc falls into the blind spot. When the green disc falls across the blind spot, it will disappear and the space it occupies will be perceptually filled-in by the horizontal bars. Now close your left eye and fixate the cross with your right eye while attending to the pink and yellow target. Again, move the page closer and further away until the target falls into the blind spot. When the yellow disc falls across the blind spot, the appearance will be of a large pink circle, with the yellow disc disappearing and becoming filled-in by the surrounding pink. Similar to example shown in Komatsu, H. *Nature Reviews Neuroscience*, 2006;7:220-31.



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KEPPRA® 100 mg/ml concentrate for solution for infusion

Active Ingredient: Tablets: levetiracetam 250, 500, 750 and 1000 mg. *Oral Solution:* levetiracetam 100 mg per ml. *Infusion:* levetiracetam 100 mg per ml.
Uses: Monotherapy for partial onset seizures with or without secondary generalisation in patients from 16 years of age with newly diagnosed epilepsy. Adjunctive therapy for partial onset seizures with or without secondary generalisation in adults and children from 4 years of age, for myoclonic seizures in adults and adolescents from 12 years of age with Juvenile Myoclonic Epilepsy and for primary generalised tonic-clonic seizures in adults and adolescents from 12 years of age with Idiopathic Generalised Epilepsy.
Infusion: an alternative for patients when oral administration is temporarily not feasible. **Dosage and Administration:** *Oral solution* should be diluted prior to use. *Infusion:* Keppra concentrate must be diluted in at least 100 ml of a compatible diluent and administered intravenously as a 15-minute infusion. **Monotherapy (adults and adolescents from 16 years):** Recommended starting dose of 250 mg twice daily which should be increased to an initial therapeutic dose of 500 mg twice daily after two weeks. The dose can be further increased by 250 mg twice daily every two weeks depending upon the clinical response. The maximum dose is 1500 mg twice daily. **Adjunctive therapy:** *Adults and adolescents older than 12 years or weighing 50 kg or more:* 500 mg twice daily can be increased up to 1500 mg twice daily. Dose changes can be made in 500 mg twice daily increases or decreases every two to four weeks. *Elderly:* Adjustment of the dose is recommended in patients with compromised renal function. *Children aged 4 to 11 years and adolescents (12 to 17 years) of less than 50 kg:* 10 mg/kg twice daily, increased up to 30 mg/kg twice daily. Do not exceed increases or decreases of 10 mg/kg twice daily every two weeks. The lowest effective dose should be used. (For full dosage recommendations see SPC.) **Patients with renal impairment:** Adjust dose according to creatinine clearance as advised in SPC. **Patients with hepatic impairment:** No dose adjustment with mild to moderate hepatic impairment. With severe hepatic impairment (creatinine clearance <70ml/min) a 50% reduction of the daily maintenance dose is recommended, as the creatinine clearance may underestimate the renal insufficiency. **Contraindications, Warnings etc.:** **Contraindications:** Hypersensitivity to levetiracetam, other pyrrolidone derivatives or excipients. **Precautions:** If discontinuing treatment reduce dose gradually as advised in SPC. Due to its excipients, the oral solution may cause allergic reactions (possibly delayed). **Infusion:** Keppra concentrate contains 7.196 mg of sodium per vial. To be taken into consideration by patients on a controlled sodium diet. Monitor patients for signs of suicidal ideation and behaviours. Advise patients and carers to seek medical advice should such signs emerge. **Interactions:** Keppra did not affect serum concentrations of phenytoin, carbamazepine, valproic acid, phenobarbital, lamotrigine, gabapentin or primidone. Drugs excreted by active tubular secretion could reduce the renal clearance of the metabolite. Levetiracetam 1000 mg daily did not affect the pharmacokinetics of oral contraceptives (ethinyl-estradiol and levonorgestrel). Levetiracetam 2000 mg daily did not affect the pharmacokinetics of digoxin and warfarin and prothrombin times were not modified. **Pregnancy and lactation:** Should not be used during pregnancy unless clearly necessary. Breast-feeding not recommended. **Driving, etc.:** Caution recommended when performing skilled tasks, e.g. driving vehicles or operating machinery. **Adverse Effects:** Incidence of undesirable effects considered to be at least possibly related in controlled clinical studies. **Very common (≥10%):** asthenia/fatigue, somnolence. **Common (between 1%–10%):** GI disturbances, anorexia, weight increase, accidental injury, headache, dizziness, hyperkinesia, tremor, ataxia, convulsion, amnesia, balance disorder, disturbances in attention, memory impairment, emotional lability/mood swings, hostility, depression, insomnia, nervousness/irritability, agitation, personality disorders, thinking abnormal, vertigo, rash, eczema, pruritus, diplopia, vision blurred, myalgia, infection, nasopharyngitis, cough increased, thrombocytopenia. Consult SPC in relation to other side effects. **Pharmaceutical Precautions:** **Tablets:** None. **Oral solution:** Store in original container. After first opening use within 2 months. **Infusion:** Use immediately after dilution. **Legal Category:** POM. **Marketing Authorisation Numbers:** 250 mg x 60 tabs: EU/1/00/146/004. 500 mg x 60 tabs: EU/1/00/146/010. 750 mg x 60 tabs: EU/1/00/146/017. 1000 mg x 60 tabs: EU/1/00/146/024. **Solution x 300 ml:** EU/1/146/027, **Infusion (500 mg/5 ml) x 10 vials:** EU/1/00/146/030. **NHS Cost:** 250 mg x 60 tabs: £29.70. 500 mg x 60 tabs: £52.30. 750 mg x 60 tabs: £89.10. 1000 mg x 60 tabs: £101.10. **Solution x 300 ml:** £71.00, **Infusion (500 mg/ 5ml) x 10 vials:** £135.00. **Name and Address of PL Holder:** UCB Pharma S.A., Allée de la Recherche 60, B-1070 Bruxelles, Belgium. **Further information is available from:** UCB Pharma Ltd., 208 Bath Road, Slough, Berkshire, SL1 3WE. Tel: 01753 534655. Fax: 01753 536632. Email: medicalinformationuk@ucb.com **Date of Revision:** January 2009

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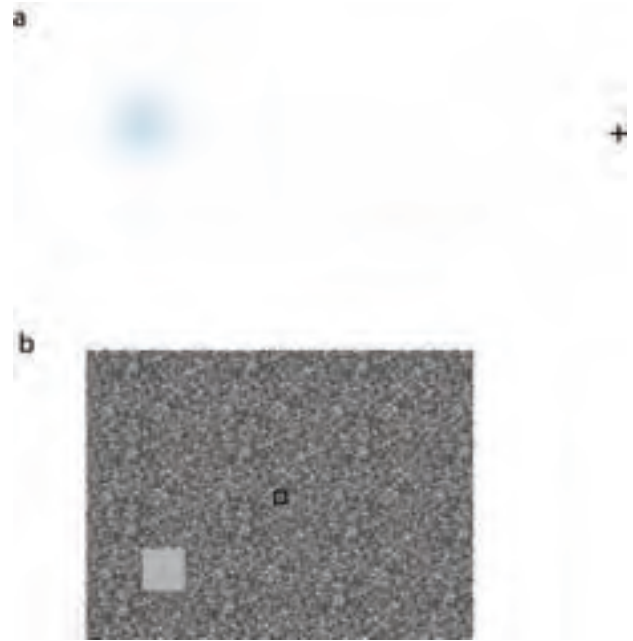


Figure 2: Filling-in after prolonged fixation. (a) Example of Troxler fading.⁷ Hold the page 20cm away from your face, fixate the cross with both eyes open, after a few seconds, the blue pattern will fade and disappear. (b) Example of an artificial scotoma. A square figure is placed in the near periphery on the background of dynamic twinkling noise. Participants fixate centrally and the square figure gradually fades and disappears.

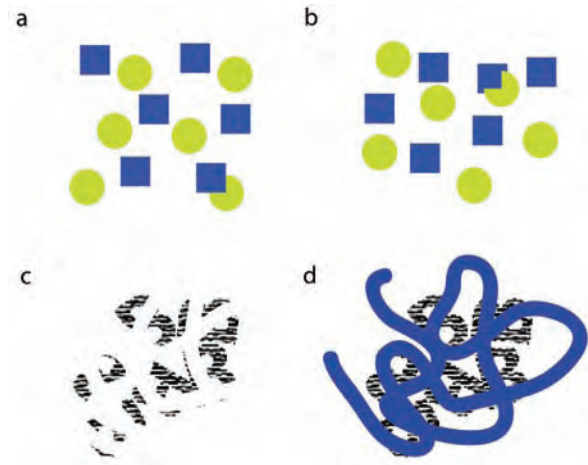


Figure 3: Occluded objects (a,b) Visual search with for amodally completed target. Identifying the notched circle is harder in (A) as it is amodally completed and perceived as a circle among the other circles. In (B), the notched circle 'pops out'. Search display similar to those used in⁸ (c,d) Depth cues to identify occluded objects. The left-hand image (c) is difficult to interpret. (d) Adding a blue snakelike occluder helps to define the occluded figures as uppercase Bs. Similar to example shown in Nakayama et al., 1989.⁹

more likely to 'fill in' and disappear.¹⁴ Thus, although filling-in may be generated by low-level, early retinotopic neural processes, it is also modulated by higher cognitive factors.

Filling-in behind occluders

The world is very cluttered and most objects do not present themselves in isolation but are seen at least partially occluded by other objects. Yet we do not have the impression of being surrounded by fragmented objects. The brain 'fills-in' the missing information and our impression is the familiar one of viewing complete objects. This type of filling-in of objects behind occluders is also known as amodal completion and seems to occur at slightly later stages of visual processing than the filling-in of artificial scotomas and the blind spot. The effects of amodal completion can be seen when subjects are asked to search for a notched circle

in an array of circles and squares. If the notched circle abuts the edge of one of the squares so that it seems to be occluded by it, the notched circle takes longer to find (see Figure 3a)¹⁵ as it is perceived as a complete circle in a sea of complete circles. Occluded objects are also easier to recognise than those with the equivalent portions deleted (see Figure 3b)^{16,17} suggesting that inferred depth is used to inform the visual system of object boundaries, as objects are far more likely to be partly occluded than have bits missing. This would suggest some involvement of object related areas in identifying occluded items. Indeed, a recent neuroimaging study showed increased activity during presentation of occluded objects in the lateral occipital complex (LOC), a region known to be involved in object processing; and in the posterior intraparietal region.^{18,19} The process of filling-in behind occluders is likely to involve a large number of information processing steps such as distinguishing between the boundaries of the occluded and the occluding object, assigning each of the resulting partial views a surface and then filling-in the missing information of each part¹⁷ using clues from depth disparity and colinear edges.

Understanding the processes involved in filling-in in the healthy brain can provide insights into filling-in following visual loss

Filling-in as a response to disorders of vision

Patients with retinal scotomas due to macular degeneration and toxoplasma also experience perceptual filling-in.^{20,22} This can be problematic, especially in age-related macular degeneration, as early detection of the macular disease is essential to preserve foveal function with newer treatments²⁹ and when patients fill-in across their scotomas they are unaware of their visual field deficits.

The mechanisms of filling-in across retinal scotomas are still debated. In monkeys, cells within primary visual cortex representing the lesion expand their receptive fields within minutes after inducing a retinal lesion²⁴ and several months after the lesion, the receptive fields have expanded and shifted to outside the lesion. Similar reports of receptive field reorganisation in V1 (primary visual cortex) have been shown in retinal lesions in cats^{25,26} and following cortical lesions in kittens.²⁷ In humans, reports are less consistent. Visual cortex (including V1) deprived of retinal input due to macular degeneration shows increased activation with functional MRI to stimuli outside the corresponding region in visual space.^{28,30} Reorganisation also occurs following loss of visual input due to optic radiation damage following stroke.²⁹ However, other studies have failed to find consistent evidence for cortical reorganisation in macular degeneration³¹ and a recent study suggests that large scale cortical reorganisation may only occur with complete absence of functional foveal vision.³⁰ The processes underlying this cortical reorganisation remain unknown. One possibility is that it arises from disinhibition of pre-existing long-range horizontal connections in V1,³² but this would require connections longer than those known to occur in primate V1.³³ Alternatively, new horizontal connections might be formed.³⁴ A third possibility is that reorganisation occurs due to new or unmasked feedback projections from higher visual areas with larger receptive fields (see also reference 35 for an example).³⁵

Conclusion

Perceptual filling-in, in many different forms, plays a critical role in completing missing information in normal human vision and is also a consequence of visual loss. The mechanisms are likely to differ between the various types of filling-in but may be important in designing treatments to encourage cortical reorganisation following damage to visual structures. ♦

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Congenital Insensitivity to Pain

I am a 32-year-old woman, and both my sister and I were born with a rare condition, congenital insensitivity to pain (CIP). Although we have normal nervous systems, our nerve endings are unable to respond to pain due to a mutant gene, SCN9A. As a result I've lived a life without normal physical pain. The condition also means I lack a sense of smell and have a lack of overflow tears. It's difficult writing a short article about the condition and my experiences, as so much has happened to my sister and I. CIP has affected most parts of our lives, both physically and psychologically, and I could write a good doorstop of a book! However, the condition hasn't held us back in life. We are both university graduates with good full-time jobs. We have loving partners, lots of friends and enjoy active social lives.

I rarely divulge the fact that I don't feel pain when meeting new people, but when I do I usually get a response such as, 'That's amazing, I wish I had that condition!' Well, no they shouldn't. As I sit and write this, my seven-month-old baby daughter is sleeping upstairs and I am sat on a large cushion recovering from a severely fractured pelvis with nerve damage. Yet another thing to add to my long list of physical damage I've suffered over the years. I also receive other comments such as, 'You are like a superhero!' and probably the one I can place money on, 'So you wouldn't feel it if I punched you?' Well, I would actually. I can feel pressure, aches, sensation and temperature (although I have a higher tolerance). I have my own sort of 'pain'; I just don't feel pain the same way that other people do. It's always hard to explain, as it's how I've been born and I have nothing to compare it to.

My parents realised that my sister and I had this condition when we were little. We would fall over and not cry and were very accident prone and clumsy. My mother had a terrible time in the 70s and 80s convincing doctors of our condition, as it was so rare and very little was known about it. One of many examples is the time I broke my hand when I was around eight years old. My mother noticed my hand was red, hot and swollen, but A&E dismissed this as a bee sting and she had to fight for an X-ray that confirmed the break. I feel so sad when I think of the tough times my parents went through. Pain is there for a reason, to protect yourself. As a parent you want to protect your child and keep them safe, but this became impossible. Some people even assumed my mother was lying and accused her of child abuse. We were never wrapped in cotton wool though: we had to learn to look after ourselves. We simply learned that hurting ourselves equalled blood, scars, cuts, breaks and burns rather than pain. My mother became extra vigilant and began daily checks of our bodies. She never had the radiators too hot and kept us away from the icebox. She ordered Medic Alert necklaces that we could carry around in case of an emergency.

We were naturally more clumsy, heavy-handed and heavy-footed than other children, and still are! When you learn to walk, run and jump as a child you do so to soften the blow to your limbs and joints, but without pain this is impossible.

Our family photo album is full of pictures of us covered in bandages and plasters. To name just a few terrible incidents: chewing the mouth and tongue until they are deformed, ironing hands, falling asleep on a hot water bottle, running on a broken leg until it crumpled beneath and not feeling an eye ulcer, resulting in being almost blind in one eye.

We kept the condition to ourselves and only told close family and friends. We never tried to exploit it in the media like other families would, or gain any financial benefit. The danger of telling other school children would be that they would punch you and then say, 'Did that hurt?' There was also a danger of feeling invincible and showing off. We are aware of a child with the same condition who jumped from a building over and over again to impress friends.

By our teens we became responsible for our physical health and were aware of the dangers we faced in life. We rarely thought about it through our teens and twenties. There were odd trips to hospital for X-rays and checks and safety measures became part of my daily routine. Examples include: putting on the cold tap before the hot, checking my nails aren't sharp before I go to sleep, placing magazines on my lap before placing down a hot dinner tray and using blunt knives in the kitchen.

My sister and I didn't know the reason why we didn't feel pain. I started to think about this more carefully in my late twenties and now that the internet was at hand, decided to carry out my own investigation. I sent off emails around the country to different doctors. That led to finding out more information from the lovely Dr Bowsher at the Liverpool Pain Institute and finally being properly diagnosed by the wonderful Dr Woods at Addenbrookes. The internet was also brilliant for getting in touch with people all over the world who have the same condition or a variance of it. I found that I shared such similar experiences both physically and psychologically with others.

I was hoping I wouldn't experience any further problems as an adult but I've been through hell over the last seven months. Our friend in Norway who has the same condition and has two children said that having children was payback for all the trouble you had when you were young: you can have a wonderful experience giving birth pain free! I was quite anxious about having a baby as I thought if anything happened to the baby inside me then I wouldn't be able to feel it. However the nine months flew past and I had a lovely pregnancy and felt really healthy throughout. My waters broke and I had to be induced after no sign of baby appearing. The labour went on for hours and I felt no pain at all, and the only reason I knew I was having a contraction was that

I could see my tummy going up and down. The midwives realised that the baby's heartbeat was slowing every time I had a contraction so I had to have an emergency C-section. Luckily my daughter was delivered a beautiful and healthy baby.

When I left hospital I felt stiff down one side and couldn't walk properly. This got worse and worse over the next seven weeks until I was in so much 'pain' that I couldn't walk properly and felt wrong inside. During these weeks I questioned doctors, midwives, health visitors and physiotherapists about my problem and explained my pain condition. Initially they said it was because of the C-section, and later they said it was SPD. I was even sent home from A&E with post-natal depression! I knew something was seriously wrong with me. I soon started to lose sensation in my lower half but luckily an amazing physiotherapist saved me and got me back into A&E and scanned.

The results were a severely fractured pelvis, nerve damage and a haematoma. I was devastated but in a way also relieved as finally I knew what was wrong and could be treated. I had to spend six weeks in Addenbrookes on strict bed rest. Being apart from my baby girl was heartbreaking: I had to stop breastfeeding and missed her first Christmas. I'm so grateful to my family, friends and wonderful hospital staff for providing physical and mental help and support at such a traumatic time. Unfortunately my lack of pain is just physical and not emotional.

Since then I've been recovering at home, and the whole experience has really damaged me emotionally as well as physically. I was quite a puzzle to the doctors, and it still isn't clear what exactly happened to me. My consultant believes that the pregnancy caused stress fractures to my pelvis and then it finally broke during labour; I then walked around with the fractures for weeks, making it worse. A doctor also believes I had osteoporosis in pregnancy. I was basically extremely unlucky. I now have lost feeling in lower parts of my body and have leg length discrepancy.

It is a worry, thinking about what will happen to me later in life. I guess I just have to enjoy life as much as I can now and not worry about what is round the corner. I'm aware that there are people in this world that are physically a lot worse off than me and I am so lucky in so many other parts of my life.

It would be amazing if some good could come of all these problems that I and my family have endured over the years. Perhaps by using me for further physical studies and tests, one day a pain-free drug could be created that mimics what I feel; pain relief without any side effects. Or perhaps a drug could be created which enables children to feel pain so they don't have to go through what I did when I was growing up. This sounds awful but I felt great joy and relief when I took my baby daughter to have her first injections and she screamed her head off! ♦



Inspired by

Terry

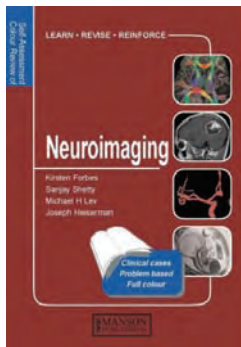
*Terry: diagnosed with
Parkinson's disease at age 46*

Parkinson's disease didn't stop Terry from staying on track ... and running 17 marathons all over the world.

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Self-Assessment Colour Review of Neuroimaging



Authors: Kirsten Forbes, Michael H Lev, Sanjay Shetty, Joseph Heiserman
Published by: Manson Publishing Ltd (2007)
ISBN: 978-1840760781.
Price: £21.95.

Reviewed by:
 John Bowen,
 Consultant Neurologist,
 Lincoln County Hospital,
 Lincoln.

This book pleases, educates, and frustrates, though not in equal measure.

The authors provide “a case-based teaching text on imaging of the central nervous system...offering readers over one hundred real-life clinical cases for interpretation”. Hmm, but how often in anyone’s real-life practice does a cerebellopontine angle lesion in a dizzy forty-one year old come slap bang after a case of alobar holoprosencephaly in a foetus?

This book “while primarily written for radiologists...will also be of interest to neurologists” say the authors, and it is. But I’ll tell you what I want (what I really, really want) is not a book of completely random cases. It is order, Mr Speaker.

Though the cases are informative, well illustrated, and accompanied by helpful radiological differential diagnoses, the “crikey what’s the next case going to be?” frisson of excitement is rather trumped by the mind-boggling leap from rhombencephalosynapsis (I hadn’t heard of it, either) to Gibb’s “artifact” (which drew a heavy sigh and a “you really should get out more” type expression from one of my neuroradiologists when I tried to show off by lobbing it into a discussion recently).

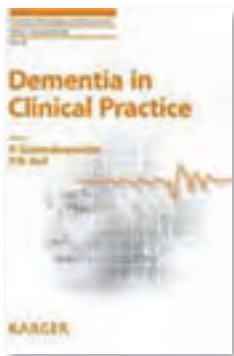
What would be really helpful is something

small that fits easily into a briefcase which I can dip into when faced with colleagues ambushing you as you nip to the loo with a “can I quickly show you these scans?” type corridor consult. What neurologists would find more practical (I think) would be a book structured into sections such as – “tumour or abscess – when you can be sure” or “perivascular space or stroke – you decide” or “multifocal cerebral calcification – sorting the wheat from the chaff”, that sort of thing.

Accessing, learning, and retaining information is facilitated by order and there seems little if any order (other than an alphabetical index) to this otherwise excellently presented series of radiological case vignettes which for this neurologist (and I imagine at least some radiologists) will make reading this book slightly more of a struggle than the pleasure it would otherwise be.

Oh and one other thing. I think that black or white (but not both?) is technically a colour but there are a grand total of two images in this entire book with hues other than these so in this current climate of transparency and accountability I’m not sure that the title of this book quite cuts the mustard. ♦

Dementia in Clinical Practice



Editors: Giannakopoulos P, Hof PR.
Published by: S Karger AG;
 1st edition (2009).
ISBN: 978-3805590150.
Price: €141.50.

Reviewed by:
 AJ Larner, Cognitive Function Clinic,
 WCNN, Liverpool, UK.

This short and well-produced text, from the Karger Frontiers of Neurology and Neuroscience series, comprises four sections, devoted to Alzheimer’s disease (seven chapters), vascular dementia, Lewy body dementia, and frontotemporal dementia (four chapters each). Each section has short chapters describing clinical features and investigation, neuropathology, neuroimaging, and pharmacotherapy, the additional chapters in the Alzheimer’s section addressing mild cognitive impairment, electrophysiological markers, and novel neuroimaging methods with PET ligands.

Although the UK National Dementia Strategy has emphasised the need for dementia to be diagnosed by a “clinician with specialist skills”, this book, by authors from continental Europe and North America, aims to “facilitate reading for a non-specialist” and the role of primary care physicians (PCPs) is emphasised (e.g. p. 54 et seq., 66 et seq. 126, 135 et seq.), although it is not clear to me whether PCPs will wish to immerse themselves in the arcana of frontal lobe dementia neuropathology and nomenclature or the molecular techniques of imaging in Alzheimer’s disease.

Having recently been accused, by a very experienced book reviewer who frequently contributes to these pages, of being a “fuss pot”

Overall, I would think this book well suited to trainees developing an interest in cognitive disorders

in my reviews, I shall eschew all comments on the typography etc. of this book, merely observing that some chapters seem a little truncated, for example the abstract of Kertesz’s chapter on the clinical features and diagnosis of frontotemporal dementia states that “galantamine in aphasia had symptomatic benefits in small trials” but there is no subsequent mention of this in the text of the chapter.

Overall, I would think this book well suited to trainees developing an interest in cognitive disorders, as well as more experienced dementia specialists, rather than for PCPs. However, cost may prove prohibitive. ♦

If you would like to review books for ACNR, please contact Andrew Larner, Book Review Editor, clo.rachael@acnr.com

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apomorphine hydrochloride

ABBREVIATED PRESCRIBING INFORMATION

Consult Summary of Product Characteristics before prescribing. **Uses:** The treatment of disabling motor fluctuations ("on-off" phenomena) in patients with Parkinson's disease which persist despite individually titrated treatment with levodopa (with a peripheral decarboxylase inhibitor) and/or other dopamine agonists. **Dosage and Administration:** Apomorphine hydrochloride is administered subcutaneously either as an intermittent bolus injection or by continuous subcutaneous infusion. Its rapid onset (5-10 mins) and duration of action (about 1 hour) may prevent an "off" episode which is refractory to other treatments. Hospital admission under appropriate specialist supervision is necessary during patient selection and when establishing a patient's therapeutic regime. Please refer to the Summary of Product Characteristics for full details before initiating therapy. Treatment with domperidone (typical dosage 20mg three times a day) before and during apomorphine HCl therapy is essential. The optimal dosage of apomorphine HCl has to be determined on an individual patient bases; individual bolus injections should not exceed 10mg and the total daily dose should not exceed 100mg. **Contraindications:** Children and adolescents (up to 18 years of age). Known sensitivity to apomorphine or any other ingredients of the product. Respiratory depression, dementia, psychotic disease or hepatic insufficiency. Intermittent apomorphine HCl treatment is not suitable for patients who have an "on" response to levodopa which is marred by severe dyskinesia or dystonia. **Pregnancy and lactation:** Caution should be exercised if prescribing apomorphine to pregnant women and women of childbearing age. Breast-feeding should be avoided during apomorphine HCl therapy. **Interactions:** Patients should be monitored for potential interactions during initial stages of apomorphine therapy. Particular caution should be given when apomorphine is used with other medications that have a narrow therapeutic window. It should be noted that there is potential for interaction with neuroleptic and antihypertensive agents. **Precautions:** Use with caution in patients with renal, pulmonary or cardiovascular disease, or who are prone to nausea or vomiting. Extra caution is recommended during initiation of therapy in elderly and/or debilitated patients. Since apomorphine may produce hypotension, care should be exercised in patients with cardiac disease or who are taking vasoactive drugs, particularly when pre-existing postural hypotension is present. Neuropsychiatric disturbances are common in Parkinsonian patients. APO-go should be used with special caution in these patients. Apomorphine has been associated with somnolence and other dopamine agonists can be associated with sudden sleep onset episodes, particularly in patients with Parkinson's disease. Patients must be informed of this and advised to exercise caution whilst driving or operating machines during treatment with apomorphine. Haematology tests should be undertaken at regular intervals as with levodopa with given concomitantly with apomorphine. Pathological gambling, increased libido and hypersexuality have been reported in patients treated with dopamine agonists, including apomorphine. **Side Effects:** Local induration and nodules (usually asymptomatic) often develop at subcutaneous site of injection leading to areas of erythema, tenderness, induration and (rarely) ulceration. Pruritus may occur at the site of injection. Drug-induced dyskinesias during "on" periods can be severe, and in a few patients may result in cessation of therapy. Postural hypotension is seen infrequently and is usually intransient. Transient sedation following each dose of apomorphine may occur at the start of therapy, but this usually resolves after a few weeks of treatment. Nausea and vomiting may occur, particularly when APO-go treatment is initiated, usually as a result of the omission of domperidone. Neuropsychiatric disturbances (including transient mild confusion and visual hallucinations) have occurred during apomorphine therapy and neuropsychiatric disturbances may be exacerbated by apomorphine. Positive Coombs' tests and haemolytic anaemia have been reported in patients receiving apomorphine and levodopa. Local and generalised rashes have been reported. Eosinophilia has occurred in only a few patients during treatment with apomorphine HCl. Patients treated with dopamine agonists, including apomorphine, have been reported as exhibiting signs of pathological gambling, increased libido and hypersexuality (especially at high doses). Apomorphine is associated with somnolence. Breathing difficulties have been reported. Prescribers should consult the Summary of Product Characteristics in relation to other side effects. **Presentation and Basic NHS Cost:** Apo-go ampoules contain apomorphine hydrochloride 10mg/ml, as follows: 20mg in 2ml – basic NHS cost £37.96 per carton of 5 ampoules. 50mg in 5ml – basic NHS cost £73.11 per carton of 5 ampoules. APO-go pens (disposable multiple dosage injector system) contain apomorphine hydrochloride 10mg/ml, as follows: 30mg in 3ml – basic NHS cost £123.91 per carton of 5 pens. APO-go Pre-filled syringes contain apomorphine hydrochloride 5mg/ml, as follows: 50mg in 10ml – basic NHS cost £73.11 per carton of 5 syringes. **Marketing Authorisation Numbers:** APO-go Ampoules: PL04483/0064. APO-go Pens: PL04483/0065. APO-go Pre filled syringes: PL05928/0025. **Legal Category:** POM. **Date of last revision:** November 2008. 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Neurological Signs: Geophagia (Geophagy) and Pica (Pagophagia)

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29th November [1870]. – *Safura* is the name of the disease of clay or earth eating, at Zanzibar; it often affects slaves, and the clay is said to have a pleasant odour to the eaters, but it is not confined to slaves, nor do slaves eat in order to kill themselves; it is a diseased appetite, and rich men who have plenty to eat are often subject to it. The feet swell, flesh is lost, and the face looks haggard; the patient can scarcely walk for shortness of breath and weakness, and he continues eating until he dies.

This extract from the last journals of Dr David Livingstone^{1,2} describes geophagia (geophagy), earth or clay eating. This may also fall under the rubric of pica, or pagophagia, a morbid craving for unusual or unsuitable food. Another example may be found in the novel *One hundred years of solitude* by Gabriel Garcia Marquez, first published in 1967, concerning an eleven year old girl, Rebeca, who arrives in the town of Macondo carrying a canvas sack which contains her dead parents' bones: "Rebeca only liked to eat the damp earth of the courtyard". The behaviour recurs later in her life when she experiences the passion of unrequited love.³

Although one might possibly dismiss the latter account as nothing more than "magic realism", pica is a recognised symptom in childhood, sometimes associated with brain damage, learning disability, and emotional distress. Other inedible items which are sometimes eaten include paper and paint. Sufferers are obviously at risk of infection from contaminated foods, such as soil.⁴ An association of pica with iron deficiency is well recognised,⁵ as is a link with pregnancy. Livingstone noted that "clay built in walls is preferred, and Manyema women when pregnant often eat it".¹ Reports of geophagia have been found dating back to Hippocrates.⁶

Geophagia may be associated with neurological complications. Cases have been reported of flaccid quadriplegia⁷ and of proximal myopathy⁸ associated with profound hypokalaemia in the context of geophagia. Livingstone mentioned weakness associated with clay eating (see above); he also mentioned "A Banyamwezi carrier, who bore an enormous load of copper, is now by safura scarcely able to walk".¹ A previous review of neurological problems described by Livingstone in his many writings failed to note this particular syndrome of geophagia-associated weakness.⁹ The loss of flesh associated with geophagia which was noted by Livingstone was re-reported almost a century later as "Cachexia Africana".¹⁰ ♦

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Longitudinal Neurophysiologic Assessment of Disease of the Peripheral Nervous System



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Electrophysiologic methods used to assess peripheral nerve, neuromuscular junction and muscle are collectively known as electrodiagnostic studies. As the name implies, they provide valuable tools for diagnosis of neuromuscular disorders; their utility, however, extends beyond initial diagnosis. Longitudinal electrodiagnostic studies can assess the progression of neuromuscular disease and guide therapeutic decisions. This review summarises the role of longitudinal studies in evaluating disorders of peripheral nerves, motor neurons, neuromuscular transmission and muscle.

Peripheral nerve

Electrodiagnostic studies play a pivotal role in the prognosis and management of traumatic nerve injuries. Initial studies, usually performed within the first month, serve to determine the location and degree of injury. Both of these will influence prognosis and management decisions. Nerve conduction studies may identify conduction block, the hallmark of neurapraxia, which typically portends spontaneous recovery within a few months.¹ For cases with more axonal injury, initial needle EMG determines the level of denervation. Particularly important is detection of low-level innervation remaining within clinically paralysed muscles. Since this may eventually provide considerable recovery, it argues for conservative management.

Repeated electrodiagnostic assessment guides management of nerve injuries that have completely denervated muscles. It is important to identify early evidence of successful regeneration as it generally contraindicates surgical intervention. Needle EMG will often demonstrate reinnervation of muscles months before clinical return of motor function.^{2,3} This is of particular importance in assessing muscles at some distance from the site of injury. If surgical intervention is required, it cannot be delayed for too long since axons regenerating through sutured or grafted segments must ultimately reach their target muscles before atrophy and fibrosis supervene.

If standard EMG does not provide evidence of regeneration within a reasonable time window, surgical exploration with intraoperative nerve

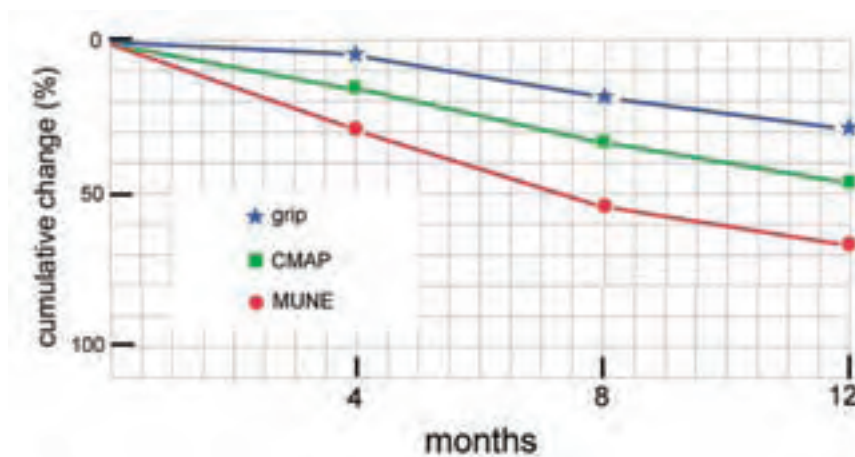
conduction studies becomes the best guide for management. The crucial question is whether there has been significant regeneration of axons through injured segments or neuromas remaining in gross continuity. Following surgical exposure, the injured nerve segment is suspended between paired hook electrodes. A nerve action potential recorded across the segment signifies sufficient regeneration to obviate any nerve resection, suturing or grafting.⁴

The electrodiagnostic evaluation of polyneuropathy serves to identify the relative contributions of demyelination versus axonal loss. Decrease in compound motor action potential (CMAP) and sensory nerve action potential amplitude correlates reasonably well with axonal loss, though a few caveats bear consideration. Occasionally, low CMAP and SNAP amplitudes reflect very distal conduction block rather than denervation.⁵ Furthermore, CMAP amplitude may vary with electrode placement. Summed values of CMAP amplitudes from multiple nerves, therefore, provide a more consistent and reliable assessment of severity. Inflammatory demyelinating neuropathies such as CIDP or MMN will typically evolve with an increasing burden of secondary axonal degeneration. If repeated electrodiagnostic studies document progressive axonopathy, then a prolonged course of immunomodulating therapy may be required before any clinical improvement becomes apparent.

Nerve conduction studies can influence the management of diabetic neuropathy by identifying features of coexistent inflammatory neuropathy or nerve entrapments. Apart from these features, conduction studies add little to the management of neuropathy in individual diabetic patients. Clinical trials investigating treatments for diabetic neuropathy, on the other hand, have made use of serial nerve conduction studies. Composite scores of multiple nerve conduction parameters appear to be a particularly helpful tool for assessing the course of neuropathy in multicenter clinical trials.⁶

Motor neuron

Given the paucity of established treatments for motor neuron disease, serial electrodiagnostic



Serial measurements documenting the progression of ALS over one year. Motor unit number estimates (MUNE) decline earlier and faster than isometric grip strength or thenar compound motor action potential (CMAP) amplitude. Adapted from ref. 7.

studies currently play more of a role in clinical trials than in guiding management of individual patients. Techniques aimed at estimating the number of anterior horn cells innervating a particular muscle (Motor Unit Number Estimation or MUNE) provide a more direct and more sensitive measure of disease progression than standard nerve conduction studies or EMG. A number of MUNE techniques have been employed to follow the course of ALS. They generally show good test-retest reliability and document decline earlier than standard nerve conduction parameters, quantitative strength testing or global functional scales.⁷ (see figure). However, one particular MUNE technique applied in a clinical trial of Celecoxib became less useful once extensive reinnervation led to unstable motor units.⁸ Though this issue poses a major challenge to certain techniques, there is hope that alternative MUNE methods could prove more reliable.

Neuromuscular Transmission

Neuromuscular transmission is amenable to physiologic assessment over time because electrodiagnostic tools accurately quantify the underlying physiologic deficit. Disease at the neuromuscular junction results in reduction of the safety factor of neuromuscular transmission, which when insufficient, causes failure of neuromuscular transmission and muscle weakness. Single fibre EMG (SFEMG) measures jitter, a manifestation of the variation in time it takes the endplate potential to reach threshold for action potential activation, this variation indicating the robustness of the safety factor.^{9,10,11} Repetitive nerve stimulation is limited to measuring only those instances in which neuromuscular transmission fails, and does not appreciate endplates in which safety factor is impaired but not deficient. Repetitive nerve stimulation showed no change in decrement despite significant improvement in quantitative myasthenia gravis score in a treatment trial of myasthenia gravis.¹² Serial studies of myasthenia gravis indicate individual fibre pair jitter, mean jitter, and percentage of block-

ing fibres all reflect disease change, for better or for worse.¹³ In two thirds of patients with clinical worsening between SFEMG studies, there was at least a 10% rise in mean jitter. A decline in jitter of 10% or more had a strong correlation with clinical improvement.¹³ Serial SFEMG jitter measurement is also valid in individuals,^{14,15} as jitter and blocking closely mirror any changing clinical picture, including improvement after treatment, and postpartum exacerbation. SFEMG also mirrors treatment response as studies of myasthenic patients before and after treatment with cholinesterase inhibitors or immunomodulation found improvement in jitter corresponded to clinical improvement after immunomodulatory therapy.^{14,16} No changes were seen in jitter in patients treated with only cholinesterase inhibitors.

The situation is somewhat different in pre-synaptic disorders. Repetitive nerve stimulation remains a poor physiologic measure of clinical course, as shown by treatment trials of Lambert-Eaton myasthenic syndrome which found little or no change in decrement despite improvement of clinical and other electrodiagnostic measures.¹¹ Serial SFEMG has been shown to be an accurate measure of clinical improvement.¹⁷ But CMAP amplitude at rest is the most useful parameter to follow in pre-synaptic disorders. Virtually every serial study of LEMS has measured resting CMAP amplitude, whether or not the patient was treated.¹¹ With one exception,¹⁸ resting CMAP amplitude

always increased as the patient improved, and declined as the patient worsened. It has correlated with changes in treatment, strength, endurance, and clinical status.¹¹ Pre-synaptic disorders may be thought of as rapidly reversible distal motor axonopathies. CMAP amplitude accurately reflects the number of functioning distal motor axonal termini, i.e., pre-synaptic membranes, with precision.

Muscle

In general, needle electromyography parallels the course of myopathy, particularly those characterised by muscle fibre necrosis. Simulation studies indicate that conditions increasingly likely to occur over time, such as reduced number of muscle fibres, increasing variability of mean fibre diameter, and regenerating muscle fibres, will result in complex MUPs, with longer durations and higher amplitudes than normal.^{19,20} In contrast, early in the course of myopathy, loss of muscle fibres occurs alone, creating simple MUPs of normal amplitude but short duration.¹⁹ Correlation of EMG with muscle pathology in polymyositis confirms these conclusions, with worse EMG findings indicative of more severe pathology.¹⁹ Short-duration MUPs become longer-duration polyphasic MUPs as disease progresses from acute to chronic,^{21,22} corresponding to the presence of regenerating muscle fibres on muscle biopsy. Abnormal spontaneous activity, common in the acute phases of polymyositis/dermatomyositis, becomes less prevalent with duration of symptoms and with response to treatment.^{21,22,23}

The longitudinal pattern is somewhat different in muscular dystrophy. In pre-symptomatic muscular dystrophy, muscles are unlikely to show abnormalities using conventional EMG.²⁴ However, QEMG has shown increased MUP amplitudes in apparently normal muscles of patients with muscular dystrophy. This may arise from either hypertrophy from overuse to compensate for other weak muscles or from fibre splitting.²⁴ As disease progresses and muscles weaken, polyphasic MUPs appear,²⁵ most likely due to fibre-diameter variation and fibre necrosis causing desynchronisation of muscle fibre electrical potentials within the MUP.²⁴ The interference pattern is full and recruitment of MUPs is early.²⁵ Fibrillation potentials and positive waves indicate ongoing muscle fibre necrosis.²⁶ As the dystrophy

Neuromuscular transmission is amenable to physiologic assessment over time because electrodiagnostic tools accurately quantify the underlying physiologic deficit



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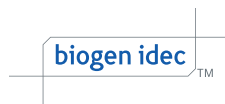
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progresses, MUP amplitude declines, MUP duration shortens and fibrillations become scarcer, from further fibre loss and fibrosis, and the small diameter of surviving muscle fibres.²⁵ Satellite potentials are also seen, secondary to dramatic slowing in propagation velocity in regenerating or small muscle fibres.²⁷ In endstage muscle, electrical silence ensues, with no voluntary MUPs and decreased insertional activity. Fibrillation potentials are no longer seen. CMAP amplitudes decline over time but at a less useful pace for following the disease and usually do not become obviously abnormal until the muscle is overtly atrophic. ♦

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Recent Developments in the Pathology of Motor Neurone Disease



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Motor neurone disease (MND), or amyotrophic lateral sclerosis (ALS), is a progressive neurological condition characterised primarily by the degeneration and loss of motor neurones. Although the term MND is sometimes taken to include spinal muscular atrophy (SMA), a pure lower motor neurone degeneration in almost all cases associated with mutations in the survival motor neuron (SMN) gene, it is used here to refer only to those mixed upper and lower motor neurone degenerations of usually adult onset which occur predominantly sporadically (90%), although rare genetic forms are well known.¹ In this article, we will briefly describe the clinical features of MND before discussing the pathology in the context of recent discoveries which have already fundamentally altered our approach to histopathological diagnosis, and which have the potential to enhance greatly our understanding of MND pathogenesis.

Clinical features of MND

MND usually presents from middle age onwards. The classical form shows signs of upper and lower motor neurone dysfunction, although occasionally pure upper or lower motor neurone signs may be present; in these instances the clinical syndrome may be termed primary lateral sclerosis or progressive muscular atrophy respectively. A further variant, bulbar-onset MND, presents as difficulties with speech or swallowing. A large proportion of cases of non-classical MND will evolve into a more typical form of the disease over time. In approximately 10% of cases, MND is associated with frank frontotemporal dementia (FTD), reflecting pathological involvement of the non-motor cortex. The course of the disease is inexorable and median survival in cases of classical MND is 3-5 years, death usually being due to involvement of respiratory muscles. The only available effective treatment for MND is Riluzole, a drug which seems to block mechanisms of neuronal glutamate-mediated excitotoxicity and has been shown to increase survival by around two months.²

Genetics of MND

Although the great majority of cases are sporadic, a number of families have been described in which MND is inherited in a monogenic fashion. Although some of these pedigrees do not manifest classical MND, there are a number of autosomal dominant mutations that do segregate with a typical clinical syndrome, notably those in genes encoding superoxide dismutase (SOD1),¹ TAR DNA-binding protein of 43KD (TARDBP),³ fused in sarcoma (FUS)⁴ and angiogenin (ANG),¹ as well as an as yet unidentified gene on chromosome 9.¹ Using genome-wide association studies,

attempts have also been made to identify alleles which modify the risk of developing sporadic MND. However, despite the substantial size and statistical power of many of these analyses, no robust associations have yet emerged.⁵

Pathological features of MND

Macroscopically, there may be little to see in a case of MND. Atrophy of the primary motor cortex (prefrontal gyrus) may sometimes be apparent, and there is usually shrinkage and brown/grey discoloration of the anterior nerve roots at all levels of the spinal cord, reflecting myelin loss secondary to lower motor neurone axonal degeneration (Figure 1a,b). Similarly, upper motor neurone degeneration may be reflected in a loss of myelin staining within the corticospinal tracts of the spinal cord. Microscopically, there is loss of motor neurones from the anterior horn of the spinal cord, from the primary motor cortex and from the hypoglossal nucleus in the lower medulla. Cell loss is accompanied by gliosis, and some of the surviving motor neurones contain ubiquitinated cytoplasmic inclusions of a variety of morphological types, including spherical Lewy body-like inclusions and skeins of thread-like structures⁶ (Figure 1g). Bunina bodies, which are bead-like eosinophilic cytoplasmic inclusions, may also be present and are very specific for classical MND (Figure 1d). In cases where FTD has developed, inclusions may also be seen in the neocortex, hippocampus and deep grey nuclei. Mild extramotor pathology may also be noted in cases without a clinically apparent dementia.

The inclusion bodies of MND, in common with those of most other neurodegenerative diseases, are immunoreactive for ubiquitin, the protein tag that most cell types use to mark misfolded or otherwise damaged proteins for degradation. However, those seen in most other diseases also contain a specific disease-associated protein which usually constitutes the majority of the inclusion. The best-known example of this is probably α -synuclein in the Lewy bodies of Parkinson's disease,⁷ which also underscores the point that these disease-associated proteins have, in most cases, been shown to play a major role in pathogenesis. Until recently, no such protein had been identified in MND, although the existence of a form of pure FTD in which the pathological cortical intraneuronal inclusions demonstrate the same ubiquitin-only immunoreactivity seen in MND suggested that the underlying disease process may in fact give rise to a wide clinicopathological spectrum of disorders.⁸ Finally, in late 2006, a landmark study published by the laboratory of Virginia Lee at the University of Pennsylvania adopted a novel, if labour-intensive, approach to unmask the dominant protein component of the inclusions seen in these diseases.⁹ Using cases of ubiquitin-

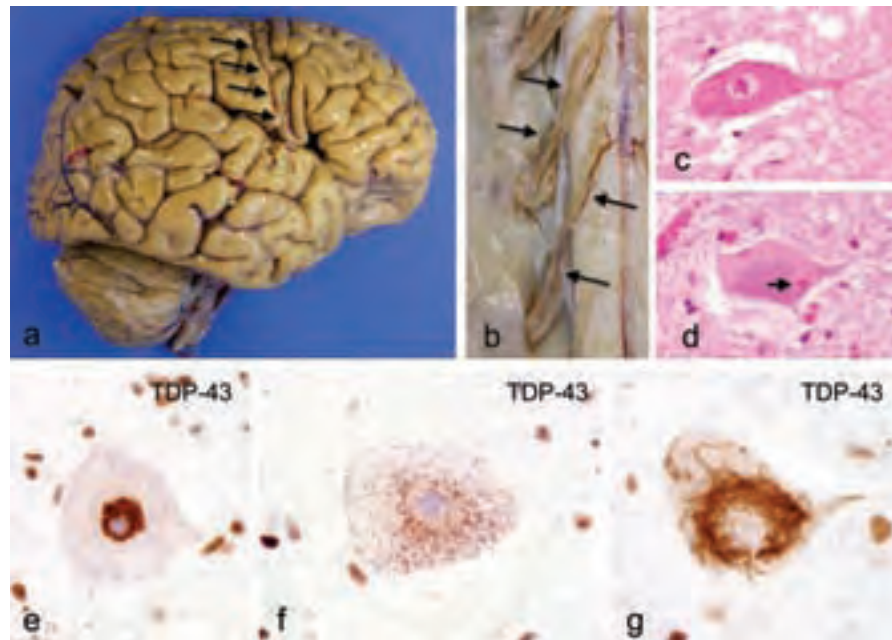


Figure 1: Pathology of classical MND: (a) Gross atrophy of the primary motor cortex (arrows) in a patient with the primary lateral sclerosis variant of MND. (b) Note thinning and brown discoloration of atrophic anterior roots (arrows). (c, d) Compare a normal anterior horn cell (c) with a degenerating cell containing eosinophilic 'Bunina bodies' (arrow) which are typical of classical MND. (e, f, g) TDP-43 protein (brown

reaction product) is normally located in the nucleus of anterior horn cells (e), note sparing of the nucleolus (blue). In classical MND TDP-43 is predominantly located in the cytoplasm (f, g). Granular dispersion (f) is believed to be a precursor of more compact aggregates such as the filaments (or 'skeins') shown in (g). (e, f, g: TDP-43 immunocytochemistry against native protein).

Table 1: The presence or absence of TDP-43 pathology in motor neuron disease subtypes.	
	MND
SUBTYPES	TDP-43 PATHOLOGY
Sporadic disease	
MND/ALS	Yes
Basophilic inclusion variant	No
MND due to single gene mutations	
SOD1	No
Chr 9p-associated	Yes
TDP-43	Yes
FUS	No
ANG	Unknown
VAPB	Unknown

only immunoreactive FTD, size-restricted fractions were prepared from cortical protein extracts by urea extraction, and used to immunise mice. Hybridoma cultures were then prepared from these mice, and supernatants from these were screened by immunohistochemistry on sections of cortex from the same FTD cases. Two distinct monoclonal antibodies were thus identified which strongly labelled the pathological inclusions, and both were found to be directed against the TAR DNA-binding protein of 43KD (TDP-43), a ubiquitously expressed nuclear RNA splicing factor previously implicated in transcriptional repression and exon skipping. Antibodies against TDP-43 were found to label inclusions in almost all of the diseases which were previously classed as ubiquitin-only immunoreactive, including sporadic pure MND. The data suggested that TDP-43 is eliminated from the nucleus of

diseased neurons prior to forming cytoplasmic inclusions (Figure 1f,g) in which it exists mainly as cleaved, phosphorylated fragments.

Numerous follow-up studies confirmed TDP-43 as the dominant component of inclusion bodies in sporadic, and most familial, forms of MND¹⁰ (Table 1). However, a few inherited forms of MND were shown not to be associated with TDP-43 immunoreactive pathology, among them MND resulting from SOD1 mutations.¹¹ These findings have led to the recognition of so-called primary TDP-43-proteinopathies as a new aetiological class of neurodegenerative diseases.¹² The discrepancy between presence of TDP-43 pathology in the vast majority of MND cases and its absence in SOD1-linked disease may have profound implications for basic research, which has relied heavily on SOD1-linked models for the past 15 years.¹³

Pathogenesis of MND

Over the years, a number of factors have been postulated to have a role in MND pathogenesis, most notably mitochondrial dysfunction, oxidative stress and abnormalities of intracellular transport.¹⁴ With the discovery of TDP-43 as the core component of MND pathology, attention has now shifted to the role it may play in disease development. The identification of TDP-43 in disease-associated inclusion bodies does not in itself demonstrate a pathogenic role; however, it was shown early last year that mutations in the TARDBP gene, which codes for TDP-43, were sufficient to cause MND in rare cases of familial disease.³ Although the precise pathophysiological mechanisms linking TDP-43 to disease remain largely obscure, it is becoming clear that aberrant mRNA splicing may be critical, as pathogenic mutations in another mRNA splicing factor (FUS) have been identified in another


inherited form of typical MND.⁴ The discovery of a role in mRNA processing for the SMN gene implicates this process more generally in anterior horn cell loss syndromes.¹

Future developments

Although it is hoped that these recent advances in understanding MND might one day translate into therapeutic approaches, it is clear that the current research priority is to gain a fuller understanding of the molecular events which link dysfunction in TDP-43 or in other components of the mRNA splicing machinery to the disease. Nonetheless, if a central role for dysfunctional mRNA splicing can be confirmed, this raises the intriguing possibility that MND could potentially be treated with RNA-based agents which modulate this process. The broad approach has already been well validated in vitro and in experimental animals, and clinical trials of such treatments for a range of other diseases are already underway.¹⁵ ♦

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Anita Harding (1952-1995)



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Anita Harding, professor of neurology in the University of London, died from cancer in 1995 shortly before her 43rd birthday; she had been ill for only five months. With an indefatigable zest for life, an earthy sense of humour and feet placed firmly on the ground despite a soaring reputation, possessing a rare talent for friendship amongst the many and varied people with whom she interacted, and having a natural flair for sensing and patrolling the complex and mysterious ingredients of elite professional success, early death denied Anita the many accolades and appointments that her combination of personality and ability would inevitably have yielded in due course. And, in turn, neurology never benefitted to the full from the many further contributions and outstanding leadership that she would surely have provided. Anita was unable to participate in the discoveries of neurogenetics that modern molecular medicine has made possible. And a generation of neurologists trained since the mid-1990s lost the opportunity of mentorship and supervision by an outstanding clinical neurologist and a very special person. There is no sense in which these losses might be considered speculative or judged ambiguous. Anita was on a trajectory to greatness that was unstoppable. Her achievements in a career which was active from 1977 until a few days before her death were already outstanding; and as the leading clinician scientist of her generation working in the United Kingdom, Anita already ranked as a major figure in late-20th century world neurology.

Born in Ireland, Anita Harding grew up and was educated in Birmingham; she trained in medicine at the Royal Free Hospital School of Medicine (1970-1975) winning a number of undergraduate prizes. As a student she visited the neurological department of the Montreal General Hospital. After hospital appointments at the Royal Free with Professor Dame Sheila Sherlock and Professor PK Thomas (whom she later married), and in Oxford, she trained in general medicine, becoming a member of the Royal College of Physicians in 1977. She worked first at the National Hospital, Queen Square (where her later career was to be based) in 1977 and subsequently joined Dr Cedric Carter as a research fellow in the MRC Clinical Genetics Unit at the Institute of Child Health. Thus began the work that was to shape her career. First she classified monogenic diseases of the nervous system with an emphasis on the hereditary ataxias and peripheral neuropathies. These studies formed the basis for her doctoral thesis on *The Hereditary Ataxias and Paraplegias: a Clinical and Genetic Study*; for this work, she was awarded the Clinical Genetics Society prize and the Edith Pechey Phipson Postgraduate Scholarship from her medical school. Later, she reworked the text into a



monograph on *The Hereditary Ataxias and Related Disorders* published by Churchill Livingstone in 1984. Her single most important discovery, published in *Nature* with Ian Holt and John Morgan-Hughes in 1986 was the first identification of a mitochondrial DNA mutation in human disease and the concept of tissue heteroplasmy of mutant mitochondrial DNA. But Anita also published on the spectrum of trinucleotide repeat disorders in neurodegenerative disease, and on the population genetics of diseases showing ethnic or geographic restriction. Her curriculum vitae records that she secured substantial grant support for her work, supervised five doctoral theses, wrote almost 200 original articles, over 100 reviews or chapters, edited 3 books in addition to her monograph, gave 100 presentations at scientific meetings, and delivered more than 200 invited lectures in the United Kingdom and abroad.

In the year before taking up her post as senior lecturer and honorary consultant at the Institute of Neurology in 1986, Anita had visited laboratories in Cardiff (United Kingdom) and the California Institute of Technology, Massachusetts General Hospital, Seattle, Duke and Denver (USA); these visits proved pivotal in matching her clinical expertise with a knowledge of the emerging discipline of molecular genetics. The subsequent rise in Anita's career was meteoric. She was appointed reader in the University of London and consultant in neurology to the National Hospital in 1987, elected to a personal professorship in 1990, and to the established chair of neurology at the Institute of Neurology in 1995.

Anita's appointments outside Queen Square were equally distinguished. She was elected to Fellowship of the Royal College of Physicians in 1989 and to ten other societies, including corresponding membership of the American Neurological Association. With others, she founded the European Neurological Society in 1986. Anita

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served on numerous university and hospital committees, was a member of the editorial boards of eleven journals, and a member of eighteen research committees, including the neuroscience panels of the Wellcome Trust and the Medical Research Council; she was a regular member of the teaching faculty of the American Academy of Neurology; and held visiting professorships at eight universities in the United Kingdom, Europe, north America and Australia.

Anita was due to take over as head of the department of clinical neurology in October 1995. In that post, she would have followed Roger Gilliatt and David Marsden, and she was succeeded by Ian McDonald. This is a formidable quartet and her position in that company deserves comment. The early history of clinical neuroscience in the United Kingdom is a record of individual achievement but without overall strategy and with some discontinuities. With the establishment of a university department at Queen Square in 1962, the discipline and methods of clinical neurology were transferred into investigative work; schools developed and strategic programmes emerged. Anita was at the vanguard of the second wave in this process and she came to

Anita Harding's clinical wisdom, enthusiasm, talent for research, and extraordinary personality epitomise all that is valued most in a clinical scientist

epitomise its style and activities better than any of her contemporaries. Through her marriage to PK (Peter) Thomas (1926 - 2008), himself a huge figure in British neurology from the 1960s, Anita witnessed at first hand the diffusion of academic neurology away from the Institute of Neurology; and, as a close confidant of Roger Gilliatt, she saw at the same time the long-term significance of Queen Square as a National Hospital. Her special trick was to balance the need to nurture both the centre and the periphery, and to export and maintain excellence and influence through a network of clinical, scientific and personal collaborations. Because she knew her trade, and provided what every patient wants - knowledge, experience, interest, time and hope - her clinical opinion was extensively sought; and Anita blossomed in the warmth of good doctoring.

Anita was a devoted worker for British neurology. The trappings of academic life were heaped upon her because, as a woman of inexhaustible energy, Anita met deadlines and she delivered. These were remarkable achievements for a woman in a traditionally chauvinist specialty; that so much was achieved by the age of 43, in a career which was fully active for only 10 years is sobering; that it was done in a style from which respect and friendships grew exponentially is a mark of Anita's personality; and that it was not done at the expense of

domestic pleasures was to the advantage of her husband, family and friends. As a trainee neurologist at Queen Square, Anita challenged the conventional sartorial uniformity of her male colleagues. Later she dressed with style; Armani suits for the clinic and designer jeans for assigning genes. More than once she was found absent from a scientific meeting through having disappeared with another lady-professor, to which accusation she retorted "when the going gets tough, the tough go shopping".

Outwardly self-assured but never over confident, she was privately self-effacing and there always remained that endearing hint of the gamin. These were essential qualifications for her type of success and they were traits that attracted her to neurologists throughout the world. In their social life, Anita and 'PK' showed remarkable stamina - much more so than many of their guests who, visiting from the other side of the world or the provinces would be entertained until the early hours. On these occasions, Anita excelled in conversation and revealed her breadth of interests - football and cricket in season, contemporary literature and popular culture; she was a tease without mal-

ice or waspishness, but above all Anita was the mother of neuro-gossip. She maintained her network of informants by telephone; Sunday was her night for collecting information, and you could be sure that leaks would reach their intended destinations early on Monday morning. In fact, it was a general principle that synaptic transmission in the social nervous system was always first detected by tuning-in to Radio Anita. Her style did not change with success. By chance, a conversation was overheard shortly after her death in which reference was made to Anita's obituary in a national newspaper; she was described as having spent time with each of her staff and professional dependents planning their lives during the last few days of her own, and wryly commenting that it would not now be necessary for her to master Windows 95. "She must have been a wonderful person" remarked the unknown conversationalist.

Anita Harding was ahead of the pack in selecting genetics as a field of study which not everyone would have predicted was heading for such prominence in medicine from the 1990s; she should be remembered for that vision and for the common sense way in which she managed the entry of molecular genetics into neurology. Anita Harding's clinical wisdom, enthusiasm, talent for research, and extraordinary personality epitomise all that is valued most in a clinical scientist. She

was an ambassador for British neurology, who patrolled the far corners of a still significant empire which had its roots at Queen Square where she worked and was happy. The evidence for her scientific achievement is in the writings, but the style and significance are in the memories; and both will last. ♦

SUGGESTED FURTHER READING

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Epilepsy charity asks Department of Health to reconsider drug substitution plans

From January 2010 pharmacists will be obliged to substitute expensive branded drugs with a cheaper generic version. Although essentially the same, there are subtle differences in how different generic forms of a drug are made up and for people with epilepsy those differences could have a catastrophic effect.

Professor John Duncan, NSE's medical director, said, "Epilepsy is different from other conditions. A single seizure has severe consequences. It impacts on the ability to drive, employment, well being and increases the risk of injury and harm. The cost saving on the drug budget is not worth the potential harm caused and the cost of dealing with seizures."

The Department of Health's plans are part of the 2009 Pharmaceutical Price Regulation Scheme. NSE's communications manager Amanda Cleaver said, "The Department of Health appears not to have consulted with patient groups on this decision. As the UK's leading medical epilepsy charity our message is clear – anti epileptic drugs must be exempt from the scheme." NSE has submitted to the Department of Health recommendations from a round table discussion with key representatives from the pharmaceutical industry who unanimously agreed with NSE's stance. The full report and recommendations can be found at www.acnr.co.uk/epilepsy

Tell us what you think

Do you agree that epilepsy drugs should be exempt from the 2009 Pharmaceutical Price Regulation Scheme?

Take part in our 10-second survey on the website at www.acnr.co.uk/epilepsy or email your comments to Rachael@acnr.co.uk

The NSE's letter to the Department of Health

Andy Burnham MP, 10 Market Street, Leigh WN7 1DS
July 20 2009

Dear Mr Burnham
Re: generic substitution

I am writing to you in response to the 2009 Pharmaceutical Price Regulation Scheme and the proposal of generic substitution from January 2010. As far as I am aware, there has not been any discussion with patient groups regarding this decision. As Chief Executive of the National Society for Epilepsy I would like to highlight to you the particular issues which face people with the condition. Epilepsy is different from other conditions. A single seizure has severe consequences. It impacts on the ability to drive, employment, well being and increases the risk of injury, harm and death. Adverse side effects can also have a high impact on day to day living. The cost saving associated with generic substitution is not worth the potential harm caused.

Anti-epileptic drugs have a narrow therapeutic index – differences between the minimum toxic concentration and the minimum effective concentration are slim. As the UK's leading medical epilepsy charity we recently initiated a round table discussion with leading pharmacists, pharmaceutical companies and representative bodies to gauge industry views on this important topic.

The unanimous message from that meeting is that anti-epileptic drugs should be exempt from the scheme. Tick in, or tick out, options on prescriptions, which I understand have been suggested, are simply not clear enough.

Enclosed are key points for consideration, a full report of the round table discussion and the presentations made by Professor John Duncan, Medical Director NSE, Professor Phillip Patsalos, Consultant Clinical Pharmacologist NSE and Frank Widdowson, a patient affected by drug substitution.

I have also enclosed a statement from Dr Henry Smithson, GP and Deputy Head Academic Unit of Primary Medical Care School of Medicine University of Sheffield who was unable to attend and letters from the Association of the British Pharmaceutical Industry and Beacon Pharmaceuticals who were also unable to be present.

I really hope you find this report useful. Please do not hesitate to contact me if you would like any further information and I look forward to receiving your response.

Yours sincerely
Graham Faulkner, Chief Executive
graham.faulkner@epilepsysociety.org.uk

Epilepsy Action Research Grants Programme 2008-2009



Epilepsy Action invites applications from researchers and students interested in carrying out non-laboratory research into epilepsy. Research project grants, PhD studentships, postgraduate bursaries and travel bursaries are available. Researchers and students working within the British Isles, including Eire, are eligible to apply for funding.

Epilepsy Action is the largest member-led epilepsy organisation in Britain. It acts as the voice for the UK's estimated 456,000 people with epilepsy, as well as their friends, families, carers, health professionals and the many other people on whose lives the condition has an impact.

Closing date for applications is 9 October 2009

Further information can be found on Epilepsy Action's website <http://www.epilepsy.org.uk/research/awards.html> or by contacting Margaret Rawnsley on 0113 210 8800, email research@epilepsy.org.uk

New Anstey House, Gate Way Drive, Yeadon, Leeds LS19 7XY
tel: 0113 210 8800 fax: 0113 391 0300
epilepsy helpline freephone: 0808 800 5050
email: epilepsy@epilepsy.org.uk www.epilepsy.org.uk

Epilepsy Action is a working name of British Epilepsy Association
A Company Limited by Guarantee (registered in England No. 797997)
Registered Charity in England (No. 234343)

The Research Series



Boyd Ghosh

is currently carrying out research for a PhD in Cambridge, investigating biomarkers and social cognition in progressive supranuclear palsy. He is the current secretary for the ABNT.

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Honorary Clinical Fellow,
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Box 83, Addenbrooke's Hospital,
Herchel Smith Building,
Robinson Way,
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CB2 0SZ.
Tel: +44 (0)1223 768006,
Email: bcpagl@cam.ac.uk

STOP PRESS

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.

If, like me, you are a trainee contemplating an academic career, the various stages of an academic career can be very confusing. What does an intermediate fellowship involve? How do you get one? Is post doctoral time allowed in partnership with clinical work? In the course of my involvement with the ABN Trainees Committee (ABNT), I have seen many trainees who have completed research and fought hard to get a neurology trainee place, particularly after modernising medical careers (MMC). After having fought so hard, it would be a shame if trainees couldn't make decisions because of a lack of information.

The ABNT has developed a number of ideas to plug this information gap. The initial drive and vision came from Dan Blackburn, previous chair of the ABNT at the time of MMC. Having attended a research forum in the US and seeing its' potential to inform trainees, he has set about creating a UK version. He organised one this year with the research committee of the ABN (CRAC) and the ABNT research representative Beth Mallam, and has written about it in the following pages.

As secretary of the ABNT, I have taken on the editing of this research series in *ACNR*, in order to provide trainees with the information that they need. Over the next year, we will look at the different steps in the academic pathway. We will ask funders to inform us about their funding strategies, mentor agencies to describe their work and leading figures in Neurology to give us their advice and insight. The series of articles will cul-

minate next year by setting the scene for the research forum next year in Bournemouth, at the ABN conference.

The final resource which the ABNT is providing for trainees is provided by Beth Mallam, our research representative, who is instituting a research networking database. This will include cross-referenced lists of academic neurologists, research groups and research posts available in the UK and will quickly become a vital resource for junior researchers looking for posts. These three strands should combine to provide trainees with the answers to their questions.

One of the questions that the ABNT are often asked is when trainees should do a PhD. The ABNT feel that trainees should aim to secure their training in neurology before committing to neurological research. However, we recognise that in competitive deaneries, research may be required and that with decoupling of ST2 and ST3 posts, more opportunities may be available. Rather than seek to be prescriptive, we suggest that trainees discuss this issue with the deanery and the head of department. In this first part of the research series, we have sought others advice on this issue. Geraint Fuller, departing chair of the SAC, the committee who decides about our training, has written about the new landscape for PhD research after MMC. He has succinctly explained the different options for trainees about to embark on the journey. I hope that it helps trainees when it comes to making decisions about undertaking research. ♦Boyd Ghosh, *Series Editor*.

The Research Forum



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.



Dan Blackburn

is a Neurology SpR, training in Sheffield and is writing up his PhD, which was on the role of glial cells in Motor Neuron Disease. He was Chair of the ABNT from 2005-2007.

The background to the ABN Research Forum

Attempting to forge a career in academic medicine can be difficult. Apart from the complexities of the research itself, the process of progressing through the different stages of academia can be almost impossible at times. Several recent reports, such as the Walport report, have highlighted these difficulties. However a research forum may help lessen these difficulties (see Box 1).

The idea for a research forum developed from a survey Dan carried out as Chair of the ABNT. This

found that over 90% of neurologists had done research, most either an MD or PhD. Approximately 50% chose research as a way of moving up the career ladder, but very few received explicit advice prior to starting. These findings were published in *Practical Neurology*¹ and presented at the American Academy of Neurology (AAN) meeting in 2007. At this meeting Dan attended a 'Research Forum', an AAN sponsored session, with presentations by junior and senior researchers explaining their academic career pathways and the available funding options. After the talks people were

encouraged to mingle so that trainees could approach senior academics for advice and to establish a mentor relationship.

MMC allows access into research at multiple entry points and aims to improve retention in academic medicine. However, there are concerns that it may preclude research experience for those without clear research intent from the outset. We felt that creating an AAN style research forum would be a valuable opportunity to promote high quality research in UK neurology. The first forum aimed to give practical advice on how to embark on research and move up the academic career ladder.

Research Forum - ABN Academic Meeting Liverpool July 09

We invited a range of speakers in order to gain varied insights on research in academic and NHS settings:

1. **Intermediate Wellcome Fellow.** Don Mahad told us about the skills he gained in America, in between finishing his PhD and returning to the UK to take up a Wellcome Intermediate Fellowship.
2. **Research as an NHS Consultant.** Nikos Evangelou spoke about the possibilities of doing research as an NHS consultant. He discussed National Institute of Health Research (NIHR) funding. This used to be allocated at the discretion of hospital trusts and was not necessarily always spent on research. Now it is held centrally and represents a considerable financial resource

Box 1. The aims of the Research Forum

Help trainees enter, progress and be successful in academic neurology:

- Guidance on how and where to find funding.
- Advice on how to progress into PhD training – and onto intermediate and senior fellowships.
- Explain the skills needed to be an academic within the NHS.
- Advertise the opportunities available for trainees in the UK.
- Help trainees to find research mentors.

Help academics find trainees for research:

- Establish a careers fair so that academics can advertise positions.
- Create an environment where trainees and academics can talk informally.

available for clinical research within the NHS.

3. **Senior Wellcome Fellow.** Professor Tom Solomon spoke of the beginning of his research career in neuro-infectious diseases undertaking simple but effective projects in Africa. He rapidly moved to clinical trials and epidemiological studies in S.E. Asia, spending time in America at the Centre for Disease Control and Prevention (CDC). He emphasised the importance of making the most of data around you. He also spoke about why he moved to Liverpool and how he set up his lab there.
4. **Academic Neurology in the UK.** Professor Compston spoke about changes to neurology training and the academic neurology pathways in particular.

The Future - the next research forum

This first research forum was an excellent first step in our aspirations to provide a platform for promoting research opportunities and improving dialogue between trainees, senior academics and clinicians. In the future, we aim to institute the research forum as an annual feature in the ABN conference. We intend to expand its presence, enabling more opportunity for informal enquiries and “networking”. It is envisaged that with time, senior clinicians and trainees will see it as a crucial resource for advertising and enquiring about research posts, as well as enhancing UK neurology research and training. ♦

1. D Blackburn, and DS Pengiran Tengah (2007). *Why bother with research when training to be a neurologist?* Pract Neurol 2007;7(5):282-4.



Geraint Fuller

Out-going Chairman of the Neurology SAC, Gloucestershire Royal NHS Trust, Gloucester GL1 3NN. E: Geraint.Fuller@glos.nhs.uk

The historical perspective

It used to be so easy to train in neurology. You trained in general medicine, got MRCP and did some neurology at registrar level (probably as a locum). You then completed a period of research (getting an MD or PhD), applied for registrar posts and later senior registrar posts. All of this eventually led to you becoming a consultant (Figure 1).

This changed in the mid-1990s with Calmanisation – by merging the registrar and senior registrar posts and giving the idea of programmed training (Figure 1). The place of research, as the necessary step most budding neurologists had to make, was unchanged. So easy. Or rather, so easy to know what you had to do. It was obviously rather more difficult to actually do it, stay on course and defy the neurological version of natural selection.

Research was regarded as a ‘good thing’. For the trainee it developed critical thinking; helped understanding of the scientific basis of neurology (or lack of it); developed subspe-

Doing Research in the Post MMC World

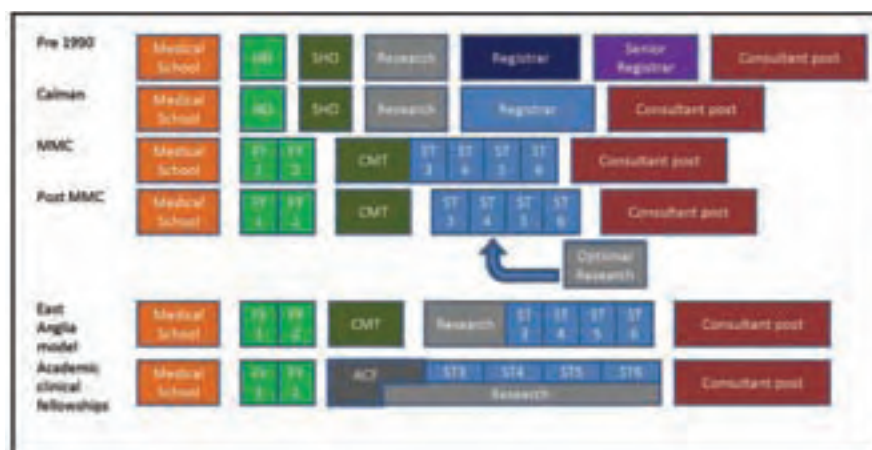


Figure 1: Schema showing different models of post graduate medical training. Gaps between boxes represent an application process.

cially interests and some areas of particular expertise. Discoveries may help patients too. To recognise this up to 1 year of research could

count towards the 5 years of clinical training.

We then had Modernising Medical Careers. Everyone would ‘run-through’ their training

(Figure 1). The immediate problem for neurology was that we had lots of people out in research, who had completed their SHO training and had not yet been able to get a training number. Much heartache resulted. A considerable number of new training posts were funded to absorb these trainees. I will not dwell on the numerous unintended consequences from MMC. The grand idea had not worked and parts of it were unpicked – most notably in medical specialties where a gap was once again introduced between Core Medical Training and Specialist training. As a result training is different and many of the certainties that made it so easy are no longer applicable.

Current opportunities for research

Let us consider the opportunities for 3 different trainees: an ST3+ trainee in neurology (previously a Specialist Registrar); an academic clinical fellow – a new position that came with MMC and a core medical trainee (CMT) who wants to do neurology (previously an SHO).

The ST3+ trainee

If you have a training number in neurology and have not done research you can apply for an out-of-programme research (OOPR) to undertake a registered higher degree. This needs to be agreed by programme/deanery and the SAC. Under the new curriculum this

will not count towards your clinical training, which, though competency based, takes a minimum of 4 years, and annual assessments need to be continued. Generally this will not be approved in your final year of training, so you will need to get moving to sort out an appropriate post/funding. The Eastern Deanery has an innovative scheme where successful applicants to clinical ST3 posts are also offered funding for a higher degree. It is hoped that the majority of those doing research will do so from within training programmes, and it would be good if other deaneries could follow the Eastern Deanery lead. Trainees can expect that they will spend a minimum of 4 years in clinical training with an additional 2 or 3 years in research.

The Academic Clinical Fellow

Another grade for a committed academic is the Academic Clinical Fellow (ACF) and the Academic Clinical Lecturer (ACL). The standard expected to obtain a clinical CCST for these trainees is the same as for those neurologists who train in the conventional post. The expectation is that they will also require a minimum of 4 years of clinical training. The posts are within large academic departments which should make it easier to identify relevant research and for this research interest to run alongside the clinical training – useful if you wish to develop a lifelong academic interest.

Trainees should expect the same duration of clinical and research training post ST3 as other trainees (ie 4 clinical plus 2 or 3 research).

The CMT trainee

A trainee leaving CMT will have the opportunity to apply for ST3 posts but may be tempted to go into research, particularly if they failed to get a post in neurology at their first attempt. This route has not been tested in the current post-MMC world. It would seem a shame if this were to be perceived as a standard route for neurology, and we recreated a large pool of trainees in 'limbo' between ST2 and ST3. The temptation should be resisted by trainees and professors looking for research fellows.

Summary

Research is a good thing; it contributes to training in a number of important ways. However, it is not an essential part of the training needed to be a clinical neurologist. It is not mandatory and should only be done by those who want to do it – recognising that many of those attracted to neurology are likely to be keen to do research.

Useful further reading:

Gold Guide – on specialty training can be accessed at:
<http://www.mmc.nhs.uk/pdf/Gold%20Guide%202008%20-%20FINAL111.pdf>

Royal Berkshire
NHS Foundation Trust



Consultant Neurologist

The post is a replacement post and is offered on a whole time basis, although applicants unable to work full time for personal reasons are invited to apply as are those wishing to job share.

Applicants would need to be on the Specialist Register for Neurology or be within 6 months of their accreditation date at the time of the interview.

The successful candidate would join our three other Neurology Consultants and two Consultants in Neurorehabilitation in providing a specialist inpatient and outpatient service for people with Neurological

illnesses. The Neurology team also includes an experienced Associate Specialist, and several specialist nurses for disorders such as Multiple Sclerosis, Parkinson's Disease, Stroke and Motor Neurone Disease.

The department is committed to training, with two Neurology Specialty Registrars and a Stroke Medicine Specialty Trainee rotating from Oxford. There are strong academic and clinical links with Oxford. There is access to excellent Radiology and Neurophysiology. The postholder would be expected to undertake outpatient

clinics and to take part in inpatient work including Stroke Thrombolysis. Inpatient facilities include a 16-bed Neurorehabilitation ward and a 28 bed Stroke Unit, and inpatient beds shared with Rheumatology on a General Medical Ward.

The appointment will be subject to the new terms and conditions of service for Consultants (England) 2003. The post attracts 10 Programmed Activities (PAs) per week (full time), with one PA spent in the regional neuroscience centre at the John Radcliffe Hospital for CME. Visits to the Department are welcomed.

Please contact Dr Jane Adcock (telephone 0118 322 6624), Dr Andrew Weir (telephone 0118 322 5475) or Dr Marko Bogdanovic (telephone 0118 322 5474) for further information.

To apply please go to www.jobs.nhs.uk quoting reference MS333.

Closing date: 11th September 2009. Interview date: 6th October 2009.

214003 0

To list your event in this diary, email brief details to Rachael Hansford at rachael@acnr.co.uk by 8 October, 2009

2009

SEPTEMBER

Synaptopathies: Dysfunction of Synaptic Function

2-4 September, 2009, Newquay, UK
T. 020 7280 4150,
E. meetings@biochemistry.org

3rd Eilat Int. Educational Course Pharmacological Treatment of Epilepsy

6-13 September, 2009; Eilat, Israel
T. 97 235 175 150,
E. eilatedu@targetconf.com

2009 European Glial Cell meeting - 9th European Meeting

8-12 September, 2009, Paris, France
E. info@euroglialcell.org

BAS Biennial Conference

9-10 September, 2009
www.ncore.org.uk

IDMC-7 International Myotonic Dystrophy Consortium

9-12 September, 2009; Würzburg, Germany
E. brigitte.wolf@mail.uni-wuerzburg.de

Evolution of Brain, Behaviour & Intelligence

9-12 September, 2009; Cambridge, UK
E. Lucy Criddle, lcriddle@wtconference.org.uk or wtmeetings@wtconference.org.uk

25th Congress of the European Committee for Treatment and Research in Multiple Sclerosis

9-13 September, 2009; Düsseldorf, Germany
Tel. +49 211 81 17880,
E. ectrim2009@uni-duesseldorf.de

Arrhythmia Alliance Regional Meeting

10 September, 2009; Cardiff, UK
Melanie Quinlan,
E. events@stars.org.uk
www.hearthrhythmcharity.org.uk

14th International Headache Congress/51st Annual Scientific Meeting

10-13 September, 2009; Philadelphia, US
T. +1 (0)856-423-0043,
E. ahsmtgs@talley.com

13th Congress of the EFNS

12-15 September, 2009; Florence, Italy
www.kenes.com/efns2009/

2009 World Congress on Huntingtons Disease

12-15 September, 2009; Vancouver, Canada
T. +1-604-875-4111 x 69155,
E. Sandy.m@ubc.ca

41st European Brain & Behaviour Society Meeting

14-18 September, 2009; Rhodes, Greece
E. traceymole@wfnr.co.uk

Dementia Services Development Centre: 3rd International Conference

14-16 September, 2009; York, UK
T. 01786 467740,
E. jemma.galbraith@stir.ac.uk

Understanding and Managing Occupational Stress

15 September, 2009
www.ncore.org.uk

MS Trust Stirling Study Day for Health & Social Care Professionals

15 September, 2009; Stirling, UK
T. 01462 476704,
E. education@mstrust.org.uk
www.mstrust.org.uk/studydays

Acupuncture, Maintain your AACCPD Points

17 September, 2009
www.ncore.org.uk

Neurology Update Meeting 2009 – IICN

18 September, 2009; Dublin, Ireland
E. info@iicn.ie, www.iicn.ie

12th ILAE Specialist Registrar Teaching Weekend in Epilepsy

18-20 September, 2009; Oxford, UK
www.genesisadoration.com/epilepsy.html

ESNR XXXIII Congress and 17th Advanced Course

18-21 September, 2009; Krakow, Poland
Professor Marek Sasiadek,
T. 48 713 425 833,
E. markes@rad.am.wrocl.pl

Understanding and dealing with behaviour problems following brain injury

18-19 September, 2009; Gatwick airport, London, UK
E. enquiries@braintretraining.co.uk
www.braintretraining.co.uk

World Alzheimer's Day

21 September, 2009
www.alz.co.uk/adi/wad/

2009 World Stem Cell Summit

21-23 September, 2009; Baltimore, USA
T. 001 908 605 4203,
E. rob@genpol.org

British Association of Cognitive Neuroscience Annual Meeting 2009

21 September, 2009; London, UK
www.ich.ucl.ac.uk/education/short_courses/courses/25.05

Neurological Upper Limb for Occupational Therapist

22 September, 2009
www.ncore.org.uk

BIRT 2009: Innovations: Models and Management in Brain Injury Rehabilitation

23-24 September, 2009; Birmingham, UK
E. frances.pitwell@thedtgroup.org
www.birt.co.uk

2nd Annual Stem Cells & Regeneration Medicine Europe

23-25 September, 2009; Edinburgh, UK
Matthew Ames,
E. M.Ames@selectbiosciences.com
T. 01787 315119.

Developing the Disease-Modifying Possibilities of Exercise on Parkinson's

24-25 September, 2009; Gatwick, UK
E. secretary@springparkinsons.org.uk

15th International Network for Psychiatric Nursing Research conference

24-25 September, 2009; Oxford, UK
www.rcn.org.uk/events
E. laura.benfield@rcn.org.uk
for more information

Practical Pearls in Neuro-Ophthalmology - International Symposium in Honour of Dr. James Sharpe

25 September, 2009; Toronto, Canada
T. 416.978.2719/1.888.512.8173,
E. help-OPT0907@cmertoronto.ca

Migraine Education Day

26 September, 2009, London, UK
www.migraine.org.uk/index.php?sectionid=526

Matthew's Friends European Dietitian & Nurse Training Meeting for the Dietary Treatment of Epilepsy & Glut 1DS

28- 29 September, 2009; Harrogate, UK
www.matthewsfriends.org
E. julie@matthewsfriends.org
T. 07748800438.

Autumn School in Cognitive Neuroscience

28 September - 1 October, 2009; Oxford, UK
E. autumn-school@dpag.ox.ac.uk

BSRM Silver Jubilee Meeting

30 September-2 October, 2009; Oxford, UK
T. 01992 638865
E. admin@bsrm.co.uk

8th European Paediatric Neurology Society Congress

30 September-3 October, 2009; Harrogate, UK
Diane Rodie,
E. epns2009@bnpa.org.uk

MS Trust Bedfordshire Study Day for Health & Social Care Professionals

30 September, 2009; Luton, UK
T. 01462 476704,
E. education@mstrust.org.uk
www.mstrust.org.uk/studydays

OCTOBER

Update on headaches

1 October, 2009; Cardiff, UK
http://216.25.88.43/upload/NS_BASH/Update%20on%20Headaches%25B2%5D%5B2%5D.doc

Anxiety and Depression 2nd National Conference

1-2 October, 2009; London, UK
MA Healthcare Ltd,
www.mahealthcarevents.co.uk
T. 0207 501 6762

5th Canadian Conference on Dementia

1-3 October, 2009; Toronto, Canada
Jane Sessenwein,
T. 1-514-767-6166,
E. info@ccd2009.ca

EPDA Multidisciplinary Conference and General Assembly

2-5 October, 2009; Budapest, Hungary
T. 01732 457 683,
E. lizziegraham@btconnect.com

International Symposium on Stem Cell Transplantation in Multiple Sclerosis: Sharing the Experience

5 October, 2009; Moscow, Russian Federation
Tatyana Ionova,
T. 74-954-634-923 / 79-627-101-711,
E. qlife@rambler.ru

World Stem Cells & Regenerative Medicine Congress Asia 2009

5-7 October, 2009; Singapore
www.terrapinn.com/2009/stemcellasia/

Behaviour Change Training Part 1

5, 6, & 7 October, 2009; Derby, UK
www.ncore.org.uk

Integrative Approaches to Brain Complexity

7-10 October, 2009; Cambridge, UK
E. wtmeetings@wtconference.org.uk

AANEM Annual Scientific Meetings

7-10 October, 2009; San Diego, California, USA
T. + (507) 288-0100,
F. + (507) 288-1225,
E. aanem@aanem.org

International League Against Epilepsy (UK Chapter) Annual Scientific Meeting

7-9 October, 2009; Sheffield, UK
Denise Hickman,
T. 01323 740612,
E. denise@conference2k.com
www.conference2k.com

British Geriatrics Society Autumn Meeting

7-9 October, 2009; Harrogate, UK
E. hmc@hamptonmedical.com

BISWG 9th Annual Brain Injury Legal Seminar

8 October, 2009; London, UK
T. 020 8780 4500 #5161,
E. lbellgard@rh.nhs.uk

Practical Cognition Course at Newcastle University

8-9 October, 2009; Newcastle, UK
www.staff.ncl.ac.uk/t.d.griffiths/practical_cognition_2009.pdf, T. 0191 222 8320

Basic Splinting

8th & 9th October, 2009; Derby, UK
www.ncore.org.uk

MS Trust Annual Conference

Quality and MS Care: Leading the Way
8-10 November, 2009; Kenilworth, UK
T. 01462 476704,
E. education@mstrust.org.uk
www.mstrust.org.uk/studydays

Controversies in Neurology

8-11 October, 2009; Prague, Czech Republic
E. cony@comtecmed.com

TLRs (Toll-like receptors), NLRs (Nod-like proteins) and RLRs (RIG-like receptors), pathogens sensors of innate immunity

9 October, 2009; Welwyn Garden City, UK
www.regonline.co.uk/TLR09
E. astrid.inglezou@euroscicon.com

Annual Meeting of the American Neurological Association

11-14 October, 2009; Baltimore, United States
E. Julieratzloff@llmsi.com
T. 001 952 545 6284

Posture & Balance in Neurological Conditions, upper limb, Assistant staff

12 October, 2009; Derby, UK
www.ncore.org.uk

ELISPOT technology: The latest tricks

October 15, 2009; Welwyn Garden City, UK
www.regonline.co.uk/elispot09
E. enquiries@euroscicon.com

International Symposium on Neurorehabilitation. From basics to future

15-16 October, 2009; Valencia, Spain
E. catedrasg@cac.es
www.neurorehabilitationvalencia.es

7th Meeting of the British Society of Neuro-Otology

16 October, 2009; Leicester, UK
E. neuro-otology@imperial.ac.uk

Neuroscience 2009

17-21 October, 2009; Chicago, US
T. 202 962 4000,
E. info@sfn.org

Normal Movement for Musculoskeletal Therapists (Module 1: The Lumbopelvic Hip Region).

17-18 October 2009, London
www.physiok.co.uk

Headway Conference

19 October, 2009; Stratford Upon Avon, UK
Rachel Broughton,
E. eventsandconferences@headway.org.uk

BNS Autumn Meeting

22 October, 2009; London, UK
E. dana.samson@nottingham.ac.uk

Trigger Points, Pain & Muscle Tone

24-25 October, 2009; Birmingham, UK
www.physiok.co.uk

19th World Congress of Neurology

24-30 October, 2009; Bangkok, Thailand
www.wcn2009bangkok.com

Operative Skills in Neurosurgery

28-30 October, 2009; London, UK
T. 020 7869 6336,
E. neurosurgery@rcseng.ac.uk,
www.rcseng.ac.uk/education/courses/specialty/neurocourses.html

Law and Cognition: Our Growing Understanding of the Human Brain and its Impact on our Legal System

26-31 October, 2009; Aquafredda de Maratea, Italy
Dr. Eva Hoogland, European Science Foundation,
E. ehoogland@esf.org

3rd International Conference on Movement Dysfunction

30 October- 1 November, 2009; Edinburgh, UK
Nina Cosgrove, T. 01865 843297,
E. n.cosgrove@elsevier.com

Law and Cognition: Our Growing Understanding of the Human Brain and its Impact on our Legal System

28-31 October, 2009; Maratea, Italy
Dr. Eva Hoogland, E. ehoogland@esf.org

DATE FOR DIARY

10th Annual UK Movement Disorders Meeting

Friday 4th and Saturday 5th December 2009
London, UK

Programme to be finalised. CPD approval will be sought

Chaired by

Prof Anthony Schapira,
Professor of Neurology,

*Institute of Neurology, UCL and Royal Free Hospital and
National Hospital for Neurology and Neurosurgery, Queen Square, London, UK*

Prof P Barone, *Professor of Neurology, Naples, Italy*
Prof A Lang, *Professor of Neurology, Toronto, Canada*
Prof W Poewe, *Professor of Neurology, Innsbruck, Austria*
Prof O Rascol, *Professor of Neurology, Toulouse, France*
Prof E Tolosa, *Professor of Neurology, Barcelona, Spain*

UK FACULTY:

Prof D Burn, *Professor of Neurology, Newcastle, UK*
Dr P Fletcher, *Consultant Physician, Cheltenham, UK*
Prof A Lees, *Professor of Neurology, Institute of Neurology, UCL, London, UK*
Dr D MacMahon, *Consultant Physician, Truro, UK*
Dr G Macphee, *Consultant Physician, Glasgow, UK*
Prof K Ray Chaudhuri, *Professor of Neurology, London, UK*

who require it in order to attend the meeting.

As these meetings have become very popular and always
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To register your interest in attending please e-mail: neurology@boehringer-ingenheim.com

Educational Meeting Sponsored by Boehringer Ingelheim Ltd
Date of preparation: August 2009



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A course for consultants and trainees who want to develop
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this to clinically relevant neuroscience. Open to trainees
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20th International SYMPOSIUM on ALS/MND

Berlin, Germany,
8-10 December 2009



The International Symposium on ALS/MND is a
unique annual event which brings together
leading international researchers and health and
social care professionals to present and debate
key innovations in their respective fields. Taking
place over three days, the Symposium features a
scientific meeting and a clinical meeting.

Proposed biomedical sessions include:

- Proteinopathies
- Protein regulation and degradation
- Motor neuron biology
- Stem cell biology
- Genetics
- Cell biology and pathology
- Axonal transport and maintenance
- Emerging disease models
- Neuro inflammation

Proposed clinical sessions include:

- Palliative care
- Translating evidence into practice
- Spiritual care
- Multidisciplinary care management
- Cognitive change
- Quality of life/decision making
- Exercise and metabolism
- Respiratory management
- Caregiver support
- Clinical electrophysiology and imaging



For more information and to register, contact the Conference Team by
email: symposium@mndassociation.org, or register
online at: www.mndassociation.org/symposium.

Organised by the MND Association in co-operation with the
International Alliance of ALS/MND Associations.

International Conference on Alzheimer's Disease (ICAD)

Conference details: 11-16 July, 2009, Vienna. **Reviewed by:** Dennis Chan, Senior Lecturer in Neurology, Brighton and Sussex Medical School.

As appears now to be the norm, the main conference was preceded by a one day Imaging Consortium. This is of mixed benefit; while the concentration of imaging talks benefits those researchers based principally in this field, there is repetition of the same material within presentations within the main conference.

Several groups presented updated results relating to molecular neuroimaging in Alzheimer's disease (AD). One of the interesting aspects of the work described by Bill Klunk and co-workers from Pittsburgh using Pittsburgh Compound B (PiB) was the longitudinal study involving amyloid imaging of patients with mild cognitive impairment (MCI); previous work has shown that around 50% of patients with MCI progress to AD within three years but that there is also a significant proportion whose symptoms remain static or even improve. Analysis of the PiB-PET data reveals that 50-60% of "PiB-positive" MCI patients converted to AD over two years, whereas over the same period none of PiB-negative MCI cases progressed to AD and three out of ten PiB-negative cases reverted to normal (see also related paper in the May 2009 edition of *Annals of Neurology*). PiB-positivity was found to be highly correlated with reduced levels of A β 42 in the CSF. These data were echoed by those of Chris Rowe from Melbourne, who presented evidence indicating that the presence of PiB-positivity in MCI patients was 87% predictive of progression to AD.

In addition to the PiB-related talks, mention was made of the 18F-related ligands with amyloid-labelling capability. They benefit from a longer half-life than the 11C-PiB; at present the usage of the latter is limited by its short half-life and so is essentially restricted to those centres with an in-house cyclotron. By comparison the 18F-ligands have the potential for widespread usage.

Cliff Jack of the Mayo Clinic presented a comparison of serial PiB and MRI data in controls, MCI and AD patients over a one year test period. There was little difference between the MCI and AD patient groups in terms of the change in degree of PiB labelling whereas there was a significant group difference with regard to rate of ventricular expansion (used as a measure of change in whole brain volume). Change in ventricular size, and not in PiB labelling, correlated with decline in cognitive and clinical state. The dissociation between the two sets of imaging data may provide an insight into the differing pathological processes in AD; in line with other investigators, it is proposed that deposition of amyloid occurs from a very early stage of the disease,

with very little change in the rate of further deposition once an individual become symptomatic, whereas neurodegeneration (and associated brain parenchymal loss) is a manifestation of later stages of AD and parallels the cognitive decline. These findings have important implications for the use of these complementary techniques in tracking the disease at different stages.

Finally, on the imaging front, Reisa Sperling and colleagues at Harvard demonstrated in cognitively normal and minimally impaired individuals that extracellular amyloid deposition as seen on PiB imaging is associated with a disruption of the normal pattern of activity within the "default resting network" of brain regions thought to be involved in successful memory encoding and retrieval, including the precuneus and posterior cingulate cortex, as observed on fMRI. These early data suggest that amyloid deposition is related to dysfunction of brain regions subserving memory processes. However, it remains to be seen whether the relationship is causal, and these observations do not provide any clear explanation for the role of tau-related tangle pathology within the AD process (a criticism common to all PiB-based work).

Away from neuroimaging, Niklas Mattsson from Gothenburg presented data from a large scale longitudinal study of CSF biomarkers in MCI. A two year follow-up study of 750 MCI patients revealed that those patients converting to AD had lower CSF levels of A β 42 and higher levels of tau and phosphorylated tau than non-converters with a positive predictive value of 62% and negative predictive value of 88%. This follows on from the publication by Visser and colleagues concerning CSF profiles in patients with memory impairment who are at risk of progressing to AD, which was accompanied by the challenging editorial which raised the issue of lumbar puncture as a potential routine investigation for patients presenting with memory impairment.

By comparison with ICAD 2008, the news on potential new drugs was relatively muted; to a large extent this was due to the fact that there was no major presentation detailing Phase II or Phase III study results. Following on from the presentation of Phase II data last year, the Phase III study of bapineuzumab (the monoclonal antibody directed against the N-terminus of A β 42) is now in progress and provisional results will not be available until 2012. Away from AD immunotherapy, there is interest in the antihistamine drug Dimebon, whose proponents suggest that it may have neuroprotective qualities related to the enhancement of mitochondrial function. While the promise of multiple future drugs with potential disease-

modifying capability is undoubtedly exciting, several speakers rightly drew attention to potential difficulties. For instance, there is concern that the majority of drugs currently undergoing trial for AD are directed at "upstream" targets within the AD pathological process (such as β -secretase inhibitors) and as a result may have limited efficacy due to the lack of effect on the downstream processes that ultimately lead to neuronal dysfunction and death. Additionally, while there was a general consensus that drugs of this kind were likely to be of greatest benefit when applied early during the disease process, this will be problematic not least due to a) the difficulty of identifying patients in the earliest (effectively presymptomatic) stages of AD and b) the need for very large scale and prolonged trials to detect treatment effect of drugs applied at early stages of disease.

Finally, from a UK perspective it was gratifying to witness the presentation of a Lifetime Achievement Award to Professor Martin Rossor of the Dementia Research Centre, London. Professor Rossor's work in the field of dementia now spans nearly a quarter of a century and takes in such notable achievements as the identification of the first pathogenic mutations in familial AD. The timing of the award is particularly appropriate given the increasing international emphasis on the management of dementia, exemplified nationally by the introduction of the National Dementia Strategy. ♦

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Welcome
to the



19th World Congress of Neurology

October 24th-30th, 2009
Bangkok, Thailand



“Innovation in Neurology”

www.wcn2009bangkok.com

New Developments in Clinical Trials in Neuroscience & Psychiatry

Conference details: 10 June, 2009; Edinburgh, UK. **Reviewed by:** Professor Peter Sandercock, Edinburgh, UK.

Translational neuroscience offers enormous potential, but has yet to deliver really substantial benefits for patients with the disorders of the nervous system that cause such a large burden of disability: stroke, dementia, neurodegenerative diseases and the major psychiatric disorders. This meeting sought to take a step back to examine the strengths and weaknesses of translational research in the field, to identify key barriers and potential solutions. Gordon Murray, Professor of Medical Statistics at The University of Edinburgh gave the opening lecture which set the scene. He drew a sharp contrast between cardiology and neuroscience. In cardiology, the availability of useful and reliable surrogate markers (coronary artery patency, left ventricular function, blood pressure) had underpinned the development of large-scale trials able to detect effects on major clinical outcomes. These trials then established the benefits of aspirin, beta blockers, angiotensin converting enzyme inhibitors and thrombolysis, just to name a few. By contrast, in acute stroke, thrombolysis had skipped the translational pathway and was developed in stroke 'on the back of' experience in cardiology. Neuroprotection, which had shown so much promise in animals, has yet to show benefits in man. Very presciently, Professor Murray outlined the themes that many of the speakers would return to during the afternoon. The most important of these was the need for careful methodological development of better surrogate markers, both of the underlying biological processes, but also of the clinical outcomes those processes were mostly likely to influence. Professor Joanna Wardlaw then went on to outline the rather chequered history of imaging as a surrogate outcome in acute stroke research. One illustrative example which she drew on, was the use of advanced neuroimaging to outline cerebral tissue that was ischaemic but potentially rescueable by therapy. Whilst it is relatively straightforward to produce attractive colour-rendered pictures of cerebral perfusion it has become clear that the use of different measurement algorithms can produce radically different results. In brief, there is a need for much greater methodological rigour in the development and application of such techniques and the research community needs to reach consensus on an optimal and standardised approach. Several of the themes of her talk are reflected in a recent editorial in the journal 'Stroke'.

Next on the podium was Professor Stephen Lawrie, Professor of Psychiatry and Neuroimaging at The University of Edinburgh, who outlined the promises and challenges of



neuroimaging in major psychiatric disorders. His talk ran along the theme that although there were undoubtedly structural and functional changes in the brain in people at risk of, or with established psychotic disorders, there were many challenges in measuring these changes precisely or understanding their underlying biological substrate. Multicentre imaging studies, offer greater statistical power to help detect and clarify the nature of the subtle structural and functional changes that occur in the brain. Neurogrid, Neuropsygrid and the Scotland-wide SINAPSE collaboration certainly seem to be forging ahead, developing the technological advances needed that will facilitate multicentre imaging studies to help take the field further forward.

Dr Roger Staff from the University of Aberdeen showed results of work in progress on the use of SPECT and PET imaging in dementia and Alzheimer's disease. The techniques do seem to show promise as useful surrogate outcomes and the promising results in a small phase II trial are now being tested on a larger scale in a phase III trial of a therapeutic agent for this major group of diseases.

Dr Carl Counsell moved away from imaging to consider how to improve the clinical assessment of outcome in Parkinson's Disease and neurodegenerative disorders. His talk was a reminder that while biomarkers (imaging, molecular biology and genetic) have some role in the assessment of new treatments for Parkinson's Disease and in neurodegeneration, in parallel with those developments, the science of clinical measurement needs to be applied to assess the impact of disease on the patient and their life. He outlined the path forward that developments in clinimetrics would need to take to achieve this goal.

This exciting and fruitful symposium was rounded off by a lecture from Dr Walter Koroshetz, Deputy Director of the National Institute of Neurologic Disorders and Stroke, at the National Institutes of Health, Bethesda, USA. He outlined themes that were all too familiar to the audience: the difficulties of moving successfully from identifying a potential therapeutic target, selecting an agent that might act on that target and then establishing its effects in animals and subsequently in humans. In parallel with the challenges of scientific development of agents, there is also a difficulty – on both sides of the Atlantic – of developing the careers of the next generation of clinical trialists. They will need stamina to overcome the bureaucratic and organisational hurdles to clinical trials and combine it with the scientific vision and charisma that are needed to lead the large collaborative groups to undertake multicentre international clinical trials. He ended on a note of optimism. Whilst these problems are significant, they are all potentially soluble and we must work on them one step at a time.

This well-attended meeting was supported by the following academic institutions, research groups and NHS research networks: The University of Edinburgh Centre for Clinical Brain Sciences, Edinburgh Neuroscience, the Edinburgh Clinical Trials Unit Collaboration, the Scottish Collaboration of Trialists, the Scottish disease-specific research networks in stroke, mental health and neuro-degenerative disorders, the SFC Brain Imaging Centre and a grant from The Royal Society of Edinburgh. ♦

The lectures are available on-line at
<http://www.cbs.ed.ac.uk/bcm.html>

RECENT ADVANCES IN BRAIN INJURY REHABILITATION

Homerton University Hospital, London
Wednesday 7th October 2009
Cost £105

This conference is aimed at Medical Doctors, Psychologists, Nurses, Physiotherapists, OTs, Speech & Language Therapists, Researchers, Academics, Social Workers and all who work with brain injured people.

Speakers include:

Dr Sam Cooper-Evans, Consultant Clinical Psychologist,
Brain Injury Centre, St Andrew's Healthcare, Northampton

Self-esteem as a predictor of psychological distress after brain injury - (to be confirmed)

Rudi Coetzer, North Wales Brain Injury Services

Community based rehabilitation for identity change after brain injury

Jane Bache & Gary Derwent

Royal Hospital for Neurodisability, Putney

Computer-based leisure in profound neuro-disability

Dr Dave Sharp, Consultant Neurologist

Hammersmith Hospital, London

The frontal lobes and traumatic brain injury – structural and functional imaging studies of connectivity

Dr Penelope Talleli, Consultant Neurologist

Homerton Hospital, London

Plasticity and its impact on rehabilitation

Another three speakers to be confirmed

For further details and application enquiries please contact:

Nick Hall, Conference Organiser

Email: nicholas.hall@homerton.nhs.uk, Tel: 020 8510 7970



THE NEUROLOGY OF OLD AGE

Thursday 18 February 2010

**Joint conference with the
British Geriatrics Society**

Medical clerking often omits the Central Nervous System or describes it in a cursory way. Many non-specialists feel rather vulnerable when assessing a complex elderly person with poor mobility, falls, incontinence or cognitive impairment.

The aims of this conference are to improve diagnostic acumen when assessing old people with neurological disorders, to know whom to refer and when and to be aware which investigations have therapeutic payoff and which are inappropriate or unnecessary.

Target audience: Hospital doctors especially neurologists, geriatricians, acute physicians, rehabilitation specialists, physiotherapists and speech and language therapists.

Programme and booking forms are available on-line at www.rcplondon.ac.uk/conferences or from:

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The lecture programme is available on our website at www.ion.ucl.ac.uk or from the Education Unit, UCL Institute of Neurology, 7 Queen Square, London WC1N 3BG.
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The UCL Institute of Neurology promotes teaching and research of the highest quality in neurology and the neurosciences

GlaxoSmithKline, UCL Institute of
Neurology Advanced Lecture Series
Autumn Term 2009

GENES AND DISEASE

This series will be given on **WEDNESDAY EVENINGS** during the Autumn term 2009; the first lecture will commence at 5.15pm. The venue will be the Lecture Theatre, Basement of 33 Queen Square (unless stated otherwise), National Hospital for Neurology & Neurosurgery, Queen Square, London WC1.

These lectures are open to anyone practicing and researching in the field. No charge is made for attendance.

Wednesdays:

**14th October – 2nd December 2009
inclusive**



**The British
Neuropsychiatry
Association**

**23rd Annual General Meeting
10/11/12 February 2010**

The British Neuropsychiatry Association
23rd Annual General Meeting
11/12 February 2010
With a joint meeting, 10 February, with the
Section of Neuropsychiatry, RCPsych
Venue: The Institute of Child Health,
Guilford St, London

Topics to include:

- Memory (SoN/BNPA)
- Encephalopathy and delirium
- Head Injury
- Neuropsychiatry and the Self

For outline programme and registration form visit:
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contact: Jackie Ashmenall on
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Email: admin@bnpa.org.uk
or jashmenall@yahoo.com

**The Birmingham
Neuro-Ophthalmology Course**

Wednesday 11th November 2009
Postgraduate Medical Centre, City Hospital, Birmingham, West Midlands B18 7QH

Organisers
Mike Burdon
Andrew Jacks
Tim Matthews

Secretary
Hilary Hopkins,
Birmingham
& Midland
Eye Centre,
City Hospital,
Dudley Road,
Birmingham,
B18 7QH
Direct telephone
0121 507 6785
Email:
Hilary.Hopkins@swbhb.nhs.uk

The Birmingham Neuro-Ophthalmology Course is a four year rolling programme of one day lectures aiming to teach the principles of diagnosis and management of disorders of the visual pathway, eye movements, and pupils. The Michael Sanders lecture enables an invited speaker to review a topic of his or her choice in greater depth.

Target Audience

Ophthalmologists, Neurologists, and Orthoptists

This Year's Topic: Optic Nerve Disease

Lectures to include

- Imaging of the anterior visual pathway
- The anomalous optic disc
- Papilloedema
- Ischaemic optic neuropathies
- Optic neuritis
- Optic nerve tumours
- Inherited optic neuropathies
- The 4th Michael Sanders Lecture, to be given by Gordon Plant

Invited Speakers:

- Swarup Chavda – University Hospital Birmingham
- Philip Griffiths – Royal Victoria Infirmary Newcastle
- Simon Hickman – The Royal Hallamshire Hospital
- Paul Riordan-Eva – King's College Hospital
- David Taylor – London

Course Fees

- Medical **£ 200=00**
- Orthoptists **£ 150=00**
- Includes lunch and morning and afternoon coffee/tea

Further Information and Applications

- By post, telephone or email to the Conference Secretary, Mrs Hilary Hopkins
- Please note: space is limited to 120 delegates



**EUROPEAN CHARCOT FOUNDATION
UNIVERSITY CLASSES VI**

Focussed on the Natural Course of the Disease

An educational programme on Multiple Sclerosis

November 11, 2009, Lisbon, Portugal

Faculty:

M.P. Amato, T. Berger, M. Clanet, G. Comi,
C. Confavreux, G. Ebers, O. Fernandez, C. Heesen,
H. Lassmann, Ch. Lebrun, R. Marignier, J. De Seze,
M. Tintoré

Call for Biogen Idec young investigators travel grants

The European Charcot Foundation is pleased to announce that Biogen Idec has provided an unrestricted educational grant to sponsor 20 young investigators with a travel grant of € 1500,- to attend the University Classes in Multiple Sclerosis VI.

Young investigators are invited to apply before October 1, 2009. Conditions for applications are available on our website.

For detailed information and registration visit our website www.charcot-ms.eu



**EUROPEAN CHARCOT FOUNDATION
SYMPOSIUM**

A new Treatment Era in Multiple Sclerosis

November 12, 13 and 14, 2009, Lisbon, Portugal

15th European Charcot Foundation Lecture

Prof. M. Clanet

'Trends in Treatment Strategies'

Sessions on:

- Pathology, pathophysiology and clinical application of new concepts
- Options, challenges and risks of new drugs
- Response measurement and how to use the tools. MRI, CSF, Biomarkers, Pharmacogenomics
- Atypical syndromes
- The future

28th International Epilepsy Congress

Conference details: 28 June-2 July, 2009, Budapest, Hungary. **Reviewed by:** Therese Schwender, Römerswil, Switzerland.

This year's International Epilepsy Congress was a very special one as the International League against Epilepsy (ILAE) is celebrating its first 100 years. The ILAE meeting was held on 30 August 1909 at a meeting in Budapest, the same city where the organisation was founded. The League is the oldest international subspecialist organisation in the field of neurology, and one of the oldest in medicine.

During the Presidential Symposium Peter Wolf from Denmark, President of the League, expressed his hopes for the future. "We expect that ILAE and IBE together will make progress toward a world where nobody needs to suffer from epilepsy or its consequences because they don't have access to the existing diagnostic and therapeutic possibilities." Furthermore, he was confident that both diagnostics and therapies, pharmacological and other, will become still more effective in the future. "If we achieve remission in 90% of patients instead of the current 70%, we will have achieved a lot."

Promising future

One of the new drugs which will hopefully help to achieve higher remission rates in the future is lacosamide. It has recently been approved in the US and EU for the adjunctive treatment of partial-onset seizures in adults. Lacosamide appears to selectively enhance slow inactivation of voltage-gated sodium channels without affecting fast inactivation. Preliminary in vitro studies suggest a potential interaction of lacosamide with collapsin response mediator protein 2 (CRMP-2), a protein involved in neuronal differentiation, polarisation and neurotrophin-induced axonal outgrowth. Lacosamide has quite a favourable pharmacokinetic profile. It is rapidly and completely absorbed (bioavailability of 100%), has a half-life of 13 hours permitting a twice daily dosing schedule and a low protein binding (under 15%).¹ No clinically significant drug interactions could be identified.²

The safety and efficacy of this new drug have been evaluated in three well-controlled Phase II/III clinical trials. Individual and pooled data from these trials were used to evaluate lacosamide efficacy across the 200 – 600mg/day dose range studied. The pooled analysis, presented by Elinor Ben-Menachem (Goteborg/Sweden) showed a reduction of the median seizure frequency by more than 40%.³ This is particularly remarkable considering that 77% of the patients included had tried four or more lifetime antiepileptic drugs before entering the trial. A further advantage of lacosamide is that its efficacy seems to be independent of the concomitant antiepileptic treatment. Lacosamide was generally well tolerated, with dizziness, nausea, headache and diplopia being the most common side effects.



Another 'new kid on the block', although not yet approved, is carisbamate. This novel drug with neuromodulator activity is currently under development for adjunctive treatment of partial-onset seizures. Its efficacy and tolerability over periods of 12-16 weeks have been demonstrated in three well-designed, controlled trials. Rosenfeld et al. presented data from the ongoing open-label extension phase.⁴ Here, the median percent seizure reduction compared to initial baseline (cumulative cases) was 37.4% at six months and 40.5% at 12 months (dosages of 400mg - 800mg/day). Responder rate (50% seizure reduction) was 37.7% at six months and 40.1% at 12 months. Carisbamate was well tolerated with low cognitive and behavioural/psychiatric adverse event rates.

Peter Halász (Budapest/Hungary) reported on the efficacy and safety of eslicarbazepine acetate as add-on treatment to carbamazepine in patients with partial-onset seizures.⁵ Seizure frequency over the 12 week maintenance period was significantly reduced by 800mg and 1200mg eslicarbazepine both in patients with and without carbamazepine co-treatment. The incidence of treatment-emergent adverse events was higher in patients with CBZ.



First Symposium of the Ring Chromosome 20 Foundation

During the IEC, the first international symposium of the genetic epilepsy condition called ring chromosome 20 syndrome was held, organised by the Ring 20 Foundation (The symposium was filmed and can be viewed on www.ring20.org). Over 250 delegates participated. Ring chromosome 20 syndrome, r(20), is a chromosomal anomaly caused by the joining of each end of chromosome 20 resulting in ring formation. It is characterised by medically intractable epilepsy, nocturnal subtle seizures, behavioural problems and mild mental impairment. Diagnosis is often missed or delayed due to under-utilisation of chromosomal testing in epilepsy patients. Steward Ford, chairman and founder of the Foundation said, "I hope that in the future more physicians will pursue r(20) research so that we might be able to find some answers for all the people affected. The Foundation is currently engaged in two important international research studies: The genetic analysis of ring chromosome 20 and the phenotype characterisation of ring chromosome 20 epilepsy syndrome. ♦"

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5. Halász P. *Efficacy and safety of eslicarbazepine acetate as add-on treatment to carbamazepine in patients with partial-onset seizures*. IEC 2009, Budapest. Poster 299.

Focus on concordance in epilepsy

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PHARMACEUTICALS

13th International Congress of Parkinson's Disease and Movement Disorders The Movement Disorder Society

Conference details: 7-11 June, 2009, Paris, France. **Reviewed by:** Dr Tien K Khoo, Rhoda Lockhart Parkinson's Disease Research Fellow, Institute for Ageing and Health, Newcastle University.

The 13th International Congress of Parkinson's Disease and Movement Disorders was held on June 7th-11th 2009 at Le Palais des Congrès in Paris. Despite overcast Parisian skies, the event was an overwhelming success with more than 4,600 participants from 39 countries. The 5-day event comprised various plenaries, parallel sessions, video and skill workshops as well as discussions in the format of a 'video olympics' and a lively debate on some controversies in movement disorders. A variety of poster sessions attracted impressive participation from various groups around the world. This year's special theme was 'Anatomy, physiology and pathology of the basal ganglia'.

Some of the many highlights included Professor Stan Fahn's plenary that provided a thorough overview of the various therapeutic agents currently used in the treatment of early Parkinson's disease (PD) and also highlighted certain areas such as neuroprotective strategies. Evidence from therapeutic trials on monoamine oxidase B inhibitors (MAO-B) are supportive in slowing down disease progression (DATATOP, TEMPO, PRESTO, ADAGIO studies) and delaying onset to freezing of gait (BLIND-DATE study). Other important aspects of therapeutic intervention include the use of dopamine agonists that delay the need to use levodopa but do not prevent dyskinesia when used in combination with levodopa. The important potential side-effects of dopamine agonists such as impulse control disorders, somnolence and peripheral oedema were mentioned. There was also a brief mention of current trials involving potential neuroprotective agents such as the QE3 study (co-enzyme Q10) and creatine. Professor Fahn reiterated the need to always individualise treatment.

The management of motor complications following medical and surgical therapy was discussed by another group of international specialists. Professor Heinz Reichmann highlighted that the wearing-off effect of levodopa that can occur as soon as 6 months after commencement. Motor fluctuations are thought to be due to fluctuating dopamine levels and 'downstream changes' within medium sized spiny striatal neurones. In the ELLDOPA study 17% of participants receiving levodopa experienced mild dyskinesia and 30% experienced wearing off approximately six months after commencing therapy. The panel also discussed the use of amantadine and its antidyskinetic effect that may be useful but decreases in efficacy over time. The use of surgical therapy, specifically deep brain stim-

ulation (DBS), was also discussed by Dr Patricia Limousin-Dowsey and it was agreed that subthalamic nucleus (STN) stimulation can greatly improve motor symptoms in the 'off' phase such as tremor and dyskinesia. Importantly, STN stimulation is cost effective. Limited information is known about the effect of DBS on non-motor symptoms but some have reported benefits for hyperhydrosis, hyposmia, sleep and pain. Common adverse effects associated with DBS include weight gain and speech impairment. Other potential disabling side-effects include eyelid apraxia, dyskinesia and psychiatric changes (including suicidal ideation). Though STN stimulation is the most commonly performed type of DBS for PD, potential therapeutic benefits of globus pallidus interna (GPi) and thalamic (ventralis intermedius nucleus) stimulation were also discussed. The role of lesion therapy (e.g. unilateral pallidotomy, gamma knife thalamotomy) was also briefly discussed. Key points to be considered as selection criteria for surgical therapy include the patient's general health, disability, cognition, speech, swallowing and their pre-operative expectations.

Dr Anette Schrag and Professor David Burn provided insights into the disease-related psychiatric and behavioural abnormalities of PD, as well as the assessment and management of cognitive impairment in Parkinson's disease dementia (PDD). Among the useful cognitive screening tools currently utilised are the Montreal Cognitive Assessment (MoCA) and the Addenbrooke's Cognitive Examination - Revised (ACE-R). Professor Burn briefly touched on the use of antipsychotics in PDD and the potential benefit of cholinesterase inhibitors such as rivastigmine, donepezil and galantamine as well as glutamate antagonist, memantine, that is currently being studied by various groups. Emphasis on the importance of non-pharmacological approaches in the management of cognitive impairment in PD includes rehabilitation (e.g. auditory cueing and gait retraining), exercise and potential for 'medical foods'.

The topic of new therapeutics in PD was explored by Professor Warren Olanow and Professor Werner Poewe. The lack of significant results from the STRIDE-PD study examining the use of Stalevo to decrease pulsatile fluctuations of levodopa and decrease motor complications was discussed. It was felt that the significantly different dopaminergic load in the Stalevo versus levodopa group may be a factor contributing to the results. Thankfully,

more promising trials on symptomatic and neuroprotective strategies are underway. Among the agents being trialed are safinamide, pramipexole, apindore, nitisinone, creatine, co-enzyme Q10, green tea polyphenol, adenosine receptor antagonist, PYM50028, inosine, and isradipine.

The Presidential Lectures on day 3 started with an informative historical account by Professor Christopher Goetz on 'Jean-Martin Charcot and movement disorders'. This was followed up by the junior award lecture by Dr Helen Ling from the United Kingdom. Dr Ling reported diagnostic accuracy in pathologically confirmed corticobasal degeneration (CBD). The diagnostic accuracy of CBD presenting to movement disorder specialists was found to be much lower compared to progressive supranuclear palsy and multiple system atrophy. Dr Carlos Juri from Spain presented on the progression of MPTP induced Parkinsonism in monkeys via a multi-ligand PET study. Different hypometabolic patterns were illustrated and compared to PET findings in PD patients that revealed some contrary results and which may provide useful information in the development of putative neuroprotective strategies. The Presidential Lecture session was finished by the C David Marsden Lecture presented by Professor Richard Morimoto from the United States of America. His thought-provoking lecture was on the stress of mis-folded proteins in ageing neurodegenerative disease. Among the science being unravelled by Professor Morimoto and his team are the regulation of the heat shock stress response via heat shock proteins and molecular chaperones.

There was also a special session on the challenge of PD management in Africa. The difficulties in diagnosis and management of PD in a third world environment were discussed by Dr Richard Walker, Dr Njideka Okubadejo and Dr James Bower. Impressive responses to drug therapy were demonstrated in patients who had been treatment naïve for years and only reinforced the need to improve provision of medication as a basic necessity to the population. Auditory cueing and rehabilitation also produced stark benefit in mobility of patients and once again, remind us of the importance of non-pharmacological treatment.

The Wednesday night 'Video Olympics' was an entertaining and educational floor for interesting neurological cases and diagnostic conundrums to be presented to the expert panel. Among the cases presented were galac-

tosialidosis, PARK9 mutation (Kufor-Rakeb syndrome), Bartonella henselae (i.e. 'cat scratch disease'), acaeruloplasminaemia, haemorrhagic pontine gnathostomiasis, Niemann-Pick Type C, creatine transporter deficiency, congenital myotonia and adult onset Alexander disease with glial fibrillary acidic protein mutation. Not exactly your typical weekly neurology meeting cases! The panel made valiant attempts to categorise, localise and diagnose, although several of the more esoteric diagnoses defied one and all.

The congress finale comprised a lively debate on controversies in movement disorders. The hot topics discussed were 'The PPN is a promising target for treatment-resistant gait disorders in Parkinson's disease', 'Do cholinesterase inhibitors make a meaningful difference in treating PDD', 'Lewy bodies in grafted dopaminergic cells: Do they tell us anything about the pathogenesis of and the promise of cell replacement therapies in PD?' and 'Transcranial sonography: A useful diagnostic tool for movement disorders?'. As with

most controversies, only time (and more research) will help us define the right from wrong.

Participants were given the opportunity to attend a variety of educational sessions held as parallel sessions throughout the duration of the congress. These sessions were chaired by experts in the field and robust discussion was always encouraged. I am sure that all participants will be looking forward to next year's congress, to be held on 13th-17th June in Buenos Aires, Argentina. ♦

WCN 2009 World-Class Speakers, Compelling Issues

By: Dr Naraporn Prayoonwivat, MD, local chairperson of the WCN 2009 Scientific Program.

PREVIEW

The scientific programs for the upcoming WCN 2009 are central to the congress being a success. Our aim is to deliver great insights and tangible value to all attendees. I would like to share with you some highlights of what we have planned for the scientific program of WCN 2009, which takes place October 24-30 in Bangkok.

The scientific program this year has the theme, 'Innovation in Neurology'. With innovation and reference to the latest research firmly in mind, WCN 2009 will analyse the latest developments in stroke, epilepsy, neurogenetics, multiple sclerosis, dementia, movement disorders, headache and pain.

The organising committee is proud to announce that Nobel Laureate, Prof Stanley Prusiner, whose discovery of an extraordinary infectious protein called 'prions' will address the latest developments in a session on PRION disease.

The urgent requirement to bring good neurological care to needy people in developing countries will be addressed by Prof Johan Aarli, the President of the World Federation of Neurology. Other advanced information on multiple sclerosis, epilepsy, neurogenetics, neurovirology, behavioural neurology, headache and pain will be presented by international experts.

Prof Vladimir Hachinski, the WFN Vice President and globally respected authority in the modern debate on stroke, will discuss the global agenda on stroke. This devastating condition affects a large proportion of the world's population, particularly in Asian countries where access to prompt treatment is still quite limited.

Of course, we will address controversial issues. Theories, research and results from the latest research in neurology will be brought out into the open. For example, whether good old aspirin still holds the reputation of the 'best antiplatelet for stroke prevention' will be debated by Prof Peter Sandercock and Prof Louis Caplan.

The conflicting opinions on whether Devic disease, a common demyelinating disease in the East, is actually the same as its western counterpart, multiple sclerosis, will be investigated by Prof Alaistair Compston and Prof Vanda Lennon.

A decision to do or not to do a genetic workup for epileptic patients should become clearer with the discussions provided by Prof Samuel Berkovic and Prof Michael Johnson.



Also, could a diagnosis of predementia, or mild cognitive impairment, be as simple as checking for a biomarker? Should neuropsychometric testing be more reliable? These topics will be analysed by Prof Serge Gautier and Prof Rachelle Doody.

Other compelling areas of neurology will be covered as well. In addition to the daily main themes on stroke, multiple sclerosis, epilepsy, neurodegenerative diseases, headache and pain, there will be parallel sessions on infections, imaging, neurosonology, stem cells, movement disorders, genetic diseases, neuropathy, myopathy, and more. The relationship between neurology and the creative arts and artists, ethics and palliative care (e.g. in motor neuron disease) will also be explored at the WCN 2009.

Delegates will have the opportunity to contribute to the WCN 2009 scientific program through abstracts based on their accomplished research. In addition, there will be many platform presentations as well as abundant space for poster presentations.

There will be time for smiles as well as learning. Teams of neurologists can have fun as well as gain knowledge by participating in a WCN favourite, the third Tournament of the Minds. We will arrange a special prize for the tournament's winning team. ♦

Would you like to write a short report for ACNR?

If so, please contact Rachael@acnr.co.uk
or call Rachael on 01747 860168 for more information.

EDITOR'S CHOICE

AUTOIMMUNITY: mimicking one's self

Hartmut Wekerle's team, from the Max Planck Institute of Neurobiology, Martinsried, are responsible for some seriously important immunological observations over the years. And this is another one....

Firstly, remember what you learnt about one possible cause of autoimmune disease at college...that an invading bacteria looks very like an ordinary part of "self" so that the appropriate immune response against the bug mistakenly leads to auto-damage. Hence "molecular mimicry".

Now, consider this. Wekerle's team have been playing around with a mouse whose entire T cell repertoire consists of one response: to the myelin peptide MOG. In theory, it should only respond to MOG. Through the mechanism of molecular mimicry from an invading bug, it can be induced to get EAE. But, when the mouse is further trans-gened not to be able to produce MOG, you would expect that it could not get EAE, because there is no MOG target to get inflamed about. However, these animals continued to develop EAE spontaneously. After a lot of fancy purification, it turns out that T cells from these animals were targeted at two neurofilament proteins. One, NF-M, turns out to contain a sequence of 7 amino acids that is nearly identical to a sequence in the core of the MOG molecule. So, one class of T cells, that should only respond to MOG, were also targeting neurofilaments. Wekerle's team have coined this "self-mimicry".

The main thing you need to know to understand the significance of all of this is that the strain of mice used (C57BL/6) is notoriously resistant to most attempts to induce autoimmunity. So Wekerle speculates that the mice's particular susceptibility to MOG-induced EAE is because one autoimmune response (against MOG) actually ends up targeting two self-antigens: a two-pronged attack. The other implication (which isn't mentioned and I thought up all myself) is that an immune attack against myelin can also, of itself, induce an immune attack against neurons (for NF-M is a neuronal antigen). Hence perhaps, an explanation for the attrition of nerves in the predominantly demyelinating disease of multiple sclerosis.

It is hard to think of a clinical application for this discovery. But I think there is a good case for us to include this paper in ACNR because of that "wow" factor.... just when we thought we knew everything, something quite unexpected comes along. Who'd have thought.... – **AJC Krishnamoorthy G, Saxena A, Mars LT, Domingues HS, Mentele R, Ben-Nun A, Lassmann H, Dornmair K, Kurschus FC, Liblau RS, Wekerle H.**

Myelin-specific T cells also recognize neuronal autoantigen in a transgenic mouse model of multiple sclerosis.

NATURE MEDICINE

2009 Jun;15(6):626-32.

COGNITIVE Dyspraxia feel the quality

Qualitative research can be a difficult concept to digest to those of us reared on the milk of the double-blind crossover trial paradigm. The lack of a p-value at the end of the results section leaves us feeling adrift and disorientated. Certain concepts do not lend themselves particularly well to the concept of quantitative research, however. A literature search for articles on "dyspraxia" will throw up a bewildering array of concepts pertaining to speech, motor control and cortical mapping. Different disciplines working within the sphere of neurological rehabilitation would, no doubt, vary in their definitions of the condition. Given rehabilitation is based around addressing the problems that the patient sees as important rather than treating abstract diagnoses, determining the particular impact of dyspraxia on an individual's daily life is an important part of planning and providing appropriate rehabilitation strategies to them.

The authors, here, provide a concise summary of the current concepts of ideational (difficulty with the conceptual organising of task sequencing) and ideomotor (difficulty with the performance of a complex task or gesture) dyspraxia. Given that approximately 50% of people with nondominant hemisphere strokes are thought to develop ideomotor dyspraxia, there is a need to have a meaningful concept of the condition in terms of its affects on an individual. To this end, eight participants were filmed giving interviews after completing one or two activities that revealed the extent of their dyspraxia. The interviews could, therefore, focus on the particular difficulties encountered in functional situations and, also, correlate with specific life events. These

videos were then analysed to identify specific themes and experiences. The findings were then presented in various settings to multi-disciplinary groups who confirmed the validity of the findings. Unfortunately, no more detail is given of the latter part of this process and this seems somewhat open-ended.

The interviews revealed a common theme of struggle. This struggle was perceived as being both "within" (pacing oneself, thought processes, control) and "without" (using tools, communicating, relationships). The interviews revealed self-directed compensatory and functional approaches employed in order to overcome the difficulties that were being experienced. Compensatory approaches included environmental adaptations, such as the use of Velcro shoes while functional strategies included breaking activities down into their component parts. These approaches mirror those employed in the rehabilitation setting.

As is often the case with qualitative research, there isn't an obvious "take home message", but what this study does demonstrate is the need to adopt an individualised approach and to work with patients to find strategies that they can use in overcoming the difficulties arising from dyspraxia. It is a shame that some of the concerns and ideas generated in such research could not be taken forward by qualitative methodologies. – **LB**

Blijlevens H, Hocking C, Paddy A.

Rehabilitation of adults with dyspraxia: health professionals learning from patients.

DISABILITY AND REHABILITATION

2009;31(6):466-75.

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POST-POLIO SYNDROME: To rehabilitate or not to rehabilitate?

Post-polio syndrome (PPS) is a complex of symptoms occurring late in polio survivors. One of the challenging aspects in planning the rehabilitation of these patients is the difference in emphasis between management of their original polio and the PPS. For polio, exercise and activity are generally encouraged. This is not the case for PPS where energy conservation and fatigue management are important.

This pilot study looked at the effectiveness of a group rehabilitation programme for PPS sufferers using a comprehensive range of outcome measures that could serve as a useful pointer for research into more "clinical" interventions in chronic neurological disease. The rehabilitation, itself, was a comprehensive three week residential programme which involved physical exercise, education and peer support. Given that this study was a pilot, control groups were not employed, although the patient group were divided into three cohorts of 10 of whom only three dropped out by the end of the six-month follow-up period.

Perhaps unsurprisingly, given the nature of the disease, no differences were identified in muscle strength at follow-up. There were, however, significant improvements in levels of depression, fatigue and improvements in exercise endurance. Given that fatigue and endurance are two of the main ongoing problems for this patient group, it is encouraging that this relatively brief intervention may be of value in ameliorating these symptoms. A smaller subgroup also had significant improvements in general day to day functioning as measured by the Canadian Occupational Performance Measure. While this study is a pilot and, as such, lacks a control group, it is an illustration of the potential and lasting (to six months, at least) benefit of a multi-disciplinary intervention for this challenging patient group for whom no specific treatment in the typical medical sense has shown to be of benefit. – **LB**

Craig Davidson A, Auyeung V, Luff R, Holland M, Hodgkiss A, Weinman J.

Prolonged benefit in post-polio syndrome from comprehensive rehabilitation: A pilot study.

DISABILITY AND REHABILITATION

2009;30(4):309-17.

MEMORY: How did you remember that?

People are sometimes disappointed to realise that the rehabilitation of memory impairments can often involve nothing more complicated than a whiteboard, diary and a pager system. Although it would be easy to imagine that electronic "brain training" computer games could help restore cognitive function following a brain injury there is little evidence that such strategies actually work. In terms of active therapeutic intervention, the concept of "errorless learning" (EL) is becoming more widespread. This suggests that for patients with memory impairments occurring in the context of brain injury, new skills and information is best learnt in a didactic manner rather than by trial-and-error. This challenging approach or "errorful learning" (EF) involves learning from mistakes, but for patients with limited capacity to process and store information, these mistakes can be reinforced.

Although the effectiveness of EL relative to EF has been demonstrated in patients with memory disturbance, there is little correlative evidence of why this should be the case. This small study from Japan has looked at 13 patients with diffuse axonal injury (DAI) learning sets of words under EL and EF conditions and comparing them with healthy controls learning the same words under the same conditions. Functional MRI was carried out during the learning process on both groups and areas of the brain that required more activation for EF than EL were demonstrated by subtracting activity during the EL condition from that engendered under EF condition. For patients with DAI as well as healthy controls, activation of the precuneus was observed. While the control group also demonstrated recruitment of the posterior cingulate gyrus, the DAI group showed bilateral posterior parietal activation.

In the learning tasks, themselves, the DAI subjects (predictably) performed more poorly than controls under the EF conditions. The authors suggest that the neuroanatomical activation patterns in each group imply that this is due to reduced metabolism in the precuneus and posterior cingulate gyrus for the DAI group. The activation of the parietal lobes seen in this group may represent compensatory activity or disinhibition. Unfortunately, insufficient consideration is given to the dynamic processes of recovery and no clear relationship is sought between the time passed since the brain injury and learning patterns. The learning process, itself, is difficult to delineate, given that individuals tend to acquire information in unique ways. A further study looking at the changes in neuroanatomical activity over time in this patient group may be more useful in terms of the potential to translate to clinical practice. – **LB**

Ueno H, Maruishi M, Miyatani M, Muranaka H, Kondo K, Ohshita T, Matsumoto M.

Brain activations in errorless and errorful learning in patients with diffuse axonal injury: a functional MRI study.

BRAIN INJURY

2009;23(4):291-8.

MEMORY: Adult hippocampal neurogenesis – a phenomena looking for a function?

The role of adult neurogenesis in the dentate gyrus of the hippocampus is an area of intense debate. The fact that new neurons are born in this area of the mature CNS is not in doubt, but the problem is what do these cells do once they have matured and been incorporated into new circuits? A couple of papers have added to the literature in this area. The first by Kim et al investigated the consequences of preventing the death of these cells using a Bax-KO mouse, Bax being a pro-apoptotic gene (such that not having it would cause neurons newly born not to die by programmed cell death). Using this model (which of course assumes that most new neurons born in the dentate gyrus are lost through apoptosis), they found that there was a readjustment of synaptic connections with impairments in both electrophysiological and behavioural hippocampal function. In other words if a population of new born neurons in the hippocampus are not removed by natural cell death, they clog up the system and cause deficits which behaviourally involve memory acquisition and consolidation. This is consistent with the study of Truche et al who followed the fate of newly dividing (BrdU positive) neurons in terms of their integration and functional abilities. In this study the authors used the activity-dependent protein Zif268 in combination with high resolution confocal imaging and co-labelling with BrdU and the neuronal marker NeuN, to follow the fate of cells in the context of controlled behaviours involving the water maze. They found that these newly born neurons are recruited into neuronal networks involved with spatial memory and that once incorporated are involved in the updating and strengthening of that memory and thus contribute in part to its durability. Thus these cells are recruited under experience specific conditions and store those conditions as part of their contribution to the spatial memory of the hippocampus. Quite how this information is then used, updated and modified in the long term is not clear, but this and the other study of Kim et al does highlight that these new neurons do make a significant contribution to some aspects of hippocampal memory. – **RAB**

Kim WR, Park OH, Choi S, Choi SY, Park SK, Lee KJ, Rhyu IJ, Kim H, Lee YK, Kim HT, Oppenheim RW, Sun W.

The maintenance of specific aspects of neuronal function and behaviour is dependent on programmed cell death of adult-generated neurons in the dentate gyrus.

EUROPEAN JOURNAL OF NEUROSCIENCE

2009;29:1408-21.

Truche S, Bontempi B, Roulet P.

Rampon Recruitment of adult-generated neurons into functional hippocampal networks contributes to updating and strengthening spatial memory.

PNAS

2009;106:5919-24.

Neurology at the Movies

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A number of previous *ACNR* articles have examined the portrayal of neurological disorders in literary texts. Novels and stories have been a potent stimulus for film adaptations, and hence it is not surprising that neurological disorders, with their dramatic possibilities ("based on a true story"), sometimes crop up in films. However, films often exercise a powerful suggestion to the masses, and hence incorrect or inauthentic portrayals of neurological disease might exert adverse effects. Here we review a number of examples of "neurology at the movies". We say nothing here of psychiatric disorders portrayed in film, examples of which have been documented,¹ but note the power of films to influence public opinion, for example *One Flew Over the Cuckoo's Nest* (1975) probably did a great disservice to the cause of ECT. We have supplemented our own film viewing experiences with recourse to an internet movie database (IMDb.com) and reviews from Time Out magazine (www.timeout.com/film).² We are sure readers can think of further examples. Documentary films are not considered here, biographies and dramas being the genres most likely to involve portrayals of neurological disease.

Epilepsy

Epilepsy in films has been systematically (and entertainingly) examined by Baxendale.³ Included are film versions of Dostoyevsky's novels *The Idiot* and *The Brothers Karamazov* which feature characters with epilepsy. Also noted in this review is a film version of Shakespeare's *Othello* (1965), presumably based on Othello's blackout which is labelled as epilepsy by Iago. Objections to the notion that Othello has epilepsy have been raised, including the circumstances and the prompt recovery, which suggest syncope as a more likely diagnosis.⁴

More recent films with an epilepsy connection include *The Exorcism of Emily Rose* (pictured) (2005) and *Requiem* (2006), both based on documented German source cases of the early 1970s.

Emily Rose believes herself to be possessed by demons and undergoes an exorcism, only to die a couple of days later. The priest conducting the exorcism is then accused of "negligent homicide" when it transpires that he suggested cessation of Emily Rose's epilepsy drugs. A courtroom drama ensues, one issue being whether this patient had epilepsy and psychosis. In *Requiem*, the protagonist is Michaela who suffers seizures and hallucinations and stops anti-epileptic drug therapy of her own volition.

Multiple sclerosis

The celebrated cellist Jacqueline du Pre (1945-87) is perhaps one of the most high profile sufferers of MS. The biopic *Hilary & Jackie* (1998) documents her relationship with her sister, but the Time Out review fails to even mention Jackie's multiple sclerosis. The theme of young talent cruelly robbed by disease is also evident in the drama *Go Now* (1995), when a young soccer player develops MS. On a more positive note, in the TV drama *The West Wing*, President Bartlett (Martin Sheen) seems able to run the White House and the USA despite his MS, although he has concealed this diagnosis from the voters. Serious neurological illness in heads of state, and whether this should be known to the electorate has been previously reviewed.⁵

Parkinson's disease

Based on the Oliver Sacks celebrated book, *Awakenings* (1990) is an account of postencephalitic parkinsonism and the effects of levodopa. Otherwise, film accounts of PD seem few, despite its prevalence. The comedy drama *What we did on our holiday* (2006) features an elderly patient with PD.

Motor neurone disease

Despite its clinical rarity there have been a few films featuring motor neurone disease. In the US, the condition is sometimes known as Lou Gehrig's disease because the legendary New York Yankees first baseman developed this condition, as seen in

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A Love Affair: the Eleanor and Lou Gehrig Story (1978). MND is a surprising backdrop for a comedy romance in *Hugo Pool* (1997) wherein an LA pool cleaner falls in love with a young man dying with the disease. More typical of the "young life blighted by cruel disease" genre is *Jenifer* (2001).

Stroke

Biopics have occasionally featured stroke, for example *The Patricia Neal Story* (1981), about the actress, sometime wife of Roald Dahl, whose stroke-related aphasia threatened her acting career.⁶ Julian Schnabel's film of *Le scaphandre et le papillon* (The diving bell and the butterfly, 2007), based on Jean-Dominique Bauby's account of locked-in syndrome from the inside, is perhaps one of the most compelling film accounts of neurological disease.

Cognitive disorders, including Alzheimer's disease

Some films featuring characters with amnesia or memory loss have already been noted.⁷ It has been suggested⁸ that *Memento* (2000), wherein Shelby (Guy Pearce) suffers from a kind of memory loss whereby he remembers life before the murder of his wife but is unable since then to recall anything for more than a few minutes, was inspired by the classic case of HM who developed profound anterograde

amnesia after bilateral anterior temporal lobe resection, including parts of the hippocampi, for an intractable seizure disorder. Viewing the film, however, is little substitute for reading the many reports on HM. Shelby is never happy, in contrast with HMs apparent contentment.

Amnesia as a feature of dementia or Alzheimer's disease (AD) has attracted screen portrayals such as Mia Farrow in *Forget Me Never* (1999) and Judi Dench in *Iris* (2001), the latter based on John Bayley's memoir of his wife Iris Murdoch's illness, and Michael Caine in *Is Anybody There?* (2008). In *Away From Her* (2006), Fiona (Julie Christie) and Gordon are an aging couple whose lives are affected by AD: Time Out stretches credibility when stating that "the most compelling element ... is the suggestion that Fiona's AD is in part Gordon's cross to bear for his past misdemeanours [infidelity]!" The film is a "rare if difficult pleasure", for which Christie was Oscar nominated. In *The Notebook* (2004), Duke reads to Allie from a storybook about the relationship of two ill-fated young lovers. Time Out spots the glaring inconsistency: "Apparently Allie can no longer recognise her husband or children, but has retained enough short-term memory and powers of concentration to follow Duke's romantic narrative from day to day". Similar qualms may be voiced about *Cortex* (2008) in which a police inspector with AD solves a murder mystery in a

clinic treating neurodegenerative disorders.

Miscellaneous others

Many neurologists may never see a case of X-linked adrenoleukodystrophy unless they attend a showing of *Lorenzo's oil* (1992), documenting the Odone family attempting to develop a treatment for this rare condition. Lorenzo's oil (4:1 glyceryl trioleate-glyceryl trierucate) reduces hexacosanoic acid levels, and following clinical trial has been recommended in asymptomatic boys with normal brain MRI results.⁸

Daniel Day Lewis won an Oscar for his rendition of Christy Brown, a sufferer from cerebral palsy, in *My left foot* (1989).

Jack Nicholson portrays a writer with obsessive compulsive disorder in *As good as it gets* (1997), although an altogether more compelling rendition is given by Tony Shalhoub in the US TV serial *Monk*.

Conclusion

To paraphrase:¹ Should neurologists watch films? What has cinema ever done for neurology? Is "biopic" simply a blend word for "biographical myopic"? Although licence is integral to the art of film making, the majority of (non-documentary) filmic portrayals of neurological disease are simply dishonest. Maybe they should carry a health warning. ♦

ABN CASE PRESENTATION PRIZE WINNER



**Galea I,
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Phillips MJ,
Gibb WR,
McMonagle P**

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Chorea – Could the Plumbing be Humming?

A right-handed 73-year-old gentleman developed problems with right upper limb coordination, most noticeable when writing and cutting meat. This occurred on a background of well-controlled hypertension and hypothyroidism. Initial examination revealed right upper limb cortical sensory loss and pseudoathetosis. A CT brain showed a left parietal infarct and he was started on aspirin. On review a month later, he had developed marked right-sided chorea affecting both upper and lower limbs, and a left carotid bruit was heard. Magnetic resonance imaging of the brain confirmed the left-sided parietal lobe infarct which involved the post-central gyrus and the underlying white matter; the basal ganglia were normal. Intracranial magnetic resonance angiography was normal. Carotid duplex ultrasonography revealed 90% stenosis in the left internal carotid artery, with a high peak systolic velocity of 430 cm/s and an abnormal waveform. Other causes of chorea were excluded.

A left carotid endarterectomy was performed under general anaesthetic and carotid bypass. Postoperatively there was immediate and complete resolution of the hemichorea. The right upper limb cortical sensory loss and associated pseudoathetosis

persisted.

One explanation for chorea is the extensive loss of proprioception secondary to parietal lobe damage which may result in extreme pseudoathetosis mimicking true chorea ("parietal chorea"). Another possible explanation is haemodynamic chorea, secondary to critical carotid artery stenosis and hypoperfusion of the ipsilateral basal ganglia. There is laboratory and clinical evidence showing that the basal ganglia are particularly susceptible to ischaemia. The right hemichorea resolved after carotid endarterectomy, and the cortical sensory symptoms attributable to the parietal infarct did not. This shows that the infarct was not the cause of chorea, but it is consistent with a haemodynamic origin for the chorea.

The incidence of haemodynamic chorea is unknown and needs further study. We have recently described three cases of hemichorea associated with contralateral critical carotid artery stenosis; complete resolution of chorea occurred after carotid endarterectomy in all cases (Neurology 2008 Dec 9; 71 (24):e80-82). It is argued that cerebral vascular imaging is an important consideration in new onset hemichorea, even in the absence of other neurological signs suggestive of cerebrovascular disease. ♦

The European Working Time Directive in Neurology – Time for training?



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The European Working Time Directive (EWTD) became part of UK law in 1998, but has only been fully applied to junior doctors since 1st August 2009. Despite having 11 years to prepare, some trusts have struggled to implement fully compliant rotas and concerns remain about the effects of reduced working hours on training. So what impact will EWTD have on trainees in neurology and how can we ensure that the quality of our training is protected?

What changes has EWTD brought?

The key change brought by the full implementation of EWTD is a reduction in the maximum hours of work each week from 56 to 48. Importantly, in contrast to the New Deal definition, all time on call at the place of work counts as work. Time on call from home is not defined as work. However, should 11 hours of uninterrupted rest not be achieved due to calls overnight, compensatory rest must be provided.

Is a 48 hour week now a reality for neurology trainees?

The vast majority of trusts will now have introduced rotas that are, at least on paper, compliant. But the reality may be different. As professionals, we are likely to stay at work until the job is done whatever our contract dictates. If hours monitoring reveals that a rota is compliant on paper but not in practice, junior doctors and clinical tutors should get involved in designing a rota that really works.

An important barrier to EWTD compliance is the increasing problem of staff shortages producing rota gaps. This has been another unintended consequence of the disastrous Modernising Medical Careers. The BMA advises that junior doctors should not be pressurised into providing cover for rota gaps. Individual doctors currently have the right to “opt out” of EWTD in order to undertake such work on a locum basis, but groups of doctors cannot be asked to opt out by trusts.

How will reduced hours affect training?

Reduced working hours potentially threaten the quality of training by limiting the clinical experience of neurology trainees. This problem is compounded if new rotas for SHOs result in inadequate

junior support. The recent ABNT trainees' survey highlighted concerns about registrars doing inappropriate tasks and missing valuable training opportunities as a consequence. In addition, the new curriculum for neurology training is four years rather than five in duration (even for those who have not done research). How then can we ensure that the quality of training is protected and the status of new consultants is not downgraded?

Possible solutions

Non-resident rotas should be safeguarded wherever possible, allowing minimal disruption to daytime working. Shift systems can also work but only where there are enough doctors on the rota. With smaller numbers, there is a risk that rotas may be EWTD compliant but not adequate for training purposes. Trusts might consider including staff grade doctors or research fellows in rotas to increase numbers and rectify this problem. Crucially, trusts must ensure that there are enough SHOs to cover routine ward work. Where this is not the case, trainees should raise their concerns with their clinical tutor as soon as possible and contact the ABNT for advice.

A fundamental change in the culture of training may also be required: we can no longer rely solely on the apprenticeship model. But “tick-box” work-based assessments are not the answer. Consultants need protected time to provide high quality training to juniors. For instance, consultants supervising registrars in clinic could have reduced lists to give them time to offer real teaching.

Finally, should we consider reverting to a five year programme of neurology training? At the ABNT forum in Liverpool there was considerable support for this idea, particularly if one year was dedicated to sub-specialty training. We are keen to consult more widely on this issue, so please do get in touch with your views.

I believe we are fortunate that the EWTD offers protection of our work-life balance that was denied to previous generations of physicians. If rotas are carefully designed and registrars' training needs are prioritised, high quality training in fewer hours should be possible. To achieve this alongside the competing pressures of service delivery, trainees themselves need to play an active role in making this work. ♦

A Reply to the ABNT

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It would be a pity for the call by British neurology trainees for a wider debate about the role of the neurologist in the UK to go unanswered.¹ Implicit in that call is a consideration of the number of neurologists needed in the UK and the nature of the jobs that they might do, an unresolved discussion that has occupied and perhaps divided British neurology (and general medicine) since the 1950s. The debate needs to continue and needs to take account of the changing political and health service climate. It can then inform those who can influence the supply and working patterns of British neurologists. The position that I take and can justify is that British neurology has failed to expand and is unlikely to expand sufficiently (in number or in geographical distribution) to fulfill its obligation to the nation's neurological health. To make matters worse, the problems caused by this failure are compounded by ever increasing demand, a consequence of well intentioned but poorly designed political imperative.

The first objective of the ABN is "to encourage nationwide availability of excellent and equitable neurological services".² In 1954, when there were 41 neurologists in the London metropolitan regions and 18 in the rest of the UK, a Royal College of Physicians Committee³ reported that there should be "an active neurological department in all such centres of population as necessary to cover the needs of the country". As the ABN approaches its seventy-seventh anniversary, with around 550 neurologists in the UK (one per 110,000) the goal of equitable access seems as elusive as ever.⁴

What's happening to outpatient neurology?

In 2005-6 the chance of an individual being seen in a neurology outpatient clinic varied hugely according to their PCT of residence⁴ despite a doubling of consultant numbers in the preceding ten years. This suggested that consultant expansion in UK neurology had not been driven by a rational initiative to improve neurological health but by a combination of outpatient waiting list targets and the prioritising of new patients with neurological symptoms. The need for outpatient neurology has proved to be much greater than predecessors anticipated and demand has yet to be satiated. David Stevens⁵ estimated that, according to need as calculated by disease prevalence figures, one neurologist was necessary per 100,000 population (or around 600 in the UK and very close to the current national figure) yet in some parts of the country there is already one neurologist per 60,000.⁶ Most areas are still struggling to meet outpatient demand but this shouldn't be a surprise. In other demand-led health systems, for example the USA or Italy, the average neurologist serves a much smaller population (1 per 22,000 USA, 1 per 8,000 Italy) and so it might have been anticipated that unchecked outpatient demand could propel the number of neurologists

needed in the UK to at least one per 60,000 (or around 1000 neurologists) if not many many more. GPs and other specialists are referring more and more⁷ as patient and professional expectations rise and they become less and less comfortable managing a medical specialty in which knowledge and practice are changing rapidly. NICE judgements on neurological conditions ask for early referral to an expert for suspected cases and continuing follow-up for established illness. Expansion has happened but, thus far, it hasn't made an impact on the lottery of neurology expertise; areas that already had a fair share have been as likely to gain more consultant neurology outpatient time over the past ten years as areas without.

What's happening to inpatient neurology?

Whilst the rising demand and continuing inequity in outpatients is visible,⁴ the situation with emergencies and in-patients is probably much worse (because ill patients don't travel unless they know to or have to) and is hidden. There are over 400 acute admitting hospitals in the UK and, in 2007, 550 neurologists (of whom 50 are counted as academic). Many hospitals have access to on-site inpatient neurology opinion for only one or two days a week, sometimes for outpatients but not for inpatients. The RCP manpower report of 2007⁶ showed that the population in the UK served by a neurologist varies by a factor of 3.9 (an imbalance only exceeded in the medical specialties by medical oncology) so what are the chances, throughout the country, of a patient admitted with an acute neurological illness being seen by someone in that place with specific training and qualification in that specialty? Does anyone know what is happening in those acute admitting hospitals without readily available neurology opinion to patients with new neurological illness or complications of existing ones? The doubling of consultant numbers since 1997 may have given more DGH's more neurology outpatient time but that doesn't necessarily imply improvement in the local management of acute neurology.

How did we get here?

The first report of the RCP committee on Neurology⁸ was published in July 1945, and recommended that "there will need to be a considerable increase in the total number of neurologists and a more even distribution of them throughout the country, in accordance with the distribution of the population". The follow-up 1954 report³ pointed out that "there had not been an expansion of the neurological services proportionate to the expansion in other medical specialties" and that "the public was not receiving as satisfactory a neurological service as it was entitled to expect". The latter report gives two explanations for the failure to expand the neurological services at that time: financial stringency and the attitude of the medical profession towards specialisation. In

1984 Hopkins⁹ asked neurologists and professors of medicine how they saw the development of neurology in the UK, his paper throwing an entertaining light on subsequent events. Whilst most neurologists argued for pure neurology posts, members of the Association of Professors of Medicine instead argued for posts of physician-with-an-interest-in neurology. In 1992, when there were 152 whole time equivalent neurologists, Richard Langton Hewer published two linked papers^{10,11} beginning with a quote from a North American colleague that "The United Kingdom must have one of the worst neurology services in the Western World". He reviewed the history of British neurology and the distribution of neurologists in the country, and found that the population served by a neurologist in the UK varied by a factor of four (so it's changed since then by 0.1). Considering the burden of neurological disease (note that it was disease, not symptoms) he wrote that it would be unrealistic that this could all be dealt with by neurologists; the majority of people with neurological symptoms, and many with serious neurological disease, would have to continue to be dealt with by non-neurologists. The ABN report of 2002 'Acute neurological emergencies in adults'¹² looked instead at inpatients and called for a national ratio of one neurologist per 43,000 in order to provide a comprehensive on-site full time neurology service in all DGHs (so about 1400 nationally in total). Another ABN report, of 2003, 'UK-Neurology the next ten years'¹³ described what is needed for a high quality neurological service and stated that "all acutely ill inpatients with neurological problems should be looked after by consultant neurologists", requiring "significant increases in staffing". British neurology began in London and went on to develop in regional centres. As the number of neurologists has grown so the regional centres have grown, with the hub and spoke system touted as the way to best serve the country's needs. But now, whilst we seem to be in a position where we have many hubs and lots of spokes, some of the spokes are only in place once, twice or however many times a week the neurologist might visit (unless they are on leave that week). For many admitting DGHs, on-site neurology opinion is not a reliable resource.

What are the consequences?

Working in a DGH one sees daily consequences of the long-term rationing of neurological expertise outside of teaching hospitals. At least one generation of British doctors may not have been taught or has not learned enough neurology to manage the commonly presenting symptoms and illnesses.¹⁴ In this context, when the outpatient barriers came down, it was inevitable that so many patients with neurological symptoms would be referred; as part of the inundation of outpatients there are many who might not have been sent had the referring doctor a little more competence and confidence. Some patients are

referred unnecessarily whilst others are referred to the wrong place; a common complaint from patients with neurological symptoms is that they have seen several other specialists first. Just as the barriers to outpatient neurology have been forced down by waiting list pressure so they appear (in my opinion, properly so) to be coming down with inpatients too. Whilst some generalists appear paralysed by managing acute neurology others seem almost too keen to "have a go" themselves or, more likely, to be too aware of the scarcity of neurologists to wait. I'm often surprised both by how some non-neurology colleagues make little effort to sort out the problem, whilst others make too much effort in the wrong direction. Neurological experience and training in the UK has been in short supply for so long, yet we still expect non-neurologists to diagnose and manage so much neurology so well.

Thrombolysis is being introduced across the country¹⁵, the acute patients in many areas to be assessed by A&E doctors or geriatricians. So a potentially lethal treatment with still-debated benefit even to those who definitely have the condition is placed into the hands either of those trained to decide and act quickly in medical emergencies (probably OK if they get the diagnosis right, possibly fatal if they don't) or those who are trained in managing the complications of growing older. There are now specifically-trained stroke doctors. The production of doctors who are experts in only one acute brain illness strikes me as being another well-intended but poorly designed response to the lack of neurologists. The recently announced national dementia strategy¹⁶ calls for a rapid and competent specialist assessment. From which specialty will these specialists be drawn? Will it be from those with training in psychiatry, from those with training in elderly care, or from those with training in neurology? The scarcity of neurologists outside of teaching hospitals also has implications for neurological research. Samples are biased towards teaching hospital patients (predominantly urban and mobile), and patients living further away are denied the opportunity to take part. In the DGH the priority, in an over-stretched specialty, has to be service delivery, not research.

What is going to happen next?

At a time when the NHS is about to feel the consequences of the global economic crisis, and after ten years of increasing funding and consultant posts, it is no longer reasonable to blame financial stringency. Perhaps instead we have to look again at the attitude of the medical profession towards specialisation, within and outside of neurology and within and outside the regional centres. It may not be a surprise to neurologists that the professors of Medicine got it so completely wrong in 1984,⁹ although, being Professors, their opinion then may not have been representative of their DGH physician colleagues. What are the opinions now? Are GPs and general physicians likely to manage and hold back as much of the

general neurological symptomatology as they did? Ten years of managing waiting lists and seeing inpatient referrals as a DGH-based consultant has taught me otherwise. Would cardiologists, endocrinologists, gastroenterologists or nephrologists be happy for a sufficient level of expertise in their specialty to be assumed and delivered by non-specialists? And when these specialists are on-call for general medicine are they or should they be comfortable with acute neurology? What about other neurologist's opinions now? Do they want expansion? My best guess is that in the less well provided areas they will and in the better provided areas they won't. If regional centre neurologists aren't keen on expansion, do they support expansion in the rest of the country to bring it up to an equivalent level?

Current prediction¹ is of, at most, 65 new neurology consultants coming out of UK training each year. At 65 per year, as long as no-one departs the specialty or chooses to work flexibly, neurology will reach 1400 nationally (the figure estimated by the ABN to reach 1 per 43,000) in about twelve years. Planning and predicting jobs has always been difficult but I'm aware of at least three unfilled jobs in very desirable parts of the country already and there may be many more. If outpatient demand carries on up, and if general physicians become more reliant on specialist opinion in neurology (as I believe they should and will), then there should be even more unfilled posts to come. The predicted NHS financial difficulties ahead may however mean that there isn't the money to fund new posts and, sadly, that British neurology will have missed a golden opportunity to improve service provision.

What can we do about it?

Can we do anything in the meantime as the demand for inpatient and outpatient neurological expertise increases and the UK underproduces neurologists? The first thing might be to develop methods for sieving and serving the demand for new outpatient neurology opinion. Turning back the tide is impossible so we may need a tier of doctors in neurology who can manage the bulk of headache, dizzy turns and query first fit and TIA referrals. They would, in effect, be community-based and could come from neurology, general practice, general medicine or geriatrics. If they are to have sufficient credibility and skill it seems important that they are trained by neurology, accredited by neurology, and continue to work in close association with neurology. Relying on self-appointed GP (or other) experts in stroke, PD and dementia is surely not good enough. Freeing some neurologist outpatient time in this way might give more time for inpatient care. Perhaps also, for the time being, we should stop appointing neurologists to areas with plenty already; it is in the district general hospitals and communities that neurologists are needed. These hospitals usually have MRI machines, and neurophysiology can travel, so the lack of investigative facilities is no longer a reason for centre-based neurologists not to get

out more. Transferring patients to the local neurological centre may be OK in large cities but it doesn't work so well when the centre is 50 miles away. If we can't train and fund sufficient neurology expertise to provide for wherever the patient is admitted, then perhaps we should be arguing that it is only neurologically safe to admit them to selected places.

Conclusion

It is to be regretted that the problems in neurological service delivery in the UK have not been noted by neurology alone. The recent All Party Parliamentary Group report on Parkinson's disease (17) identifies significant inequalities in service for patients with Parkinson's disease. This group wasn't the first (3,11,18) and perhaps its stern reprimand, what it calls "a lack of leadership for

neurological services at local and national level", is deserved. A better staffed and more equitably distributed neurology could provide local and national leadership for service delivery in Parkinson's disease, as well as for epilepsy, multiple sclerosis, stroke, dementia, muscle disease and every other neurological illness.

The UK urgently needs more predominantly DGH-based neurologists. When they become available they will need to run outpatient clinics and organise around themselves teams of medical and paramedical staff to manage the acute admissions, the new outpatient referrals and the long term neurological illness in the community. In the meantime, whilst neurological expertise remains in short supply (not enough neurologists being trained, not enough money to pay for them), the UK needs

to make the most of what is available. That may mean teaching and supervising GP's and hospital doctors in neurology so that wherever the patient presents and is admitted in the UK they can be sure of competent neurological expertise and management. It may mean imposing local quotas on outpatient referrals, perhaps by condition, by age, by postcode or by GP. It may mean ensuring that, in the short term, undersupplied areas are encouraged to provide new consultant neurology posts whilst well-supplied areas are discouraged. It must surely mean that improving the neurology service in the UK becomes the first item on each ABN council agenda.

This is my opinion, admittedly shaped (or distorted) predominantly by south England DGH experience. Can anyone offer a different view and a counter-argument? ♦

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NEWS REVIEW

Elekta provides VMAT and radiosurgery solutions for New Jersey Health System

CentraState Medical Center (Freehold, New Jersey) has purchased two new state-of-the-art Elekta radiation therapy treatment systems, both with Volumetric Modulated Arc Therapy (VMAT). The first site in the world to have both Elekta Axesse and Elekta Infinity, CentraState will offer the most advanced cancer care available to its patients.

CentraState Medical Center, a part of the CentraState Healthcare System, currently is treating 45 to 50 patients a day – with fluctuations as high as 70 patients per day, all on one treatment unit. When the time came to add another treatment system, CentraState elected to replace another manufacturer's system and install two new Elekta systems.

One key determining factors in choosing Elekta was CentraState's desire to partner with a company that would ensure the institution would remain ahead of the technological curve. Robert Smith, MS, Director of Physics, says,



"We spent a lot of time comparing Elekta with other systems, and discovered that Elekta systems had many advantages over the competition, especially in imaging capabilities. "We'll be replacing our current IMRT techniques with VMAT," he explains. "We're looking to VMAT to increase throughput, but more importantly to reduce treatment times for our patients. That, in turn, will reduce the chance of patient movement during the treatment. We feel we can deliver a better, more precise treatment to the patient by delivering the dose in a shorter time."

**For the latest Elekta VMAT news, visit elekta.com/vmat
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*If you would your news to feature in ACNR, please contact Rachael Hansford,
T. 01747 860168, E. rachael@acnr.co.uk*

Richard Hammond opens new National Rehabilitation Centre for children with brain injuries

Broadcaster Richard Hammond paid a visit to The Children's Trust in Tadworth, Surrey on 16th July to open the charity's new residential rehabilitation centre for children with acquired brain injuries. The £7 million centre, funded entirely by voluntary donations, will enable The Children's Trust to help even more children from across the UK rebuild their lives after sustaining a devastating brain injury as a result of a tragic accident or severe illness.

Richard Hammond spent the morning meeting children, parents and staff at the Trust before the opening ceremony. He was escorted on his visit by 13 year old Chas, who stayed at the Trust for rehabilitation in 2008 after being severely injured in a skiing accident.

Having sustained a serious brain injury himself in a near fatal accident whilst filming for the BBC's Top Gear in 2006, Richard Hammond explained that the care and rehabilitation of brain-injured children was a cause close to his heart.



Richard Hammond beside The Children's Trust's new hydrotherapy pool, with Sarah, a pupil at the Trust's school, and physiotherapy assistant Helen Ganderton.

"I know only too well the challenges people face following a severe brain injury, but for a child there are extra dimensions because their brains are still developing. This amazing new building will help The Children's Trust's specially trained staff give these children the best chance of rebuilding their lives."

Andrew Ross, Chief Executive of The Children's Trust, said, "It has been wonderful to celebrate the opening of our new centre with the children, families and staff who are using it, as well as the generous individuals and organisations who have funded it. Our challenge was to design a facility for the nursing and care of children with the most complex physical, psychological and social needs without losing sight of our main purpose: to give the children a road back to normality, marrying expert care with a 'can do' attitude to disability."

For more information E.pressoffice@thechildrenstrust.org.uk

Carl Zeiss offers free colour selection for LSM 710

The explosion in the number of new fluorescent dyes has opened up exciting new opportunities for life science researchers. However, each requires the microscope system to be equipped with an appropriate excitation laser, a limitation that has greatly restricted their adoption.

According to Carl Zeiss, the answer is the new In Tune laser system, which offers free selection of laser lines in the range 488 nm to 640 nm. Together with the LSM 710 laser scanning microscope, In Tune enables performance of novel fluorescence measurements for the first time. Whatever the excitation wavelength required, In Tune matches the dye perfectly to enable their use



in intensity or lifetime imaging experiments.

The choice of fluorescent dyes is unrestricted as In Tune can be used alongside other system lasers, from near UV to far red. This is particularly important for FRET (Förster Resonance Energy Transfer) as In Tune allows the unrestricted use of new dye combinations in the green-red spectral range. With its 40 MHz pulse repetition rate In Tune is also an ideal source of excitation for FLIM (Fluorescence Lifetime Imaging Microscopy) experimentation.

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

Neupro®, the only transdermal patch for Restless Legs Syndrome

The only transdermal patch in the UK for the symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome (RLS) in adults was launched recently by UCB. Applied once-a-day, Neupro® (rotigotine transdermal patch) allows for continuous drug delivery to provide stable drug levels in the bloodstream 24 hours a day and improves symptom control day and night.

RLS may present itself as a 24-hour condition with symptoms frequently occurring during periods of rest, such as during sleep, or inactivity during the day, like long car journeys. RLS is thought to affect between three and 10% of the population to some extent, causing sensations such as tingling or prickling sensations, burning, tugging and creeping. If left untreated, in some patients RLS can cause exhaustion and negatively impact quality of life.

The goal of treatment for idiopathic RLS is symptom remission. Clinical trials, evaluating the efficacy and safety of rotigotine over a six month period in almost 1000 patients with RLS showed significant and



clinically relevant improvements in RLS symptoms compared with placebo and that the treatment was generally well tolerated. The most common adverse drug reactions reported in RLS patients treated with rotigotine were nausea, application site reactions, fatigue and headache.

"The symptoms of Restless Legs Syndrome can have a significant impact on quality of life for many people, often affecting sleep, job performance and social activities. People with severe symptoms may require lifelong treatment," said Professor Ray Chaudhuri, Consultant Neurologist, University College Hospital. "The clinical trial data show that rotigotine provides us with a new and effective option for tackling this debilitating condition."

For further information contact UCB on [T. 01753 534 655](tel:01753534655).

Carl Zeiss launches user-friendly software for Quantitative Force Measurement

The microscopic manipulation of biological specimens, individual cells and cell components is becoming increasingly common in life science laboratories. The launch of the PALM MicroTweezer Force Measurement module from Carl Zeiss which eliminates the need for additional hardware and time-consuming adjustment and calibration, means that the technique can be adopted by many more users.

The Force Measurement module not only controls the manipulation of microscopic particles with the PALM optical tweezers but also enables the quantitative measurement of forces relevant to many life science disciplines, visualising the data in real-time. The new module offers users a flexible and user-friendly interface to the software's functionality, which will enable a large degree of freedom in experimental design and test configuration.

The module also enables the use of the PALM MicroTweezers system for pure specimen manipulation as well as for position detection and quantitative force measurement. This means that direct comparisons may be made between experimental results and data from the literature. Calibration routines for the characterisation of the optical tweezers are performed automatically and archived together with all experimental data and images.

The Force Measurement module is supplied together with an FM StarterKit containing the FluidCell component, which permits fast and easy sample



preparation. The PALM MicroTweezers and Force Measurement module can be combined with various solutions from Carl Zeiss, including the PALM MicroBeam and Colibri light source.

For more information [E. micro@zeiss.co.uk](mailto:E.micro@zeiss.co.uk)

Addenbrooke's places first UK order for next generation imaging system

Addenbrooke's Hospital in Cambridge will be one of the first sites to benefit from Siemens' advanced CT, the SOMATOM® Definition Flash. The hospital has placed the first UK order for the new system which will be installed later in the year.

"As a result of this installation, we will be able to image patients at a greatly reduced dose and this will be invaluable for the people we see on a more regular basis. We are also hoping to omit one phase of the diagnostic study for some patients. This will not only alleviate dose on the individual, but enable us to make efficient use of the machine," said Dr. Ashley Shaw, Lead Radiologist for CT at Addenbrooke's Hospital. "We have continued to use Siemens for our CT services at Addenbrooke's as a result of a longstanding partnership that delivers consistently good value."



The Definition Flash will image patients alongside three other Siemens CT machines. Each system in the department is used for a range of imaging requirements including neurology and whole body scanning. The Definition Flash will support the systems already in place.

The CT also introduces a new level of image quality in Dual Energy scanning, increasing the contrast without having to apply higher radiation dose. This is achieved via a new, selective photon shield which blocks unnecessary parts of the energy spectrum. With improved separation of the two simultaneous data sets, radiologists at Addenbrooke's will be able to classify the chemical composition of tissues in routine CT studies.

For more information see www.siemens.co.uk

An acute interest in ultrasound

The Royal Liverpool University Hospital has chosen SonoSite's MicroMaxx® hand-carried ultrasound system for a range of acute medical applications, including FAST scanning, insertion of central lines and detection of aneurysms. Mr Peter Burdett-Smith, a Consultant in Emergency Medicine and Director of the Medical Division at the hospital, explained, "We first introduced point-of-care ultrasound in emergency medicine approximately four years ago, using an older SonoSite instrument. Last year we upgraded to the MicroMaxx system, taking advantage of its improved resolution to perform regional nerve blocks for manipulation of fractures and injuries. Once we became familiar with the MicroMaxx system, the straightforward controls have allowed us to quickly develop techniques for a variety of applications, and we have been



working closely with radiology colleagues to extend our use of ultrasound even further."

"Focused ultrasound for emergency medicine is now widespread, and has been incorporated into the College of Emergency Medicine's training curriculum, with the first examinations due next year. All of our senior medical staff are trained in emergency ultrasound and, thanks to SonoSite's support, we are the regional training centre for emergency ultrasound, teaching these vital skills to registrars and consultants from across the region and beyond."

For information on SonoSite courses contact education@sonosite.com. For more information about SonoSite products T. 01462 444 800, Europe@sonosite.com



Confidence to take action everyday

COPAXONE® (glatiramer acetate)

PRE-FILLED SYRINGE PRESCRIBING INFORMATION

Presentation – Glatiramer acetate 20mg solution for injection in 1ml Pre-filled Syringe. **Indication** – Treatment of patients who have experienced a well-defined first clinical episode and are determined to be at high risk of developing clinically definite multiple sclerosis (MS). **Reduction of frequency of relapses in relapsing-remitting MS in ambulatory patients.** In clinical trials this was characterised by at least two attacks of neurological dysfunction over the preceding two-year period. **Dosage and administration** – 20mg of glatiramer acetate (one pre-filled syringe) administered sub-cutaneously once daily. **Children (12 – 18 years)** No specific studies. Data suggests safety profile similar to that seen in adults. **Children (<12 years)** Not recommended. **Elderly** No specific data. **Impaired renal function** No specific studies. Monitor renal function during treatment and consider possibility of deposition of immune complexes. **Contra-indications** – Known allergy to glatiramer acetate or mannitol (excipient). **Pregnancy.** **Special warnings and precautions** – Sub-cutaneous use only. Initiation to be supervised by neurologist or experienced physician. Supervise first self-injection and for 30 minutes after. One or more of vasodilatation, chest pain, dyspnoea, palpitations or tachycardia may occur within minutes after injection. These generally resolve spontaneously after a short time. If severe, treat symptomatically. Caution in patients with pre-existing cardiac disorders and review such patients regularly. Rarely convulsions and/or anaphylactic or allergic reactions. Rarely, hypersensitivity (bronchospasm, anaphylaxis or

urticaria). If severe, treat appropriately and discontinue Copaxone. **Interactions** – No formal evaluation. Increased incidence of injection-site reactions with concurrent corticosteroids. Theoretical potential to affect distribution of protein-bound drugs, therefore concomitant use of these should be monitored. **Pregnancy and lactation** – Not to be used in pregnancy. Consider contraceptive cover. No data on excretion in human milk. **Undesirable effects** – Local injection site reactions (erythema, pain, mass, pruritus, oedema, inflammation, hypersensitivity, injection site atrophy). An immediate post-injection reaction (one or more of vasodilatation, chest pain, dyspnoea, palpitation, tachycardia) may occur within minutes, reported at least once by 31% of patients receiving Copaxone compared to 13% of patients receiving placebo. >1%: Nausea, anxiety, rash, back pain, chills, face oedema, vomiting, skin disorder, lymphadenopathy, tremor, eye disorder, vaginal candidiasis, weight increased. Rarely: Anaphylactoid reactions. Please refer to the SPC for a full list of adverse effects. **Overdose** – Monitor, treat symptomatically. **Pharmaceutical Precautions** – Store Copaxone in refrigerator (2°C to 8°C). If the pre-filled syringes cannot be stored in a refrigerator, they can be stored at room temperature (15°C to 25°C) once for up to one month. Do not freeze. **Legal Category** – POM. **Package Quantity and Basic NHS Cost** – 28 pre-filled syringes of Copaxone: £524.31. **Product Licence Number** – 10921/0023. **Further Information** – Further medical information available on request from Teva Pharmaceuticals Limited, The GateHouse, Gatehouse Way, Aylesbury, Bucks, HP198DB. **Date of Preparation** – March 2009.

Adverse events should be reported.
Reporting forms and information can be
found at www.yellowcard.gov.uk.
Adverse events should also be reported to
Teva Pharmaceuticals Ltd on
telephone number: 01296 719768.

Date of Preparation: March 2009

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